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Article

Effect of Carbohydrate-Enriched Drink Compared to Fasting on Hemodynamics in Healthy Volunteers. A Randomized Trial

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Abstract: Fasting prior to surgery can cause dehydration and alter hemodynamics. This study aimed to determine the impact of a carbohydrate-enriched drink (Nutricia™ Pre-op®) on selected hemodynamical parameters, measured in a non-invasive manner. We enrolled 100 healthy volunteers and measured their weight, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), thoracic fluid content (TFC), thoracic fluid index (TFCI), stroke volume (SV), stroke volume variation (SVV), stroke index (SI), cardiac output (CO), cardiac index (CI), heather index (HI), systolic time ration (STR), systemic time ratio index (STRI), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) by a Niccomo™ device, implementing the impedance cardiography (ICG) method. Measurements were performed at the beginning of the study, and after 10 h and 12 h. We randomly allocated participants to the control group and the pre-op group. The pre-op group received 400 mL of Nutricia™ preOp®, as suggested in the ERAS guidelines, within 10 h of the study. Student's *t*-test or the Mann–Whitney U test were used to compare the two groups, and $p < 0.05$ was considered significant. We did not observe any changes in hemodynamical parameters, blood pressure, and heart rate between the groups. We have proven that carbohydrate-enriched drink administration did not have a significant impact on the hemodynamical parameters of healthy volunteers.

Keywords: impedance cardiography (ICG); fasting; enhanced recovery after surgery (ERAS); hemodynamics; cardiac index (CI); systemic vascular resistance index (SVRI); pre-op; perioperative patient management; NICCOMO

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1. Introduction

Preoperative, overnight fasting is a decades-old idea, introduced as prophylaxis for Mendelson syndrome, which is aspiration pneumonia with a poor prognosis [1]. Over the years, new evidence has come to light, and current guidelines recommend patients do not eat solid foods for 6 h and do not drink clear liquids for 2 h before surgery [2,3]. However old habits prove difficult to change, as fasting time still remains excessive in many hospitals (even up to 16 h) [4,5]. This can lead to dehydration, which has adverse effects on hemodynamic parameters, and in consequence, impairs oxygen delivery [6,7]. It is worth emphasising that a patient's hydration is not routinely measured in the operating theatre, as neither heart rate nor blood pressure are sensitive indicators [8]. Fasting can also cause unwanted metabolic changes, which can increase the complication ratio, and thus preoperative carbohydrate treatment in the form of carbohydrate-rich drinks (so-called pre-op) are recommended by both enhanced recovery after surgery (ERAS) protocol and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [2,9]. This can reduce patients' anxiety and improve general well-being [10]. Surgical injury and

fasting increase insulin resistance, causing complications in the postoperative period [11], carbohydrate treatment can alleviate this to some degree [10], and decrease the length of hospital stay [12]. Oppositely, a more recent meta-analysis shows no benefit of pre-op over placebo or water [13]. Due to inconsistent data, it is important to gather new evidence regarding this matter.

In our previous study, we measured changes in body water (total body water, intracellular water, extracellular water) and body composition in fasting individuals. We did not observe significant dehydration during overnight fasting, but nonetheless there was a significant difference in heart rate [14]. This prompted us to take a closer look at changes in hemodynamic parameters. While they are rarely measured directly in the operating theatre [15], improvements in bioelectrical impedance analysis may change this in the near future [16–18]. Although not a new concept, impedance cardiography (ICG) is becoming more and more accurate as new hardware and calculation algorithms are developed. It is already comparable to reference methods [19–21], providing a non-invasive alternative for hemodynamic monitoring.

In this study, we assessed the impact of a carbohydrate drink on cardiac output and systemic vascular resistance after overnight fasting using the ICG device. The study aimed to determine the impact of the carbohydrate-enriched drink (Nutricia™ Pre-op®, Nutricia, Warsaw, Poland) on selected hemodynamical parameters measured in a non-invasive manner. We hypothesized that the administration of liquid recommended by ERAS guidelines would improve the hemodynamical status of fasting healthy volunteers. According to our best knowledge, this relationship has not been previously studied. Furthermore, we were interested in determining the impact of fasting on hemodynamics.

2. Materials and Methods

This was an open label randomized controlled study conducted in Gdansk, Poland. The study was designed according to the regulation of Good Clinical Practice (GCP) and the 1964 Declaration of Helsinki and its amendments. Study protocol revied approval from the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk (NKBBN/562/2021). The study was prospectively registered at ClinicalTraials.gov (NCT04972500) on 9 July 2021.

2.1. Participants

The study was performed on healthy individuals. Between 12 July 2021 and 4 November 2021, we enrolled 100 adult volunteers from the American Society of Anesthesiologists (ASA) status 1 and 2. Due to lack of literature data, the ex-ante calculation of groups sizes was impossible. Volunteers' height had to be within a 120–230 cm range and the weight between 30 and 155 kg. Exclusion criteria were chronic kidney disease, circulatory failure, lung diseases, diseases of the heart valves, history of hypoglycaemic episodes, or any carbohydrate disturbance. For each participant, the study started at 9 p.m. when the first measurements were taken. Firstly, body mass and blood pressure were measured. Then, the skin was cleaned with alcohol to make skin-to-electrode impedance as low as possible. Two electrodes were placed on the thorax along the midaxillary line, and another two electrodes were placed on the neck. Hemodynamic parameters were measured in a supine position. Measurement was conducted according to manufacturer guidelines. After measurements, participants were asked to fast for 10 h; however, they could drink clear liquids for 2 h. The second and third measurements took place at 7.00 a.m. and 9.00 a.m. The measurements procedure was the same for all timepoints. After the second measurement, the participants were divided into two groups. A computer-generated randomization plan (www.randomization.com (accessed on 8 July 2021)) with allocation ratio 1:1 was implemented. The control group had to restrain from drinking till the third measurement, whereas the pre-op group received 400 mL of Nutricia™ PreOp® per os. The study protocol did not include follow up. Study protocol is presented in Figure 1.

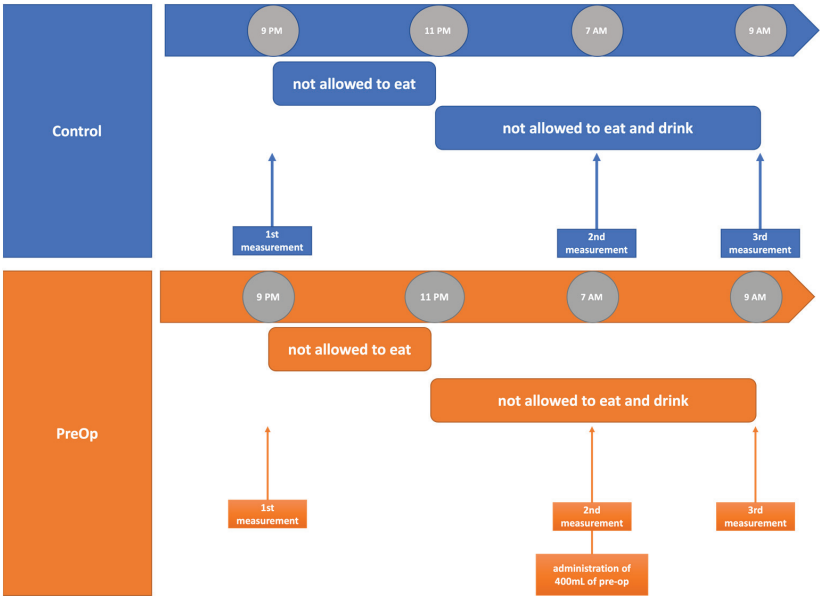

Figure 1. Study protocol summary.

2.2. Impedance Cardiography

Niccomo™ device (Medizinische Messtechnik GmbH, Ilmenau, Germany) was used to non-invasively measure hemodynamical parameters. The special algorithm allowed Niccomo™ to calculate hemodynamic-related parameters based on a variation of thoracic bio-impedance caused by changes in volume and velocity of blood in the aorta. Thoracic fluid content (TFC), thoracic fluid index (TFCI), stroke volume (SV), stroke volume variation (SVV), stroke index (SI), cardiac output (CO), cardiac index (CI), heather index (HI), systolic time ration (STR), systemic time ratio index (STRI), systemic vascular resistance (SVR), and systemic vascular resistance index (SVRI) were measured. A Signal Quality Indicator, which shows the quality of the beats used in the calculation, was used as a validation tool. All measurements had a high-quality index (>95%).

2.3. Carbohydrate Drink

Nutricia™ PreOp® was used in the study. Participants received 400 mL of liquid (50.4 g of carbohydrates), according to the recommendation of enhanced recovery after surgery (ERAS) protocol.

2.4. Statistical Analysis

The primary endpoints were changes in CI, SVRI, SV, and heart rate (HR). No interim analyses were performed. Data were analyzed with Prism 9 software (GraphPad Software, San Diego, CA, USA). Categorical variables are reported by the number and percentage of patients in each category. Continuous variables with a normal probability distribution are presented as the arithmetic mean with standard deviation. For the continuous variables with a different probability distribution, the median and the interquartile range (IQR) are given. The D'Agosition and Person test was used as a normality test. Fisher's exact test, a two-tailed *t*-Student test or the Mann–Whitney U test were used to compare two groups regarding the data type and characteristic. Results were considered to be statistically significant if $p < 0.05$. The detailed protocol for statistical analysis was previously described by our team [14].

3. Results

One hundred volunteers were enrolled in the study. All participants completed the study protocol. The allocation ratio was 1:1, each study group (control and pre-op) consisted of 50 people. No significant differences between control and pre-op groups were found (Table 1).

Table 1. Patients' characteristics at the beginning of the study. Values are number [%], or mean (SD).

Variable	Control (n = 50) Number [%] Mean (SD)	Pre-op (n = 50) Number [%] Mean (SD)	p Value
Female	27 (54%)	32 (64%)	0.4162
Age (y)	23.70 (3.51)	23.72 (3.12)	0.9761
Height (cm)	173.50 (10.12)	173.30 (9.26)	0.9263
Weight (kg)	72.45 (15.86)	67.53 (11.84)	0.0819

We did not observe any differences in systolic (SBP) and diastolic (DBP) pressure or heart rate (HR) between groups. SBP and DBP were significant lower at the 10 h time point (Table 2).

Table 2. Comparison of blood pressure and heart rate between groups. Values are median (IQR range), or mean (SD).

Variable	0 h Median (IQR) Mean (SD)	10 h Median (IQR) Mean (SD)	12 h Median (IQR) Mean (SD)		p Value (0 h vs. 10 h)	p Value (Control vs. Pre-op)
			Control	Pre-op		
SBP (mmHg)	119.50 (12.21)	114.80 (11.04)	112.90 (10.99)	111.30 (10.35)	0.0052	0.4386
DBP (mmHg)	72.37 (7.76)	68.77 (6.32)	68.70 (6.81)	68.60 (6.82)	0.0004	0.9417
HR (bmp)	69.50 (63.00–77.00)	67.91 (11.95)	62.18 (9.81)	63.60 (10.22)	0.1466	0.4802

SBP—systolic blood pressure; DBP—diastolic blood pressure; HR—heart rate.

No significant differences were observed between all measured hemodynamical parameters at the 0 h and 10 h time points. No significant differences between the pre-op and control groups were found at 12 h of the study (after randomization and carbohydrate-enrich drink administration) (Table 3). Additional parameters reported by Niccomo™ are presented in Table S1.

Table 3. Comparison of hemodynamical parameters. Values are median (IQR range) or mean (SD).

Variable	0 h Median (IQR) Mean (SD)	10 h Median (IQR) Mean (SD)	12 h Median (IQR) Mean (SD)		p Value (0 h vs. 10 h)	p Value (Control vs. Pre-op)
			Control	Pre-op		
SVV (%)	15 (11–18)	14.5 (11–19)	14.5 (11–21)	14 (11.75–17)	0.6982	0.6167
SV (mL)	104 (23.85)	102.9 (23.33)	110 (23.61)	105.3 (21.72)	0.7419	0.3007
SI (mL m^{-2})	56.45 (9.47)	56.15 (8.9)	58 (54–63)	57.5 (53–62.25)	0.8177	0.5035
CO (L min^{-1})	7.28 (1.76)	6.87 (1.51)	6.77 (1.47)	6.61 (1.39)	0.0776	0.5766
CI (L min^{-1} m^{-2})	3.94 (0.67)	3.76 (0.65)	3.65 (0.56)	3.68 (0.64)	0.0569	0.8815
SVRI (dyn s cm^{-5} m^2)	1640 (1423–1847)	1661 (314.2)	1688 (269)	1681 (306.2)	0.9985	0.9036
SVR (dyn s cm^{-5})	893 (740–1120)	904 (784.3–1064)	931.7 (198.4)	943.6 (184.8)	0.9441	0.7588

SVV—stroke volume variation; SV—stroke volume; SI—stroke index; CO—cardiac output; CI—cardiac index; SVRI—systemic vascular resistance index; SVR—systemic vascular resistance.

4. Discussion

Our goal was to access the impact of carbohydrate-rich drink on haemodynamic parameters in fasting, healthy individuals. We used the ICG device Niccomo™, which has been proven as a viable method for the non-invasive measurement of haemodynamic parameters when compared with thermodilution-derived methods [19–21]. The accuracy of the ICG method depended strictly on clinical scenario. Performed meta-analysis demonstrated good values of correlation coefficient; however, it must be noted that dose data were relatively old [22–24]. Generally, the correlation of ICG and reference method were the highest in healthy individuals (r^2 around 0.7–0.8), and much lower in ICU patients and individuals with impaired cardiac function [22,24]. The indisputable advantage of the ICG method was its non-invasive character, which allowed it to be used on patients without indication to invasive monitoring. This approach minimalized the risks while providing useful clinical data. Transthoracic Doppler echocardiography (TTE) can also be used to measure haemodynamic parameters in a non-invasive way, and generally there is no significant difference in CO compared with the thermodilution. However, when structural changes are present in the heart, TTE accuracy is questionable [25]. Interestingly, Daralammouri et al. managed to overcome this shortcoming with the use of the ICG. They used both methods in tandem to measure the aortic valve area in patients with aortic valve stenosis; this hybrid approach significantly correlated to thermodilution method [26]. Liu et al. used the ICG device during cardiopulmonary exercise testing and six-minute walk test to improve peak oxygen uptake assessment in healthy volunteers [27]. ICG proved useful in assessing the impact of postural changes on haemodynamic parameters in healthy adults [28], infants [29–31], and surgery patients [32].

Several factors can contribute to perioperative hemodynamic changes. Firstly, fasting prior to surgery can cause dehydration [33]. Intubation itself causes changes in HR, SBP, and DBP [34]. Moreover, the drugs used during general anaesthesia are cardiodepressants, and hypotension during induction is a common complication [35]. Typically, the decreased mean arterial pressure and CI, as well as increased SVRI, are observed after the induction of general anaesthesia. SV can be lower, even by 62%, in comparison with the values before anaesthesia [6]. Unfortunately, conventional monitoring used in the operating theatre cannot adequately represent changes in hemodynamics; thus, these changes can be easily omitted [36]. Fortunately, appropriate intravenous fluid management can reverse this trend [6]; however, there are no data regarding if *per os* fluid administration can also be beneficial. Given that the perioperative administration of carbohydrate-rich drink has established a role in preventing other complications such as nausea, insulin resistance, and muscle loss [37–39], the question raised in our study is important and covers gaps in current knowledge.

We determined no significant differences between the pre-op and control groups regarding changes in haemodynamic parameters in fasting volunteers. Similarly, Alves et al. showed no changes in haemodynamic parameters after fasting in healthy (ASA I/II) volunteers as well. Although they used echocardiographic methods instead, their population was older (26–67 years old) and they did not examine the carbohydrate-rich drink impact on those changes [40]. Interestingly, in healthy males during physical activity, carbohydrate rich-drink could increase CO and decrease SVR in comparison to protein-rich drinks and water [41]. Even though fasting did not influence the hemodynamic parameters in healthy individuals, it is vital to provide proper fluid therapy as both hypo- and hypervolemia have detrimental effects on surgery outcome. It has to be emphasised that goal-directed fluid therapy is part of ERAS protocol [8,33].

We are aware of several limitations of this study. This is a single-centre study, in which healthy volunteers were included. We used non-invasive methods for hemodynamic assessment, which may be less reliable than invasive methods. We also did not perform this study in a crossover design. We did not have direct control over volunteers' compliance; rather, we relied on their confirmation that they obeyed the study protocol. We also did not measure urine secretion.

5. Conclusions

We determined the impact of a carbohydrate-enriched drink (NutriciaTM Pre-op®) on hemodynamical parameters in fasting healthy individuals. We have proven that consuming this drink did not impact the volunteers' hemodynamic status.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11030825/s1, Table S1: Comparison of impedance cardiography (ICG) parameters.

Author Contributions: Study design and conceptualisation, A.A., R.O.; data acquisition, J.K., K.P.S., S.P.P., M.J.K.; statistical analysis and visualisation, K.P.S.; data interpretation, J.K., K.P.S., R.O.; writing—original draft preparation, J.K., K.P.S.; writing—critical review and editing, J.K., K.P.S., S.P.P., M.J.K., A.A., R.O.; supervision and funding, A.A., R.O. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study protocol was approved on 2 July 2021 by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (approval no. NKBBN/562/2021). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participates gave informed written consent before enrolment in the study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used to support the findings of this study are included within the article or are available from the corresponding author upon request.

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References

1. Maltby, J.R. Fasting from midnight—The history behind the dogma. *Best Pract. Res. Clin. Anaesthesiol.* **2006**, *20*, 363–378. [CrossRef] [PubMed]
2. Weimann, A.; Braga, M.; Carli, F.; Higashiguchi, T.; Hübner, M.; Klek, S.; Laviano, A.; Ljungqvist, O.; Lobo, D.N.; Martindale, R.G.; et al. ESPEN practical guideline: Clinical nutrition in surgery. *Clin. Nutr.* **2021**, *40*, 4745–4761. [CrossRef] [PubMed]
3. Anesthesiologists, A.S. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures. *Anesthesiology* **2017**, *126*, 376–393.
4. El-Sharkawy, A.M.; Daliya, P.; Lewis-Lloyd, C.; Adiamah, A.; Malcolm, F.L.; Boyd-Carson, H.; Couch, D.; Herrod, P.J.; Hossain, T.; Couch, J.; et al. Fasting and surgery timing (FaST) audit. *Clin. Nutr.* **2021**, *40*, 1405–1412. [CrossRef]
5. de Aguilar-Nascimento, J.E. Reducing preoperative fasting time: A trend based on evidence. *World J. Gastrointest. Surg.* **2010**, *2*, 57. [CrossRef]
6. Li, Y.; He, R.; Ying, X.; Hahn, R.G. Dehydration, Hemodynamics and fluid volume optimization after induction of general anesthesia. *Clinics* **2014**, *69*, 809–816. [CrossRef]
7. Gutierrez, D.S.G.; Gutiérrez, J.J.V.; Ruiz-Villa, J.O. Cardiac output estimation based on arterial and venous blood gas analysis: Proposal of a monitoring method. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 179–183. [CrossRef]
8. Miller, T.E.; Roche, A.M.; Mythen, M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery after Surgery (ERAS). *Can. J. Anesth.* **2015**, *62*, 158–168. [CrossRef]
9. Nygren, J.; Thacker, J.; Carli, F.; Fearon, K.C.; Norderval, S.; Lobo, D.N.; Ljungqvist, O.; Soop, M.; Ramirez, J. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. *World J. Surg.* **2013**, *31*, 801–816. Available online: https://pubmed.ncbi.nlm.nih.gov/23052796/ (accessed on 1 November 2020). [CrossRef]
10. Nygren, J.; Thorell, A.; Ljungqvist, O. Preoperative oral carbohydrate therapy. *Curr. Opin. Anaesthesiol.* **2015**, *28*, 364–369. [CrossRef]
11. Nygren, J. The metabolic effects of fasting and surgery. *Best Pract. Res. Clin. Anaesthesiol.* **2006**, *20*, 429–438. Available online: https://pubmed.ncbi.nlm.nih.gov/17080694/ (accessed on 31 October 2020). [CrossRef]
12. Smith, M.D.; Mccall, J.; Plank, L.; Herbison, G.P.; Soop, M.; Nygren, J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst. Rev.* **2014**, *14*, CD009161. [CrossRef] [PubMed]

13. Amer, M.A.; Smith, M.D.; Herbison, G.P.; Plank, L.D.; McCall, J.L. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. *Br. J. Surg.* **2017**, *104*, 187–197. [CrossRef] [PubMed]
14. Kukliński, J.; Steckiewicz, K.P.; Sekuła, B.; Aszkiełowicz, A.; Owczuk, R. The influence of fasting and carbohydrate-enriched drink administration on body water amount and distribution: A volunteer randomized study. *Perioper. Med.* **2021**, *10*, 27. [CrossRef] [PubMed]
15. Pang, Q.; Hendrickx, J.; Liu, H.L.; Poelaert, J. Contemporary perioperative haemodynamic monitoring. *Anaesthesiol. Intensive Ther.* **2019**, *51*, 147–158. [CrossRef]
16. Mansouri, S.; Alhadidi, T.; Chabchoub, S.; Ben Salah, R. Impedance cardiography: Recent applications and developments. *Biomed. Res.* **2018**, *29*, 3542–3552. [CrossRef]
17. Cleymaet, R.; Scheinok, T.; Maes, H.; Stas, A.; Malbrain, L.; De Laet, I.; Schoonheydt, K.; Dits, H.; van Regenmortel, N.; Mekeirele, M.; et al. Prognostic value of bioelectrical impedance analysis for assessment of fluid overload in ICU patients: A pilot study. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 10–17. [CrossRef]
18. Gijsen, M.; Simons, E.; de Cock, P.; Malbrain, M.L.N.G.; Wauters, J.; Spriet, I. Reproducibility of fluid status measured by bioelectrical impedance analysis in healthy volunteers: A key requirement to monitor fluid status in the intensive care unit. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 193–199. [CrossRef]
19. Kim, J.-Y.; Kim, B.-R.; Lee, K.-H.; Kim, K.-W.; Kim, J.-H.; Lee, S.-Y.; Kim, K.-T.; Choe, W.-J.; Park, J.-S.; Kim, J.-W. Comparison of cardiac output derived from FloTracTM/VigileoTM and impedance cardiography during major abdominal surgery. *J. Int. Med. Res.* **2013**, *41*, 1342–1349. [CrossRef]
20. Scherhag, A.; Kaden, J.J.; Kentschke, E.; Sueselbeck, T.; Borggrefe, M. Comparison of impedance cardiography and thermodilution-derived measurements of stroke volume and cardiac output at rest and during exercise testing. *Cardiovasc. Drugs Ther.* **2005**, *19*, 141–147. [CrossRef]
21. Kim, G.E.; Kim, S.Y.; Kim, S.J.; Yun, S.Y.; Jung, H.H.; Kang, Y.S.; Koo, B.N. Accuracy and efficacy of impedance cardiography as a non-invasive cardiac function monitor. *Yonsei Med. J.* **2019**, *60*, 735–741. [CrossRef] [PubMed]
22. Fuller, H.D. The validity of cardiac output measurment by thoracic impedance: A meta-analysis. *Clin. Investig. Med.* **1992**, *15*, 103–112.
23. Raaijmakers, E.; Faes, T.J.C.; Scholten, R.J.P.M.; Goovaerts, H.G.; Heethaar, R.M. A meta-analysis of three decades of validating thoracic impedance cardiography. *Crit. Care Med.* **1999**, *27*, 1203–1213. [CrossRef] [PubMed]
24. Peyton, P.J.; Chong, S.W. Minimally invasive measurement of cardiac output during surgery and critical care: A meta-analysis of accuracy and precision. *Anesthesiology* **2010**, *113*, 1220–1235. Available online: http://pubs.asahq.org/anesthesiology/article-pdf/113/5/1220/252362/0000542-201011000-00037.pdf (accessed on 26 January 2022). [CrossRef]
25. Zhang, Y.; Wang, Y.; Shi, J.; Hua, Z.; Xu, J. Cardiac output measurements via echocardiography versus thermodilution: A systematic review and meta-analysis. *PLoS ONE* **2019**, *14*, e0222105. [CrossRef]
26. Daralammouri, Y.; Ayoub, K.; Badrieh, N.; Lauer, B. A hybrid approach for quantifying aortic valve stenosis using impedance cardiography and echocardiography. *BMC Cardiovasc. Disord.* **2016**, *16*, 19. [CrossRef] [PubMed]
27. Liu, F.; Tsang, R.C.C.; Jones, A.Y.M.; Zhou, M.; Xue, K.; Chen, M.; Wang, Y. Cardiodynamic variables measured by impedance cardiography during a 6-minute walk test are reliable predictors of peak oxygen consumption in young healthy adults. *PLoS ONE* **2021**, *16*, e0252219. [CrossRef]
28. Kubota, S.; Endo, Y.; Kubota, M.; Ishizuka, Y.; Furudate, T. Effects of trunk posture in Fowler's position on hemodynamics. *Auton. Neurosci. Basic Clin.* **2015**, *189*, 56–59. [CrossRef]
29. Wu, T.W.; Lien, R.I.; Seri, I.; Noori, S. Changes in cardiac output and cerebral oxygenation during prone and supine sleep positioning in healthy term infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **2017**, *102*, F483–F489. [CrossRef]
30. Ma, M.; Noori, S.; Maarek, J.M.; Holschneider, D.P.; Rubinstein, E.H.; Seri, I. Prone positioning decreases cardiac output and increases systemic vascular resistance in neonates. *J. Perinatol.* **2015**, *35*, 424–427. [CrossRef]
31. Paviotti, G.; Todero, S.; Demarini, S. Cardiac output decreases and systemic vascular resistance increases in newborns placed in the left-lateral position. *J. Perinatol.* **2017**, *37*, 563–565. [CrossRef] [PubMed]
32. Borodiciene, J.; Gudaityte, J.; Macas, A. Lithotomy versus jack-knife position on haemodynamic parameters assessed by impedance cardiography during anorectal surgery under low dose spinal anaesthesia: A randomized controlled trial. *BMC Anesthesiol.* **2015**, *15*, 74. [CrossRef] [PubMed]
33. Kendrick, J.B.; Kaye, A.D.; Tong, Y.; Belani, K.; Urman, R.D.; Hoffman, C.; Liu, H. Goal-directed fluid therapy in the perioperative setting. *J. Anaesthesiol. Clin. Pharmacol.* **2019**, *35*, S29–S34. [PubMed]
34. Anandraja, R.; Ranjith Karthekeyan, B. A comparative study of haemodynamic effects of single-blinded orotracheal intubations with intubating laryngeal mask airway, Macintosh and McGrath video laryngoscopes. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 30–36. [CrossRef] [PubMed]
35. Bijker, J.B.; Van Klei, W.A.; Kappen, T.H.; Van Wolfswinkel, L.; Moons, K.G.M.; Kalkman, C.J. Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* **2007**, *107*, 213–220. [CrossRef]
36. Zepeda-Najar, C.; Palacios-Astudillo, R.X.; Chávez-Hernández, J.D.; Lino-Silva, L.S.; Salcedo-Hernández, R.A. Prognostic impact of microsatellite instability in gastric cancer. *Wspolczesna Onkol.* **2021**, *25*, 68–71. [CrossRef]

37. Soop, M.; Nygren, J.; Thorell, A.; Weidenhielm, L.; Lundberg, M.; Hammarqvist, F.; Ljungqvist, O. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. *Clin. Nutr.* **2004**, *23*, 733–741. [CrossRef]
38. Yuill, K.A.; Richardson, R.A.; Davidson, H.I.M.; Garden, O.J.; Parks, R.W. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively—A randomised clinical trial. *Clin. Nutr.* **2005**, *24*, 32–37. [CrossRef]
39. Hausel, J.; Nygren, J.; Lagerkranser, M.; Hellström, P.M.; Hammarqvist, F.; Almström, C.; Lindh, A.; Thorell, A.; Ljungqvist, O. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth. Analg.* **2001**, *93*, 1344–1350. [CrossRef]
40. Alves, D.R.; Ribeiras, R. Does fasting influence preload responsiveness in ASA 1 and 2 volunteers? *Braz. J. Anesthesiol.* **2017**, *67*, 172–179. [CrossRef]
41. Rontoyanni, V.G.; Werner, K.; Sanders, T.A.B.; Hall, W.L. Differential acute effects of carbohydrate- and protein-rich drinks compared with water on cardiac output during rest and exercise in healthy young men. *Appl. Physiol. Nutr. Metab.* **2015**, *40*, 803–810. [CrossRef] [PubMed]

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Early Use of Methylene Blue in Vasoplegic Syndrome: A 10-Year Propensity Score-Matched Cohort Study

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Abstract: Background: Vasoplegic syndrome is associated with increased morbidity and mortality in patients undergoing cardiac surgery. This retrospective, single-center study aimed to evaluate the effect of early use of methylene blue (MB) on hemodynamics after an intraoperative diagnosis of vasoplegic syndrome (VS). Methods: Over a 10-year period, all patients diagnosed with intraoperative VS (hypotension despite treatment with norepinephrine $\geq$0.3 µg/kg/min and vasopressin $\geq$1 IE/h) while undergoing heart surgery and cardiopulmonary bypass were identified, and their data were examined. The intervention group received MB (2 mg/kg intravenous) within 15 min after the diagnosis of vasoplegia, while the control group received standard therapy. The two groups were matched using propensity scores. Results: Of the 1022 patients identified with VS, 221 received MB intraoperatively, and among them, 60 patients received MB within 15 min after the diagnosis of VS. After early MB application, mean arterial pressure was significantly higher, and vasopressor support was significantly lower within the first hour (p = 0.015) after the diagnosis of vasoplegia, resulting in a lower cumulative amount of norepinephrine (p = 0.018) and vasopressin (p = 0.003). The intraoperative need of fresh frozen plasma in the intervention group was lower compared to the control group (p = 0.015). Additionally, the intervention group had higher creatinine values in the first three postoperative days (p = 0.036) without changes in dialysis incidence. The 90-day survival did not differ significantly (p = 0.270). Conclusion: Our results indicate the additive effects of MB use during VS compared to standard vasopressor therapy only. Early MB administration for VS may significantly improve the patients' hemodynamics with minor side effects.

Keywords: methylene blue; vasoplegic syndrome; vasoplegia; shock; cardiac anesthesia; vasopressin; cardiac surgery; cardiopulmonary bypass

1. Introduction

In cardiac surgery, vasoplegic syndrome (VS) is defined as a vasodilatory shock in the perioperative period and is accompanied by severe hypotension, i.e., therapy-refractory

mean arterial pressure (MAP) between 40 and 65 mm Hg and a systemic vascular resistance index (SVRI) between 700 and 1200 dyne × sec × cm^{-5} × m^2, and normal or elevated cardiac output [1]. The hemodynamics of VS show low wedge and low right atrial pressure [1]. VS was first described by Gomes and colleagues who reported cardioplegia in six cases in Sao Paolo, Brazil, in 1994 [1]. Since then, severe VS has been repeatedly described as a hemodynamic challenge in other diseases, such as septic shock, post-transplantation surgery, burns, anaphylaxis, and trauma [2]. VS occurs as a complication during or after cardiopulmonary bypass (CPB), with an incidence of 5–25%, and causes an increased risk of end organ dysfunction and mortality [3]. Previous studies have reported important risk factors for VS [3–6], which may result in a systemic inflammatory response syndrome with transient vascular dysfunction refractory to vasopressor therapy [7] and can lead to long-term instability intraoperatively and postoperatively. The pathophysiology of VS is complex and includes a functional dysregulation of smooth vascular muscle cells. In cardiac surgery with CPB, inflammatory mediators lead to adrenoreceptor desensitization and an immediate increase in vasoconstrictive mediators. With the subsequent depletion of the mediators and excess of nitric oxide (NO), dilating mediators predominate and vasoplegic shock persists. NO affects both vasoconstriction and dilation. By activating guanylate cyclase (GC), NO increases cyclic guanosine monophosphate (cGMP) and leads to muscle relaxation. NO also acts through adenosine triphosphate-sensitive potassium channels to inhibit vasoconstriction [8,9]. Therapeutic options in VS include fluid administration and/or vasopressor therapy with catecholamines (first-line therapy with norepinephrine and supplementation with epinephrine) and vasopressin. Modulators of NO and/or inflammation, such as methylene blue (MB), hydroxocobalamin (HY), ascorbic acid, thiamine, and corticosteroids, have been investigated as therapeutic options of VS in several studies [9–12]. Angiotensin II is the most recently published therapeutic alternative, which was reported to reduce catecholamines for VS [13,14]. The efficacy and efficiency of MB administration for VS during or after CPB has been described by several authors; however, to the best of our knowledge, evidence with larger patient collectives is lacking [15–19]. Previous studies using MB in VS revealed conflicting results, which might have been due to the inclusion of different anesthesiologist-triggered strategies and time-dependent factors. We hypothesized that MB exerts a positive effect in the early stages of severe vasoplegia and can thus prevent secondary complications. Therefore, MB may be useful to treat VS at early stages of the syndrome.

2. Materials and Methods

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich/Germany (number: 326-16). The need for patient consent was waived because of the retrospective nature of the study.

In this single-center retrospective observational study, data from all patients who developed VS during cardiac surgery with CPB at the LMU Hospital in Munich between 1 April 2006 and 31 March 2016 were reviewed. This period was chosen based on influencing cofactors. Patients who required $\geq$0.3 µg/kg/min norepinephrine plus vasopressin $\geq$1 IU/h were considered as having VS. The use of vasopressor agents as a surrogate marker for VS has been described previously [16,20] since invasive hemodynamic values, such as cardiac output and SVRI, were not regularly recorded intraoperatively. Intraoperative continuous esophageal echocardiography ensured the exclusion of cardiogenic shock and confirmed the presence of VS. Patients <18 years old, those undergoing off-pump surgery, those with preoperative venovenous extracorporeal membrane oxygenation or extracorporeal life support system treatment, those with increased preoperative c-reactive protein (CRP), and those without missing data.

The primary outcomes intraoperatively were MAP, fluid administration, and the amount and dose of norepinephrine and vasopressin. Over three days postoperatively,

liver function (alanine transaminase) and kidney function (creatinine), as well as CRP and leukocytes, were compared. Mortality was analyzed up to discharge.

Anesthesia was administered according to the Munich cardiac anesthesia standard operating procedure. In brief, patients received oral or intravenous premedication with midazolam (3.75–7.5 mg). Administration of angiotensin converting enzyme-inhibitors and sartane was stopped in elective patients the day before surgery. After the insertion of an arterial line, anesthesia was induced with midazolam, etomidate, or propofol, sufentanil, and rocuronium and maintained with a continuous sufentanil infusion (0.5–1 µg/kg/h) and sevoflurane vaporization (1.5–2.5%). After induction, a central venous catheter and an introducer were inserted to optionally apply a pulmonary artery catheter. The hemodynamic status was monitored intraoperatively by transesophageal echocardiography. For cardioplegia, a crystalloid "Bretschneider" solution (Custodiol®, Dr. Köhler Chemie GmbH, Bensheim, Germany) was used. An unfractionated heparin bolus of 400 IU/kg total body weight was injected before CPB initiation followed by additional doses to maintain a target activated clotting time $\geq$400 s. At the end of the CPB, heparinization was antagonized with a slow protamine infusion. Intraoperative hypotension was treated with the maintenance of isovolemia by fluid boluses and continuous norepinephrine administration. In addition, continuous administration of vasopressin was considered when administering norepinephrine >0.2 µg/kg/min. Additional treatment options were epinephrine to support inotropy and hydrocortisone. MB (2 mg/kg total body weight over an infusion period of 10 min) was considered as a rescue medication in the case of therapy-refractory hypotension, where stable hemodynamics could not be achieved despite continuous norepinephrine administration $\geq$0.3 µg/kg/min and vasopressin $\geq$1 IU/h and repetitive norepinephrine boluses by the attending anesthesiologist, independent of the anesthesiologist's level of training. No repetitive administration of MB was used. After surgery, all patients were sedated, ventilated, transferred to the intensive care unit (ICU), and monitored during the following days. Weaning started after cardiorespiratory stabilization and exclusion of revision triggers.

After exclusion, patients were divided into three groups based on MB use for hemodynamic rescue from vasoplegia within the first 15 min after the onset of VS (MB group), after 15 min (lMB group), and no MB use (control group, CG). After comparison, the cut off was set to 15 min to evaluate the early effect of MB. Subsequently, the MB group was compared with the CG. Medical records were reviewed to obtain patient demographics and preoperative variables, including sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical classification, surgery type, and emergency status of surgery. For analysis related to the type of surgery, the patients were divided into the following groups: thoracic aortic surgery (aorta), heart valve surgery (valve), isolated coronary artery bypass graft (CABG) surgery (bypass), heart transplantation or ventricular device (artificial heart), combination procedure (e.g., CABG + valve surgery; combination), different types of surgery (e.g., neoplasm; other), revision surgery (revision). To assess the independent effects of early MB on postoperative outcomes, a propensity score-matched analysis was performed. For propensity score matching, the variables age, sex, BMI, and procedure were used. After bivariate analysis (ANOVA) of preoperative factors of all three groups listed in Additional File 1, the propensity for receiving MB variables with a matching tolerance of 0.01 was predicted and included for the procedure. Accordingly, the cases of the MB group were matched 1:1 with corresponding cases of the CG using the propensity score matching function of SPSS® Statistics software (Version 27, IBM Corp., Armonk, NY, USA; Figure 1). This resulted in 60 successfully matched pairs, as evidenced in Table 1.

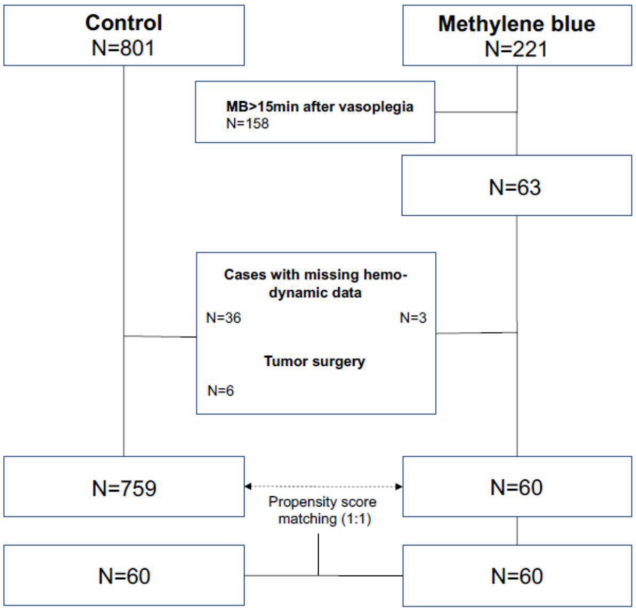

Figure 1. Study population.

Table 1. Baseline demographics of the methylene blue group compared to control group and propensity score-matched control group.

	Methylene Blue N = 60		Control N = 759		*p*-Value	Matched Control N = 60		*p*-Value
Male sex	51	85.0	580	76.4	0.082	44	73.3	0.177
Age (y)	62.3	±12.2	64.0	±13.6	0.351	62.0	±14.2	0.891
BMI (kg/m^2)	27.5	±4.5	26.2	±4.3	0.024	26.7	±4.8	0.363
ASA class					0.062			0.414
1	0	0	1	0.1		0	0.0	
2	0	0	1	0.1		0	0.0	
3	12	20.0	293	38.6		10	16.7	
4	42	70.0	419	55.2		39	65.0	
5	6	10.0	45	5.9		11	18.3	
Procedure					<0.001			0.031
Aorta	16	26.7	107	14.1		7	11.7	
Valve	21	35.0	302	39.8		20	33.3	
Bypass	8	13.3	225	29.6		18	30.0	
Artificial heart	5	8.3	69	9.1		9	15.0	
Combination	4	6.7	22	2.9		0	0.0	
Other	2	3.3	25	3.3		4	6.7	
Revision	4	6.7	9	1.2		2	3.3	
Emergency	13	21.7	151	19.9	0.738	16	26.7	0.335

Perioperative variables are shown regarding the use of MB versus standard therapy (matched control), indicating mean or percentage, respectively. This table also shows the results compared to the overall collective before matching. *p*-values indicate significance versus "methylene blue" group. BMI: Body mass index; ASA: American Society of Anesthesiologists.

For intraoperative data collection, the in-house anesthesia recording system NarkoData (IMESO-IT GmbH; Gießen, Germany) was reviewed, and the following variables were analyzed: type of surgery, MAP depending on time since VS (0, +15, +30, +60, +90,

+120 min), time-dependent norepinephrine and vasopressin dose and cumulative amount, cumulative fluid administration (crystalloid and colloid) and transfusion needs (erythrocytes, fresh frozen plasma, thrombocytes), duration of surgery, and CPB time. Serum blood samples were routinely taken 24 h preoperatively (not in the case of emergency), on arrival in ICU, and on the first, second, and third postoperative day. Inflammation values (CRP (mg/L), leukocytes (cells/nL)), and values of liver (alanine transaminase (U/L)) and kidney function (creatinine (mg/dL)) were determined for the evaluation of Secondary organ dysfunction. Outcome variables such as ventilation time, in-hospital mortality, length of ICU stay and hospitalization, and postoperative renal replacement therapy were extracted from patient record files.

For continuous variables (e.g., hospitalization), group comparisons were performed using unpaired Student's *t*-tests. In the case of multiple timepoints, comparisons were individually performed between groups on each timepoint. For categorical variables (e.g., sex), a chi-square test was performed. In the case of two possible conditions, the two-sided Fisher's exact test *p*-value was reported; for >2 possible conditions, the Pearson's chi-square *p*-value was reported. Kaplan–Meier analysis was performed for survival time (90 days) with Log-rank group comparison (Mantel Cox). A *p*-value ≤ 0.05 was considered significant for any comparison.

3. Results

During the study period, 1172 out of 9356 patients undergoing cardiac surgery with CPB at this institution were diagnosed with VS, corresponding to an incidence of 12.5%. After the first data validation, 1022 patients were further analyzed. A total of 221 of these patients received MB for hemodynamic rescue from vasoplegia, while 801 patients were not treated with MB and were therefore included in the CG. After excluding patients with missing data and tumor surgery, 759 remained in the CG. The intervention group was then compared with the CG, and the collective was examined for preoperative characteristics. Numerous preoperative and surgical factors were associated with an increased likelihood of receiving MB. The preoperative factors included were older age, higher ASA status, and the type of surgery. Regarding the operative procedure in the non-matched group, patients with thoracic aortic surgery were relatively more likely to receive MB (MB: 26.7 vs. CG: 14.1%), and BMI was significantly correlated with MB treatment (MB: 27.5 vs. CG: 26.2; $p = 0.024$). Emergency surgery status was not correlated with MB treatment (MB: 21.7% vs. CG: 19.9%; $p = 0.738$). To reduce confounding bias, a propensity score-matching analysis was performed, and patients of the MB group were balanced for preoperative covariates. After excluding patients with missing data, 60 patients met the criteria of the MB group. These patients received a bolus of MB within the first 15 min. Demographic and surgery characteristics of the matched cohort are shown in Table 1. Univariate analysis was used to compare the incidence of different intraoperative variables and outcomes in patients who did and did not receive MB (Table 2). The mean surgery duration was >7 h (MB: 421 min $\pm$152 vs. CG: 447 min $\pm$169; $p = 0.373$), and the mean CPB time was approximately 3 h (MB: 183 min $\pm$104 vs. CG: 185 min $\pm$109; $p = 0.915$). We found no significant differences in intraoperative variables.

Table 2. Perioperative variables of matched participants.

	Methylene Blue N = 60		Matched Control N = 60		*p*-Value
Duration of surgery (min)	421	±152	447	±169	0.373
Bypass duration (min)	183	±104	185	±109	0.915
Duration of mechanical ventilation (h) *	203	±338	195	±275	0.918
Length of hospitalization (d)	30	±33	27	±35	0.620
Length of ICU stay (d) **	16	±21	20	±37	0.466
90-day survival	49	81.7	48	80.0	0.270

Perioperative variables are shown regarding the use of methylene blue versus standard therapy (matched control), indicating mean (SD) or percentage, respectively. *p*-values indicate significance versus "methylene blue" group. ICU: Intensive care unit. *: only data of 25 control cases available, **: only data of 55 control cases available.

MB was administered at a dose of 2 mg/kg total body weight (mean 161.5 mg ± 57.37 mg). The hemodynamic effects compared to the matched pair group are presented in Figure 2. Compared to that in the CG, the MAP in the MB group significantly recovered (Figure 2a) within the first 30 ($p = 0.036$) and 60 min ($p = 0.015$) after diagnosis of VS. Simultaneously, the amount of norepinephrine and vasopressin could be reduced faster in the MB group than in the CG (Figure 2c,d). In addition, the cumulative amount of vasopressors used was lower in the MB group (norepinephrine MB: 7.4 mg ±3.3 vs. CG: 9.7 mg ±6.7; $p = 0.018$ and vasopressin MB: 6.1 IE ±5.1 vs. CG: 11 IE ±13.4, $p = 0.003$; Figure 2e) without the need to substitute more fluids. We only found a difference in the transfusion rates of fresh frozen plasma (MB: 1304 mL ±1200 vs. CG: 2021 mL ±1905, $p = 0.015$; Figure 2c).

In addition, the 90-day survival (MB: 81,7% vs. CG: 80%, $p = 0.270$; Figure 3) and other outcome variables did not differ between the groups: mean length of ICU stay (MB: 16 d ±21 vs. CG: 20 d ±37; $p = 0.466$), duration of mechanical ventilation (mean MB: 203 h ±338 vs. CG: 195 h ±275; $p = 0.918$), and length of hospitalization (MB: 30 d ±33 vs. CG: 27 d ±35; $p = 0.62$). In emergency cases, routine blood sampling could not be performed 24 h prior to surgery. Due to this relevant lack of data, the comparison of preoperative values was not meaningful. In the first three postoperative days, CRP and leucocytes did not differ between groups (Figure 4). Regarding comorbidities, we found no higher incidence of liver dysfunction (ALT) in the intervention group, but the MB group was associated with more severe kidney dysfunction (creatinine, $p = 0.036$). Nonetheless, there were no differences in the need of renal replacement therapy (RRT) between groups (27 of 60 patients each group, data not shown).

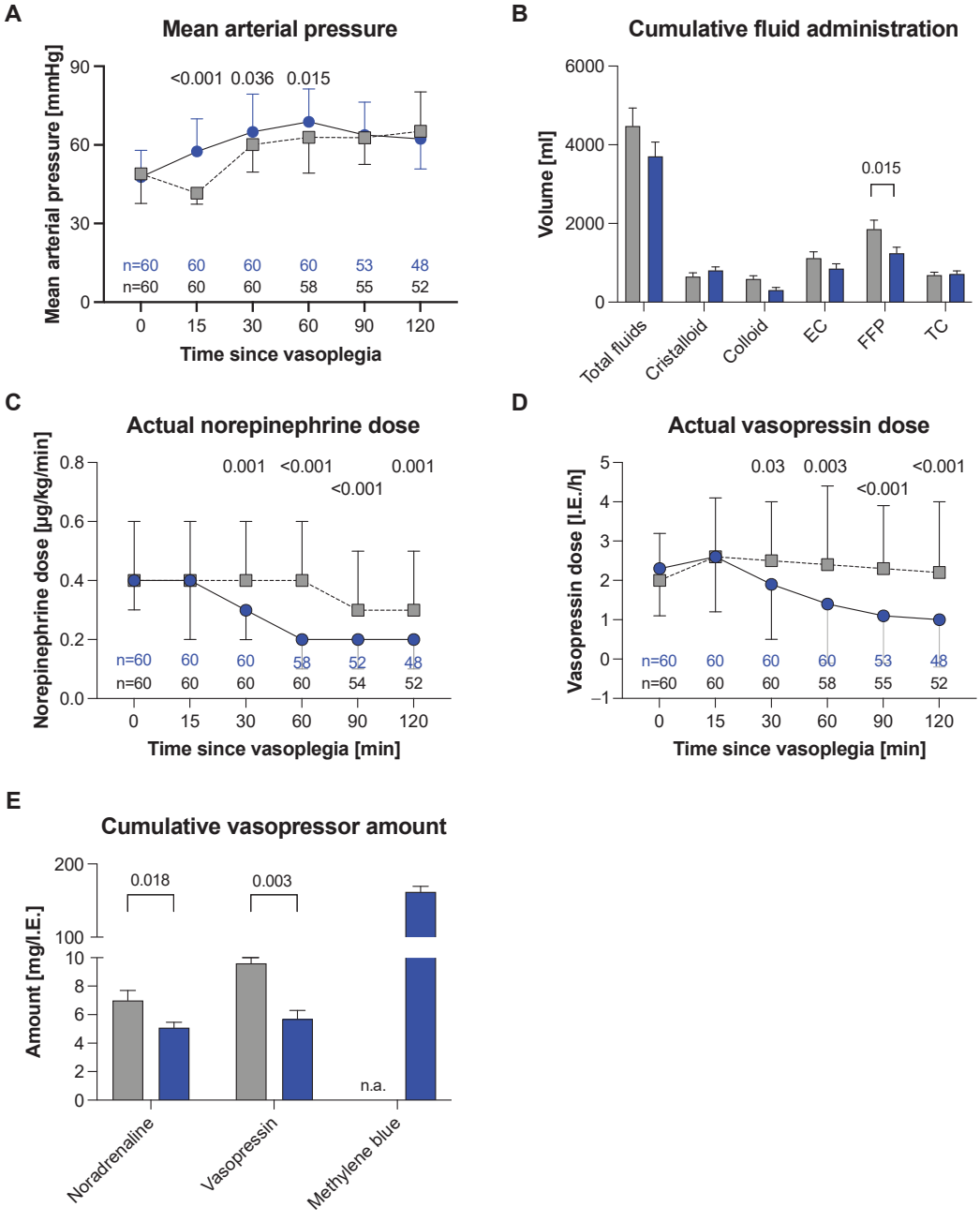

Figure 2. Effects after methylene blue administration in vasoplegic syndrome: The figures show the median (25th–75th percentile) value in the main study group with regard to the use of methylene blue (blue) versus standard therapy (grey). *p*-value indicates standard mean (SD). (**A**) Mean Arterial pressure; (**B**) Cumulative fluid administration; (**C**) Actual norepinephrine dose; (**D**) Actual vasopressin dose; (**E**) Cumulative vasopressoe amount.

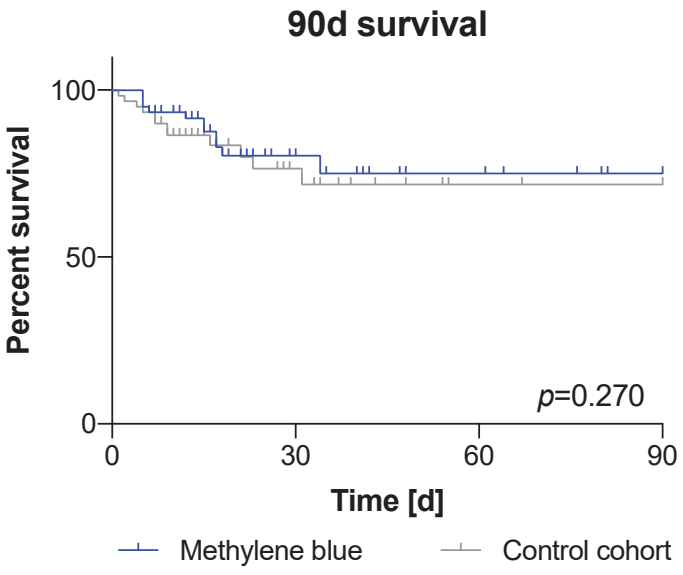

Figure 3. Ninety-day survival after vasoplegic syndrome: The 90-day survival did not differ significantly (MB: 81.7% vs. CG: 80%; $p = 0.270$).

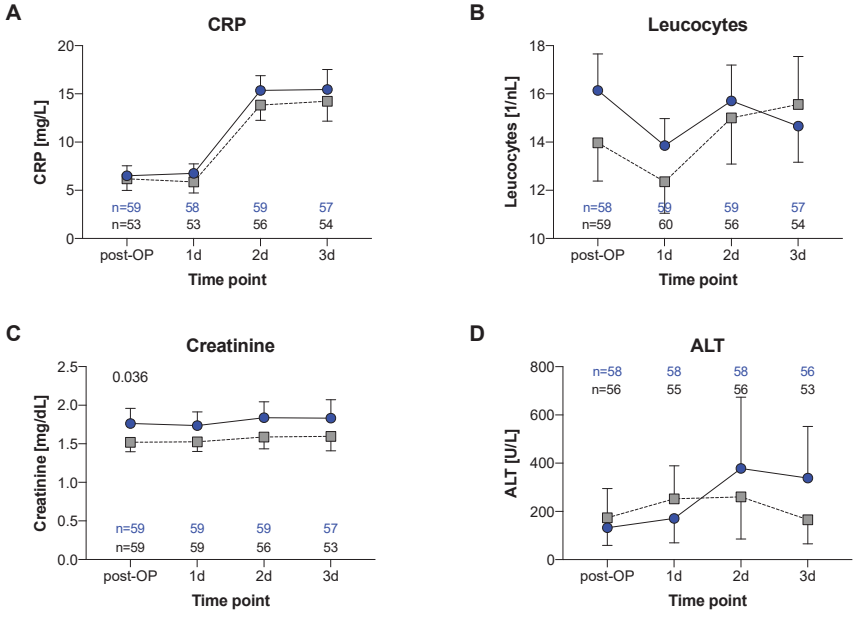

Figure 4. Postoperative variables: Variables are shown with regard to the use of methylene blue versus standard therapy (Matched Control), indicating mean (SD). (**A**) CRP; (**B**) Leucocytes; (**C**) Creatinine; (**D**) ALT.

4. Discussion

The current study demonstrated that in our homogenous patient collective, early use of MB after VS diagnosis during cardiac surgery with CPB seems to be associated with

beneficial hemodynamic effects compared to the conventional vasopressor support. For MB patients in our series, an improvement in hemodynamic stability within the first hour was associated with a reduction in vasopressor support with norepinephrine and vasopressin. In addition, even if the creatinine values in MB patients were significantly higher in the early postoperative period, the incidence of RRT and postoperative 90-day mortality were not affected.

VS can occur intraoperatively during or after CPB or postoperatively in the ICU [8]. In this study, the overall incidence of VS was 12.5%, which is in accordance with previous reports that show VS occurring among 9–44% of patients undergoing cardiac surgery with CPB [5,21]. VS can last for up to 72 h and is associated with increased mortality of up to 25% [3,21]. Therefore, it is important to recognize VS early and start goal-directed therapy immediately. Fluid administration and vasopressor therapy are considered first-line treatments for VS. Despite the lack of reports showing superiority of one catecholamine over the other, norepinephrine and vasopressin are reported to have positive effects in VS treatment, ensuring adequate perfusion pressure in all organs. Over 20 years ago, Argenziano et al. confirmed MAP increase and catecholamine reduction in VS treatment with vasopressin [22,23]. Therefore, in our institution, vasopressin is used as a second-line option in the case of vasoplegia. Nevertheless, in the case of persistent therapy-refractory VS, further escalation strategies are required.

HY is a potent direct inhibitor of NO and NO synthase and increases the elimination of an endothelial-bound endogenous vasodilator. These mechanisms are probably responsible for HY' additive effects in VS [10–12] and explain why its pharmacological effects differ from those of MB. It is thought that MB inhibits soluble GC by oxidizing the heme domain, thus preventing NO from binding and consequently decreasing the production in cGMP. This mechanism prevents the relaxation of the vascular smooth muscles without directly affecting the different nitric oxide synthase (NOS) isoforms [24,25]. Moreover, MB appears to generate extracellular superoxide anion, which converts NO to nitrate and consequently inhibits vasodilatation [26].

Out of these therapeutic options, different treatment approaches were proposed [9,27,28]. In contrast to previously published treatment regimens [28], Busse et al. recently recommended to start vasopressin administration at lower doses of norepinephrine, followed by MB in cases of therapy-refractory vasoplegia without contraindications.

Our results confirmed the beneficial effects of MB use on hemodynamics without increasing postoperative complications, such as RRT, hepatic injury, and mortality. In contrast, previous studies reported conflicting results regarding the use of MB in VS. While some studies showed decreased cardiac output, reduced renal and hepatic blood flow, higher incidence of arrhythmia, and increased early postoperative mortality after treatment with MB [16–19], others showed hemodynamic stabilization [18,29–31]. VS progresses with an immediate and profound decline in MAP without initial metabolic or organ dysfunction [20]. To prevent organ damage, we consider it crucial to stabilize hemodynamics and reduce the need for catecholamine as soon as possible. In contrast to previous studies, we, therefore, analyzed data of patients with VS who received MB within 15 min after failure of hemodynamic stabilization with data of those who received standard therapy and found that selected patients could benefit from early MB administration. Delayed MB administration after the onset of complications and in combination with NOS and GC capacity exhaustion could be responsible for the higher complication rates in other studies [16]. In addition, other authors emphasized a time-dependent correlation of MB efficacy [19,32,33], wherein MB has the best effect when NOS activity increases and GC is upregulated, that is, within the first eight hours of VS. Therefore, delayed MB administration might have no beneficial effects due to low GC and NOS levels [32,33]. Mehaffey et al. retrospectively compared intraoperative MB treatment for VS after CPB with delayed treatment in the ICU and found that intraoperative administration improved survival and reduced the risk of major adverse events [30]. Again, the results in our high-risk patient collective showed that the vasopressor support was significantly lower with

no effect on mortality following the administration of MB within 15 min after the onset of vasoplegia. Therefore, early MB use after VS onset could be a promising therapeutic strategy with low side effects. Prospective analyses are required to confirm these results. The significant difference of fresh frozen plasma substitution between the groups might be caused by the therapeutic attempt of intravascular fluid administration during persistent severe hypotension despite crystalloid infusion and catecholamine support.

Despite MB´s benefits, its contraindications or potential risk factors should always be identified. The use of MB in patients with glucose-6-phosphate dehydrogenase deficiency might cause severe hemolysis [34,35] and existing antidepressant medication could induce serotonin syndrome [36,37]. Additionally, the administration of MB leads to distorted measurements of oxygen saturations during the time of application.

The best dosing regimen for MB is suggested to be a 2 mg/kg total body weight intravenous bolus, followed by a 0.25–2 mg/kg/h continuous infusion, as reported by Evora et al. [19]. At our institution, anesthesiologists administered only an intravenous bolus without continuous infusion, which could be a limitation of this study. Due to the long duration of the study and due to personnel changes in our department during the study period, we think that practitioner effects might be compensated. Nevertheless, this fact has to be addressed in a prospective trial. Another limitation of our study is its single-center and retrospective design. In addition, we did not consider the severity of vasoplegia in our analysis. Intraoperatively, transesophageal echocardiography was used to exclude further impairment of contractility as a cause of hypotension. Within 72 h of arrival at the ICU, there were certain data gaps regarding ICU stay and duration of mechanical ventilation due to the digital documentation. Additionally, no long-term follow-up was performed. The patients included in this investigation are representative of an adult cardiac surgery population admitted at a university hospital. However, we reduced selection bias by utilizing propensity score-matching and analyzing a limited period where MB was administered.

5. Conclusions

Early application of MB after the diagnosis of therapy-refractory VS, in our study, was associated with an improvement of hemodynamic stability and reduced vasopressor support within the first hour without increment in fluid administration. In this high-risk patient collective bolus, MB use appears to be safe and seems to have additive effects to standard vasopressor therapy without affecting mortality. Randomized controlled trials are required to confirm our results.

Author Contributions: 1. O.K. made significant contributions to the conception and design of the study and assisted in the collection, analysis, and interpretation of the data; he revised the manuscript and approved the submitted version. 2. M.S. made significant contributions to the conception and design of the study and assisted in the collection, analysis, and interpretation of the data; he revised the manuscript and approved the submitted version. 3. R.T. made significant contributions to the work and assisted in the interpretation of the data and also designed and revised the work. He approved the submitted version. 4. L.C.H. helped collect and analyze data. He assisted in the interpretation of the data and approved the submitted version. 5. L.V.K. made substantial contributions to the conception and design of the work, revised it, and approved the submitted version. 6. F.U. made significant contributions to the design of the work and assisted in the analysis and interpretation of the data; he approved the submitted version. 7. F.B. assisted in data collection and approved the submitted version. 8. M.P. made significant contributions to the conception of the study and the collection of the data and approved the submitted version. 9. C.H. made significant contributions to the conception of the study and collection of the data and approved the submitted version. 10. M.A.W. accompanied the interpretation of the data and approved the submitted version. 11. B.Z. made significant contributions to the conception and design of the study. B.Z. approved the submitted version. 12. V.v.D. made significant contributions to the conception and design of the work and assisted in the collection, analysis, and interpretation of the data; V.v.D. designed and revised the work. She approved the submitted version. 13. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy

or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors have consented to the acknowledgement. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

VS—vasoplegic syndrome; MAP—mean arterial pressure; SVRI—systemic vascular resistance index; CPB—cardiopulmonary bypass; NO—nitric oxide; GC—guanylate cyclase; cGMP—cyclic guanosine monophosphate; MB—methylene blue; HY—hydroxocobalamin; BMI—body mass index; ASA—American Society of Anesthesiologists; ICU—intensive care unit; CRP—C-reactive protein; ALT—liver dysfunction; RRT—renal replacement therapy; CG—control group.

References

1. Gomes, W.J.; Carvalho, A.C.; Palma, J.H.; Gonçalves, I., Jr.; Buffolo, E. Vasoplegic syndrome: A new dilemma. *J. Thorac. Cardiovasc. Surg.* **1994**, *107*, 942–943. [CrossRef]
2. Lambden, S.; Creagh-Brown, B.C.; Hunt, J.; Summers, C.; Forni, L.G. Definitions and pathophysiology of vasoplegic shock. *Crit. Care* **2018**, *22*, 174. [CrossRef] [PubMed]
3. Fischer, G.W.; Levin, M.A. Vasoplegia During Cardiac Surgery: Current Concepts and Management. *Semin. Thorac. Cardiovasc. Surg.* **2010**, *22*, 140–144. [CrossRef]
4. Omar, S.; Zedan, A.; Nugent, K. Cardiac Vasoplegia Syndrome: Pathophysiology, Risk Factors and Treatment. *Am. J. Med Sci.* **2015**, *349*, 80–88. [CrossRef] [PubMed]
5. Byrne, J.G.; Leacche, M.; Paul, S.; Mihaljevic, T.; Rawna, J.D.; Shernan, S.K.; Mudge, G.H.; Stevenson, L.W. Risk factors and outcomes for 'vasoplegia syndrome' following cardiac transplantation. *Eur. J. Cardio-Thoracic Surg.* **2004**, *25*, 327–332. [CrossRef]
6. Liu, H.; Yu, L.; Yang, L.; Green, M.S. Vasoplegic syndrome: An update on perioperative considerations. *J. Clin. Anesth.* **2017**, *40*, 63–71. [CrossRef]
7. Wu, K.K.; Rossi, E.C. (Eds.) The damaging effects of cardiopulmonary bypass. In *Prostaglandins in Clinical Medicine: Cardiovascular and Thrombotic Disorders*; Year Book Medical Publishers: Chicago, IL, USA, 1982; p. 355.
8. Shaefi, S.; Mittel, A.; Klick, J.; Evans, A.; Ivascu, N.S.; Gutsche, J.; Augoustides, J.G. Vasoplegia after cardiovascular procedures-pathophysiology and targeted therapy. *J. Cardiothorac. Vasc. Anesth.* **2018**, *32*, 1013–1022. [CrossRef]
9. Busse, L.W.; Barker, N.; Petersen, C. Vasoplegic syndrome following cardiothoracic surgery—review of pathophysiology and update of treatment options. *Crit. Care* **2020**, *24*, 36. [CrossRef]
10. Kruszyna, H.; Magyar, J.; Rochelle, L.G.; A Russell, M.; Smith, R.P.; E Wilcox, D. Spectroscopic studies of nitric oxide (NO) interactions with cobalamins: Reaction of NO with superoxocobalamin(III) likely accounts for cobalamin reversal of the biological effects of NO. *J. Pharmacol. Exp. Ther.* **1998**, *285*, 665–671.
11. Weinberg, J.B.; Chen, Y.; Jiang, N.; Beasley, B.E.; Salerno, J.C.; Ghosh, D.K. Inhibition of nitric oxide synthase by cobalamins and cobinamides. *Free Radic. Biol. Med.* **2009**, *46*, 1626–1632. [CrossRef]
12. Bakker, J.; Grover, R.; McLuckie, A.; Holzapfel, L.; Andersson, J.; Lodato, R.; Watson, D.; Grossman, S.; Donaldson, J.; Takala, J. Administration of the nitric oxide synthase inhibitor NG-methyl-l-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: Results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). *Crit. Care Med.* **2004**, *32*, 1–12. [CrossRef]

13. Wieruszewski, P.; Radosevich, M.A.; Kashani, K.B.; Daly, R.C.; Wittwer, E.D. Synthetic Human Angiotensin II for Postcardiopulmonary Bypass Vasoplegic Shock. *J. Cardiothorac. Vasc. Anesth.* **2019**, *33*, 3080–3084. [CrossRef]
14. Evans, A.; McCurdy, M.T.; Weiner, M.; Zaku, B.; Chow, J.H. Use of Angiotensin II for Post Cardiopulmonary Bypass Vasoplegic Syndrome. *Ann. Thorac. Surg.* **2019**, *108*, e5–e7. [CrossRef] [PubMed]
15. Saha, A.; Jennings, D.L.; Ning, Y.; Kurlansky, P.; Miltiades, A.N.; Spellman, J.L.; Sanchez, J.; Yuzefpolskaya, M.; Colombo, P.C.; Takayama, H.; et al. Methylene Blue Does Not Improve Vasoplegia After Left Ventricular Assist Device Implantation. *Ann. Thorac. Surg.* **2021**, *111*, 800–808. [CrossRef] [PubMed]
16. Weiner, M.M.; Lin, H.-M.; Danforth, D.; Rao, S.; Hosseinian, L.; Fischer, G.W. Methylene Blue is Associated With Poor Outcomes in Vasoplegic Shock. *J. Cardiothorac. Vasc. Anesth.* **2013**, *27*, 1233–1238. [CrossRef] [PubMed]
17. Andritsos, M.J. Con: Methylene Blue Should Not Be Used Routinely for Vasoplegia Perioperatively. *J. Cardiothorac. Vasc. Anesth.* **2011**, *25*, 739–743. [CrossRef] [PubMed]
18. Özal, E.; Kuralay, E.; Yildirim, V.; Kilic, S.; Bolcal, C.; Kücükarslan, N.; Günay, C.; Demirkilic, U.; Tatar, H. Preoperative Methylene Blue Administration in Patients at High Risk for Vasoplegic Syndrome During Cardiac Surgery. *Ann. Thorac. Surg.* **2005**, *79*, 1615–1619. [CrossRef]
19. Evora, P.R.B.; Alves, L.; Ferreira, C.A.; Menardi, A.C.; Bassetto, S.; Rodrigues, A.J.; Scorzoni, A.; Vicente, W. Twenty years of vasoplegic syndrome treatment in heart surgery. Methylene blue revised. *Rev. Bras. Cir. Cardiovasc. Órgão Soc. Bras. Cir. Cardiovasc.* **2014**, *30*, 84–92. [CrossRef]
20. Levin, M.A.; Lin, H.-M.; Castillo, J.G.; Adams, D.H.; Reich, D.L.; Fischer, G.W. Early On–Cardiopulmonary Bypass Hypotension and Other Factors Associated With Vasoplegic Syndrome. *Circulation* **2009**, *120*, 1664–1671. [CrossRef]
21. Gomes, W.J.; Carvalho, A.C.; Palma, J.H.; A Teles, C.; Branco, J.N.; Silas, M.G.; Buffolo, E. Vasoplegic syndrome after open heart surgery. *J. Cardiovasc. Surg.* **1998**, *39*, 619–623.
22. Busse, L.W.; Ostermann, M. Vasopressor Therapy and Blood Pressure Management in the Setting of Acute Kidney Injury. *Semin. Nephrol.* **2019**, *39*, 462–472. [CrossRef] [PubMed]
23. Argenziano, M.; Chen, J.M.; Choudhri, A.F.; Cullinane, S.; Garfein, E.; Weinberg, A.D.; Smith, C.R.; Rose, E.A.; Landry, D.W.; Oz, M.C. Management of vasodilatory shock after cardiac surgery: Identification of predisposing factors and use of a novel pressor agent. *J. Thorac. Cardiovasc. Surg.* **1998**, *116*, 973–980. [CrossRef]
24. Nestler, E.J.; Duman, R.S. Guanylyl cyclase. In *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, 6th ed.; Bookshelf ID: NBK28167; American Society for Neurochemistry: Windermere, FL, USA, 1999.
25. Evora, P.R.B. Methylene Blue Is a Guanylate Cyclase Inhibitor That Does Not Interfere with Nitric Oxide Synthesis. *Tex. Heart Inst. J.* **2016**, *43*, 103. [CrossRef] [PubMed]
26. Wolin, M.S.; Cherry, P.D.; Rodenburg, J.M.; Messina, E.J.; Kaley, G. Methylene blue inhibits vasodilation of skeletal muscle arterioles to acetylcholine and nitric oxide via the extracellular generation of superoxide anion. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 872–876.
27. Levy, B.; Fritz, C.; Tahon, E.; Jacquot, A.; Auchet, T.; Kimmoun, A. Vasoplegia treatments: The past, the present, and the future. *Crit. Care* **2018**, *22*, 52. [CrossRef]
28. Ortoleva, J.P.; Cobey, F.C. A Systematic Approach to the Treatment of Vasoplegia Based on Recent Advances in Pharmacotherapy. *J. Cardiothorac. Vasc. Anesth.* **2019**, *33*, 1310–1314. [CrossRef]
29. Mazzeffi, M.; Hammer, B.; Chen, E.; Caridi-Scheible, M.; Ramsay, J.; Paciullo, C. Methylene blue for postcardiopulmonary bypass vasoplegic syndrome: A cohort study. *Ann. Card. Anaesth.* **2017**, *20*, 178–181. [CrossRef]
30. Mehaffey, J.H.; Johnston, L.E.; Hawkins, R.; Charles, E.J.; Yarboro, L.; Kern, J.A.; Ailawadi, G.; Kron, I.L.; Ghanta, R.K. Methylene Blue for Vasoplegic Syndrome After Cardiac Operation: Early Administration Improves Survival. *Ann. Thorac. Surg.* **2017**, *104*, 36–41. [CrossRef]
31. Levin, R.L.; Degrange, M.A.; Bruno, G.F.; Del Mazo, C.D.; Taborda, D.J.; Griotti, J.J.; Boullon, F.J. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann. Thorac. Surg.* **2004**, *77*, 496–499. [CrossRef]
32. Blacker, S.A.; Whalen, F.X. Vasoplegic syndrome: Does the timing of methylene blue matter? *J. Anesth. Clin. Res.* **2013**, *4*, 333.
33. Fernandes, D.; Da Silva-Santos, J.E.; Duma, D.; Villela, C.G.; Barja-Fidalgo, C.; Assreuy, J. Nitric Oxide-Dependent Reduction in Soluble Guanylate Cyclase Functionality Accounts for Early Lipopolysaccharide-Induced Changes in Vascular Reactivity. *Mol. Pharmacol.* **2005**, *69*, 983–990. [CrossRef] [PubMed]
34. Ng, B.K.; Cameron, A.J. The role of methylene blue in serotonin syndrome: A systematic review. *Psychosomatics* **2010**, *51*, 194–200. [CrossRef]
35. Grubb, K.J.; Kennedy, J.L.; Bergin, J.D.; Groves, D.S.; Kern, J.A. The role of methylene blue in serotonin syndrome following cardiac transplantation: A case report and review of the literature. *J. Thorac. Cardiovasc. Surg.* **2012**, *144*, e113–e116. [CrossRef] [PubMed]
36. Hencken, L.; To, L.; Ly, N.; Morgan, J.A. Serotonin Syndrome Following Methylene Blue Administration for Vasoplegic Syndrome. *J. Card. Surg.* **2016**, *31*, 208–210. [CrossRef]
37. Martino, E.A.; Winterton, D.; Nardelli, P.; Pasin, L.; Calabrò, M.G.; Bove, T.; Fanelli, G.; Zangrillo, A.; Landoni, G. The Blue Coma: The Role of Methylene Blue in Unexplained Coma After Cardiac Surgery. *J. Cardiothorac. Vasc. Anesth.* **2016**, *30*, 423–427. [CrossRef]

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Impact on Postoperative Pain and Recovery of a Regional Analgesia Strategy Based on the Surgical Approach for Lung Resection: A Prospective Observational Study

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Abstract: Various regional anesthesia (RA) techniques were shown to reduce pain after lung surgery, but controversies remain regarding the best technique to use to improve recovery. In this observational prospective study, the aim was to assess the efficacy of an RA strategy depending on the surgical approach. Patients who underwent lung surgery were included if an RA was planned following our unit procedure (erector spinae plane block (ESP) for video-assisted thoracic surgery (VATS) and thoracic epidural analgesia (TEA) or intrathecal analgesia (IA) for thoracotomy). Patients were compared according to the RA used. In total, 116 patients were included, 70 (60%), 32 (28%), 14 (12%) in the ESP, TEA and IA groups, respectively. Between Day 1 and Day 3, median NRS values were $\leq$4 at rest, and <50% patients experienced moderate-to-severe pain in each group. There were no significant differences in opioid consumption and in pain at rest or during chest physiotherapy on Days 1 and 2 between groups. However, patients who received an IA had lower NRS than other groups on Day 0 and 3 and a shorter length of hospital stay in comparison with those who received a TEA. Thus, in our institution, a strategy combining ESP for VATS and TEA, or IA for thoracotomy, allowed for effective analgesia after a lung resection. Interestingly, IA appeared to be more effective than TEA in reducing the length of hospital stay and pain on Day 0 and 3.

Keywords: postoperative pain; postoperative recovery; epidural analgesia; intrathecal analgesia; erector spinae plane block; lung surgery; video-assisted thoracic surgery; thoracotomy

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1. Introduction

Lung resection surgery is responsible for major postoperative pain [1], which increases both morbidity and mortality [2]. This pain has a strong impact on patient recovery and increases the length of hospital stay [3]. Regional anesthesia (RA) has a predominant role among pain relief therapies available in this context [4], as it provides strong analgesia and allows morphine consumption and morphine-related side effects to be reduced [5].

Thoracic epidural analgesia (TEA) has long been considered as the preferred technique of analgesia after thoracic surgery as it reduces postoperative pain after video-assisted thoracoscopic surgery (VATS) or thoracotomy, and reduces postoperative ileus [6–9]. However, epidural analgesia induces a sympathetic block that can cause intra- and postoperative hypotension and acute urinary retention, and catheter placement can lead to neurological damage in rare cases [10,11]. Thus, various other RA techniques have been developed and assessed in thoracic surgery, such as the paravertebral block, the erector spinae plane block (ESP), and intrathecal analgesia (IA) [12].

The paravertebral block has proved its analgesic efficiency after thoracic surgery and its ability to reduce hypotension, acute urinary retention, pruritus and postoperative nausea and vomiting (PONV) in comparison with TEA [13,14]. Its benefit in reducing postoperative pain has now been shown in both VATS and thoracotomy surgeries [15,16]. Therefore, the recent 2019 guidelines from the French Societies of Cardio-Vascular and Thoracic Surgery (SFCTCV) and of Anesthesia and Critical Care (SFAR) recommended its first-line use (i.e., before epidural analgesia) to facilitate early recovery after pulmonary lobectomy [17]. However, the ESP, more superficially, seems to have similar properties to the paravertebral block [18], and its realization seems to be easier and faster. Since 2016, the ESP has been increasingly used [19], and its use was shown to provide adequate short- [20] and long-term pain control in thoracic surgery [21]. Nevertheless, few studies so far have compared the ESP with other RA techniques. Finally, morphine IA seems to be little used in lung surgery and has been little studied in this context. However, it has shown to provide effective analgesia [22–24] and reduce the length of hospitalization stay compared to multimodal analgesia without RA [25].

ESP, TEA, and IA are commonly used in our institution for thoracic surgery, following a unit procedure. The procedure was developed to provide effective analgesia while facilitating postoperative recovery, depending on the type of surgery. To our knowledge, the three chosen blocks have not been evaluated as part of an overall strategy for the management of patients who undergo lung surgery, including different surgical approaches. The aim of our study was to assess the impact of a strategy using these three regional anesthesia techniques on postoperative recovery after lung resection.

2. Materials and Methods

We conducted a prospective observational study at Angers University Hospital in France. The study was approved by an Investigational Review Board (Comité d'Ethique du CHU d'Angers, reference number 2019/97). It was registered in the French National Technologies and Civil Liberties Commission (number: ar19-0061v0) and in the ClinicalTrials registry (number: NCT04147754). Patients were informed during anesthesia consultation, and we obtained a patient agreement before inclusion to record their data.

2.1. Population

Inclusion criteria were adult patients undergoing an elective lung resection between 1 November 2019 and 1 November 2020 and who had a pre- or intra-operative regional anesthesia technique using either erector spinae plane block, thoracic epidural analgesia or intrathecal analgesia. Non-inclusion criteria were emergency or revision surgery, patients under 18 years of age, pregnancy, patients with legal guardianship, no French-speaking patients or contraindication to regional techniques.

The duration of inclusion period (one year) was chosen in order to obtain a relevant number of patients in relation to the volume of pulmonary surgeries carried out in our unit, while having homogeneous practices in terms of surgery, anesthesia, pain management and postoperative rehabilitation.

2.2. Unit Procedure for Analgesic Management

In our department, the procedure of choice for the RA technique in lung surgery was based on the surgical approach (VATS or thoracotomy) and the estimated conversion risk to thoracotomy, assessed by the surgeon and discussed with the anesthesiologist (Figure 1). However, the final choice of the RA technique was at the discretion of the anesthesiologist in charge of the patient.

The erector spinae plane block was performed immediately after general anesthesia induction in the lateral decubitus position. A 22-gauge 50 or 80 mm needle (Braun Ultraplex® 360) was inserted at a level between T5 and T8 under in-plane ultrasound guidance. After gentle suction, about 30 mL of 3.8 mg/mL ropivacaine was slowly injected between the erector spinae muscle and its anterior fascia.

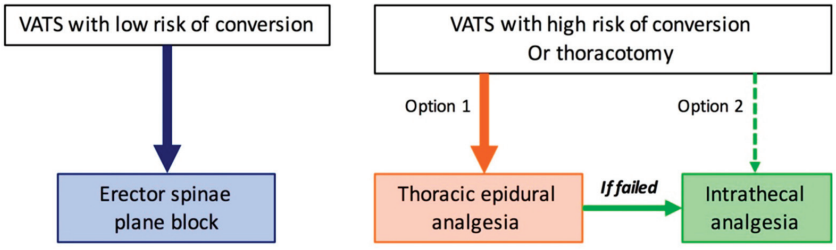

Figure 1. Choice procedure for the regional anesthesia technique to use in lung surgery at Angers University Hospital, France.

The thoracic epidural catheter was inserted on the day of surgery (before induction of anesthesia) or on the day before surgery. In the sitting position, the puncture was made at the T7–T8 interspace with an 18-gauge Tuohy needle (Braun Perifix® ONE). A 2 or 3 mL test dose of 2% xylocaine 0.0005% adrenaline was injected in the epidural space after catheter insertion. At the start of surgery, a bolus (5 to 20 mL) of a 2 mg/mL ropivacaine and 1 μg/mL sufentanil mixture could be carried out in the epidural catheter, followed by an epidural infusion of a 2 mg/mL ropivacaine and 0.5 μg/mL sufentanil mixture. The decision to inject a bolus and the initial epidural infusion rate was chosen by the anesthesiologist in charge of the patient.

Intrathecal analgesia was performed immediately before general anesthesia induction. In the sitting position, a needle (25- or 27-gauge needle depending on the anesthesiologist habit, BD Whitacre®) was inserted into the L4–L5 interspace. A single intrathecal bolus was carried out, using about 300 μg of morphine and 25 μg of sufentanil.

After surgery, patients were admitted either to the thoracic surgery ward (after at least one hour of monitoring in the postanesthesia care unit (PACU)) or in the intensive care unit (ICU). The choice was based on patient's comorbidities, type of surgery (wedge, lobectomy or pneumonectomy, VATS or thoracotomy), intraoperative complications, and the type of RA used. In our unit, patient monitoring was carried out in ICU for patients who had an IA (24 h minimum) and those who had a TEA (as long as the epidural infusion was in progress).

2.3. Outcome Measurements

Data were prospectively collected in the preoperative period, during the surgery and in the first three postoperative days. The objectives evaluating the impact of our analgesic strategy were measured in the entire group of included patients, but also in each group of patients who received a different regional analgesia. Thus, three groups of patients were compared: patients who received an erector spinae plane block (ESP group), those who received thoracic epidural analgesia (TEA group), and those who received intrathecal analgesia (IA group).

To assess the efficiency of our analgesic strategy on recovery after lung surgery, our primary outcome was the pain at Day 2 after surgery (at rest and on exertion), using the numerical pain rating scale (NRS) with values between 0 and 10.

Main secondary outcomes included pain at other perioperative times (H2, Days 0, 1, and 3), at rest (morning and evening) and during chest physiotherapy exercises, cumulative morphine consumption until the third postoperative day, morphine-related adverse effects, ICU or hospital length of stay, and effects on pulmonary function (Peak Expiratory Flow (PEF)). Respiratory complications requiring specific therapies (non-invasive ventilation (NIV), high-flow oxygen therapy, re-intubation, new pleural drainage, bronchoscopic suction, lung infection treated with antibiotic therapy), readmissions to ICU, revision surgery requirements and deaths were recorded. The incidence of postoperative neuropathic pain was also assessed.

Data assessing the safety of regional anesthesia were also collected: neurological complications (epidural hematoma, dural breach, motor function impairment, transient radicular irritation, confusion), hemodynamic complications (episodes of fluid bolus requirements or use of vasoactive drugs) and cardiac complications (supra-ventricular tachycardia, acute cardiac failure, cardiac arrest).

As oxycodone and morphine were used, orally and intravenously, an equianalgesic table proposed by the French Society for Palliative Care and Support (available at http://www.sfap.org, accessed on 28 February 2022) was used to obtain the morphine-equivalent consumption, as follows: 1 oral morphine = 1/2 oral oxycodone = 1/3 intravenous (IV) morphine and 1 IV morphine = 1 IV oxycodone.

2.4. Data Analysis

Anonymized data were recorded in Excel® software and statistical analysis was performed using JMP® software (SAS Institute, Brie Comte Robert, France).

Data are reported as medians (25–75% interquartiles) or numbers (percentages) for the entire group and for each subgroup of patients. As this study was an observational study aiming to assess the impact of a global strategy on all patients, no sample size calculation and power analysis were carried out prior to inclusions. Numerical data were compared using the Kruskal–Wallis test when a unique *p*-value was given for the overall comparison of the three groups, and a Mann–Whitney test was used when each group was compared with each other. Categorical data were compared using the chi-2 or the Fisher's exact test. All tests were two-tailed and a *p*-value of less than 0.05 was considered significant.

As pulmonary outcomes are known to be different depending on the surgical approach, and because TEA and IA were mostly carried out in patients who had a thoracotomy incision, a post hoc analysis was performed in the subgroup of patients who had a thoracotomy incision (including converted VATS, lateral, posterolateral and anterolateral thoracotomies), in order to compare outcomes of patients who had a TEA with those who had an IA.

3. Results

3.1. Population Characteristics

One-hundred and sixteen patients were included: 70 (60%) in the ESP group, 32 (28%) in the TEA group and 14 (12%) in the IA group (flow chart in the Supplementary Material, Figure S1). Patients' demographic data are detailed in Table 1. The main surgical indication was lung tumor resection (92%). Preoperative spirometry results were not significantly different between the three groups.

Table 1. Preoperative characteristics.

	All Patients (*n* = 116)	ESP Group (*n* = 70)	TEA Group (*n* = 32)	IA Group (*n* = 14)	*p*
Patients' characteristics					
Age (years)	64 (11)	64 (11)	63 (10)	66 (12)	0.48
Male	73 (63%)	41 (59%)	21 (66%)	11 (79%)	0.32
Height (cm)	169 (9)	169 (9)	169 (8)	170 (10)	0.76
Weight (kg)	72 (17)	70 (16)	72 (18)	81 (22)	0.16
ASA status					
I	5 (4%)	2 (3%)	2 (6%)	1 (7%)	0.64
II	47 (41%)	28 (40%)	14 (44%)	5 (36%)	0.87
III	63 (54%)	39 (56%)	16 (50%)	8 (57%)	0.84
IV	1 (9%)	1 (1%)	0	0	0.72

Table 1. *Cont.*

	All Patients (*n* = 116)	ESP Group (*n* = 70)	TEA Group (*n* = 32)	IA Group (*n* = 14)	*p*
Medical history					
COPD	39 (34%)	19 (27%)	16 (50%)	4 (29%)	0.08
Active smokers	27 (23%)	16 (23%)	7 (22%)	4 (29%)	0.88
Previous thoracic surgery	24 (21%)	13 (19%)	8 (25%)	3 (21%)	0.76
Previous thoracic radiotherapy	10 (9%)	6 (9%)	3 (9%)	1 (7%)	0.97
Diabetes	18 (16%)	12 (17%)	5 (16%)	1 (7%)	0.59
Chronic alcoholism	15 (13%)	10 (14%)	4 (12%)	1 (7%)	0.74
Psychiatric disease	8 (7%)	4 (6%)	3 (9%)	1 (7%)	0.80
Chronic pain	24 (21%)	16 (23%)	5 (16%)	3 (21%)	0.69
Preoperative respiratory function					
FEV1 (L)	2.4 (1.9–2.9)	2.5 (1.9–3.0)	2.4 (1.8–2.8)	2.0 (1.8–3.1)	0.36
Tiffeneau index	71 (61–79)	71 (63–80)	66 (57–78)	69 (60–78)	0.28
Surgical indication					
Diagnostic biopsy	5 (4%)	4 (6%)	0	1 (7%)	0.36
Lung infection	2 (2%)	1 (1%)	0	1 (7%)	0.22
Tumour resection	107 (92%)	65 (93%)	30 (93%)	12 (86%)	0.62
Other	2 (2%)	0	2 (6%)	0	0.07

Values are expressed as numbers (%), mean (standard deviation) or median (IQ 25–75%): ESP, erector spinae plane block; IA, intrathecal analgesia; TEA, thoracic epidural analgesia.

3.2. Anesthetic and Surgical Data

The unit procedure for the choice of regional anesthesia was followed for 103 (89%) patients, although 3 patients underwent primary thoracotomy in the ESP group, 5 patients underwent VATS only in the TEA group, and 5 patients underwent VATS only in the IA group, without prior high-risk criteria for conversion to thoracotomy (Table 2).

Table 2. Intraoperative anesthetic and surgical data.

	All Patients (*n* = 116)	ESP Group (*n* = 70)	TEA Group (*n* = 32)	IA Group (*n* = 14)	ESP vs. TEA *p* Value	ESP vs. IA *p* Value	TEA vs. IA *p* Value
Intravenous anesthesia							
Remifentanil (mg)	1.6 (1.0–2.0)	1.5 (0.9–1.9)	1.8 (1.4–2.6)	2.0 (1.5–2.6)	<0.01	0.01	0.74
Propofol (g)	1.7 (1.4–2.4)	1.6 (1.3–2.3)	1.9 (1.5–2.5)	2.2 (1.6–3.2)	0.07	0.01	0.24
IV morphine equivalent (mg)	4 (4–5)	4 (4–5)	4 (4–5)	5 (3.75–5.25)	0.57	0.9	0.69
Paracetamol	113 (97%)	69 (98%)	30 (94%)	14 (100%)	0.23	1	1
Nefopam	70 (60%)	43 (61%)	19 (59%)	8 (57%)	1	0.77	1
NSAIDs	22 (19%)	18 (26%)	2 (6%)	2 (14%)	0.03	0.5	0.57
Ketamine	78 (67%)	52 (74%)	23 (72%)	3 (21%)	0.81	<0.01	<0.01

Table 2. *Cont.*

	All Patients (*n* = 116)	ESP Group (*n* = 70)	TEA Group (*n* = 32)	IA Group (*n* = 14)	ESP vs. TEA *p* Value	ESP vs. IA *p* Value	TEA vs. IA *p* Value
Surgical incision							
Primary thoracotomy	38 (33%)	3 (4%)	27 (84%)	8 (57%)	<0.01	<0.01	0.24
Converted VATS	8 (7%)	3 (4%)	0	1 (%)	0.55	0.52	0.3
Not converted VATS	70 (60%)	64 (91%)	5 (16%)	5 (%)	<0.01	<0.01	0.24
Type of resection							
Lobectomy	69 (59%)	37 (53%)	23 (72%)	9 (64%)	<0.01	0.24	0.17
Pneumonectomy	7 (6%)	0	6 (19%)	1 (7%)	<0.01	0.16	0.65
Segmentectomy	7 (6%)	7 (10%)	0	0	0.33	1	0.41
Wedge	32 (28%)	26 (37%)	2 (6%)	4 (29%)	0.26	1	0.49
Biopsy	1 (8%)	0	1 (3%)	0	<0.01	0.02	0.4
Curage	80 (69%)	43 (61%)	26 (81%)	11 (79%)	0.06	0.3	1
Drains	1 (1–2)	1 (1–1)	2 (1–2)	1.5 (1–2)	<0.01	0.01	0.57
Rib fractures	4 (3%)	1 (1%)	3 (9%)	0	0.09	1	0.54
Operating room time (min)	173 (134–210)	170 (129–204)	191 (143–238)	170 (150–219)	0.03	0.44	0.42
PACU time (min)	131 (114–169)	132 (120–165)	120 (84–256)	131 (67–195)	0.39	0.7	0.88

Values are expressed as numbers (%) or median (IQ 25–75%): ESP, erector spinae plane block; IA, intrathecal analgesia; NSAIDs, non-steroidal anti-inflammatory drugs; PACU, post-anesthesia care unit; TEA, thoracic epidural analgesia; VATS, video-assisted thoracoscopic surgery.

Concentrations and volumes used for the different types of RA followed the unit procedure. For patients in the TEA group, TEA infusion was started intraoperatively (at the beginning of the surgical procedure) for 14 (44%) patients only, and postoperatively for the others. TEA was used with ropivacaine only (i.e., without sufentanil) for eight (25%) patients. The postoperative infusion rate was between 3 and 8 mL/h, with a median rate of 5 (5–6) mL/h.

IV anesthetic data and surgical data are detailed in Table 2. Total doses of remifentanil and propofol were less important in the ESP group. In most cases (69 patients (59%)), the lung resection was a lobectomy.

3.3. Postoperative Pain

Using the NRS, the median pain on Day 2 (primary endpoint) for all patients was 2 (0–4.8) in the morning at rest, 0.5 (0–3) in the evening at rest, and 4 (2.5–5) on mobilization, with 46 (40%) patients having at least once a pain score > 3 at rest during this day.

Detailed results of the pain scores measured between Day 0 and Day 3 are presented in Figure 2. In the post-anesthesia care unit (PACU), pain was lower in the IA group than in other groups. There were no significant differences at rest on Days 1 and 2 between the three groups (Figure 2A). On H2 and on the evening of Day 3, pain at rest was significantly lower in the IA group, in comparison with the TEA group. During chest physiotherapy exercises, there was no significant difference in pain intensity between groups (Figure 2B). On Day 0, there was a significant higher rate of patients with at least one episode of moderate-to-severe pain (NRS $\geq$ 4) in the ESP group (Figure 2C).

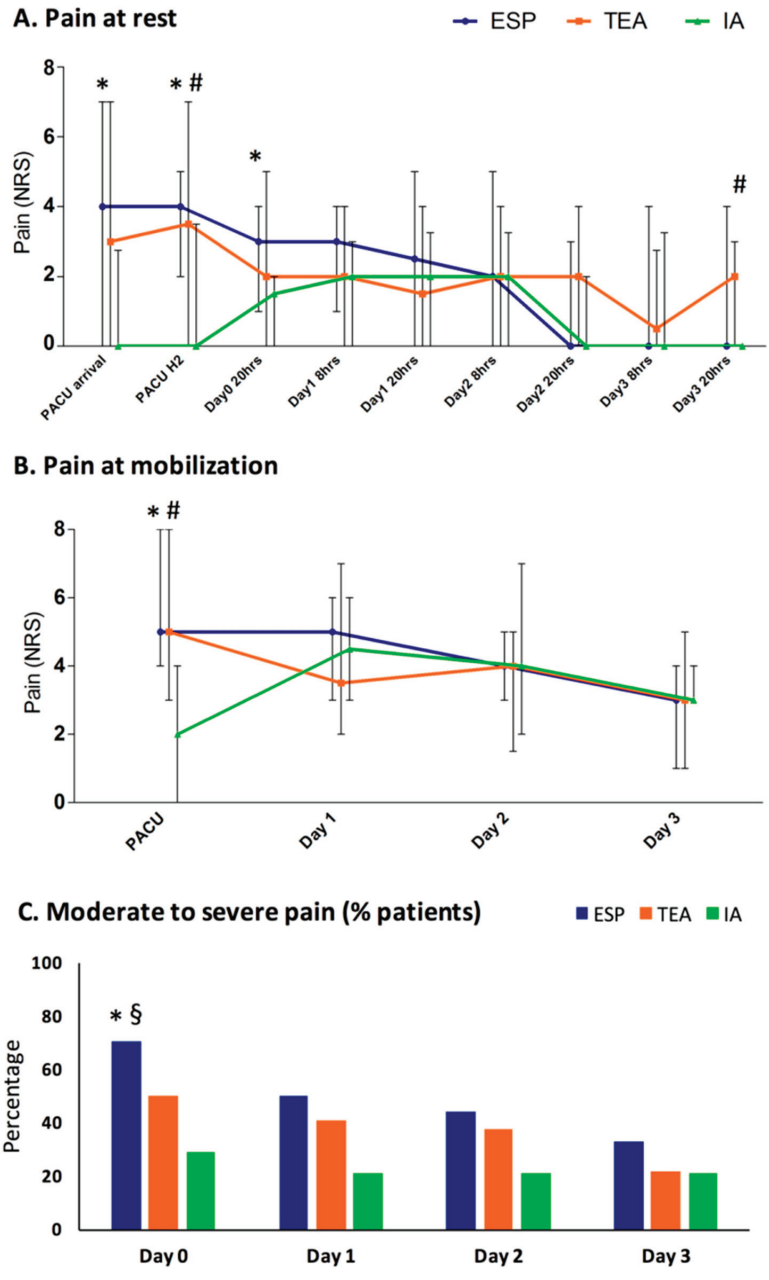

Figure 2. Postoperative pain in the three groups: (**A**) pain at rest; (**B**) pain during mobilization (during chest physiotherapy for Days 1 to 3); (**C**) percentage of patients with a moderate-to-severe pain (NRS $\geq$ 4). Points with blue line, ESP group; squares with orange line, TEA group; triangle with green line, IA group. The charts A and B show medians and (25–75%) interquartile range, and the chart C shows percentages. *, $p < 0.05$ between ESP and IA groups; #, $p < 0.05$ between TEA and IA groups; §, $p < 0.05$ between ESP and TEA groups. ESP, erector spinae plane block; IA, intrathecal analgesia; TEA, thoracic epidural analgesia; NRS, numerical rating scale of the pain; PACU, post-anesthesia care unit.

All patients received opioids in the postoperative period, in the form of IV morphine for 21 (16%) patients, IV oxycodone for 96 (83%) patients, oral morphine for 1 (<1%) patients, and/or oral oxycodone for 87 (75%) patients. The details of opioids consumption are shown in Table 3. There was no significant difference in the rate of patients who required opioids throughout the hospitalization between the groups, except on H2 where a lower rate of patients required opioids in the TEA group than in the ESP group. The amounts of morphine equivalents received (oral or IV) were not significantly different between the groups on Days 0, 1 and 2 and in total until the third postoperative day. However, these amounts were higher on Day 3 in the TEA group.

Table 3. Postoperative pain and opioid consumption.

	All Patients (n = 116)	ESP Group (n = 70)	TEA Group (n = 32)	IA Group (n = 14)	ESP vs. TEA p Value	ESP vs. IA p Value	TEA vs. IA p Value
IV or oral opioid use							
Day 0	115 (99%)	70 (100%)	31 (97%)	14 (100%)	0.31	1	1
Day 1	95 (82%)	64 (91%)	19 (59%)	12 (86%)	<0.01	0.61	0.09
Day 2	84 (72%)	50 (71%)	24 (75%)	10 (71%)	0.81	1	1.0
Day 3	69 (59%)	38 (54%)	23 (71%)	8 (57%)	0.12	1	0.49
IV morphine equivalent (for oral or IV opioids) (mg)							
H2	3 (0–7)	5 (0–8)	0 (0–3.5)	0 (0–4.5)	<0.01	0.03	0.97
Day 0	14 (5–25)	16 (7–25)	10 (0–27)	16 (5–33)	0.16	0.94	0.46
Day 1	12.3 (2.5–23.3)	12 (6.5–22)	6.5 (0–35)	16 (6–24.5)	0.31	0.6	0.49
Day 2	10 (0–14.1)	8.8 (0–12.5)	11 (0.3–29.5)	7.5 (0–16.3)	0.05	0.69	0.28
Day 3	5 (0–10)	5 (0–10)	10 (0–18)	2.75 (0–10)	<0.01	0.9	0.049
Total	44 (28.9–73.3)	44 (28.9–73.3)	41 (18–94.9)	57 (19.1–77.1)	0.96	0.80	0.86

Values are expressed as numbers (%) or median (IQ 25–75%). ESP, erector spinae plane block; IA, intrathecal analgesia; TEA, thoracic epidural analgesia.

All patients (except one deceased) had a postoperative consultation with the surgeon and/or the referring pulmonologist, and the presence of neuropathic pain was assessed for 83 (72%) of them (50 days after surgery on average). In these patients, the incidence of neuropathic pain was 34% and was not significantly different between the three groups, although higher in TEA and IA groups (14 (28%), 9 (41%) and 5 (45%) in ESP, TEA and IA groups, respectively, overall p-value = 0.39).

3.4. Postoperative Recovery

The first standing mobilization occurred earlier in the ESP group, and there were no significant differences in peak expiratory flows measured on Days 1, 2 and 3 (Table 4).

Lengths of ICU and hospital stays were significantly longer in the TEA group than in the two other groups (Table 4). When patients were hospitalized in ICU after the surgery, the length of stay in ICU was significantly shorter in the ESP group, in comparison with other groups.

There were significantly more lung infections, confusion, hypotension, supraventricular tachycardia and postoperative ileus in the TEA group compared to the ESP group. There were no significant differences between the three groups in other respiratory, hemodynamic, neurological, digestive, cardiac and urological complications (Supplementary Material,

Table S1). Moreover, there were no significant differences in the rates of ICU readmission, early surgical revision or death.

Table 4. Postoperative recovery parameters.

	All Patients (n = 116)	ESP Group (n = 70)	TEA Group (n = 32)	IA Group (n = 14)	ESP vs. TEA p Value	ESP vs. IA p Value	TEA vs. IA p Value
First time setting in the chair (days)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	0.02	0.18	0.49
First standing up (days)	1 (1–1)	1 (1–1)	1 (1–2)	1 (1–2)	<0.01	0.01	0.94
Drain removal ≤ Day 3	68 59%)	52 (74%)	9 (28%)	7 (50%)	<0.01	0.1	0.18
Urinary catheter removal ≤ Day 3	76 (66%)	39 (93%)	25 (78%)	12 (92%)	0.09	1	0.4
PEF (% theoretical value)							
Day 1	35 (25–46)	37 (27–47)	35 (27–43)	25 (21–47)	0.62	0.37	0.44
Day 2	30 (24–38)	28 (24–40)	31 (21–35)	31 (24–38)	0.8	0.8	0.6
Day 3	37 (27–46)	41 (29–46)	31 (17–54)	34 (29–53)	0.19	0.7	0.42
Postoperative admission to ICU (vs. ward)	93 (80%)	47 (67%)	32 (100%)	14 (100%)	<0.01	<0.01	1
Length of ICU stay (days)	2 (1–4)	1 (0–2)	4 (3–6)	1 (1–2.5)	<0.01	<0.01	<0.01
Length of hospital stay (days)	5 (3–9)	4 (3–5)	10 (6–15)	6 (4–11)	<0.01	0.07	0.046

Values are expressed as numbers (%) or median (IQ 25–75%). ESP, erector spinae plane block; IA, intrathecal analgesia; ICU, Intensive care unit; PEF, Peak expiratory flow; TEA, thoracic epidural analgesia.

3.5. Post Hoc Analysis in Patients Who Underwent a Thoracotomy

Forty-two patients underwent an elective or unplanned thoracotomy; 27 (64%) of them had a TEA and 9 (21%) an IA. In these patients, the length of ICU stay was reduced in those who had an IA in comparison with a TEA (2 (1–4) vs. 4 (3–6) days, respectively, p-value = 0.01). There were no significant differences in other analgesia and postoperative recovery parameters, except for pain at rest, which was significantly lower in the IA group on Day 3 in the evening (Supplementary Material, Table S2).

4. Discussion

In our center, a regional anesthesia strategy based on the surgical approach and on the risk of conversion to thoracotomy allowed for effective postoperative analgesia, regardless of the type of block used, and rapid recovery according to the type of surgery received. Interestingly, in the subgroup of patients who underwent a thoracotomy, postoperative pain and recovery tended to be better in patients who received intrathecal analgesia in comparison with epidural analgesia.

Postoperative pain after lung surgery is often severe, and RA has shown its value in this context. Epidural analgesia has long been shown to be the gold standard for this surgery because of its benefits for postoperative pain, pulmonary function and on limiting the side effects associated with the use of morphine [26,27]. However, two important developments marked a turning point for pain and recovery after thoracic surgery: the development of VATS [28], which limits the surgical incision and prevents pain associated with rib fractures, and the development of lateral and posterior wall blocks, which limit the hemodynamic and respiratory repercussions linked to central blocks [29,30]. These

blocks have been the subject of a relatively large number of studies, and most of them were shown to be effective, compared to a placebo [31,32] or epidural or other blocks [33]. In clinical practice, however, the choice of a technique remains difficult and often depends on the experience of the center and especially of the anesthesiologist in charge of the patient. In our center, we decided to adapt this choice to the risk of conversion to thoracotomy. To our knowledge, this type of strategy has been little evaluated, and, in particular, the three blocks that we chose have not been compared together, although they are likely to be frequently used in other centers.

We observed here that the use of these three blocks allowed adequate analgesia in patients, with less than 50% of patients who had at least moderate pain, and relatively low pain scores at rest. These results are compatible with those found in the existing literature. Indeed, with VATS, the mean pain score was most of the time inferior to 3 [34]. For thoracotomy, when multimodal analgesia included an RA, pain was low or moderate in most cases [14,28]. Furthermore, even if there was no intrathecal infusion when IA was used in our unit, there was no significant difference in pain scores from Day 0 to Day 2 between IA and TEA. Despite the small number of patients who had intrathecal analgesia in our study, this result is interesting because it confirms the effectiveness of this technique in thoracic surgery [35].

Despite the effectiveness of central blocks, more peripheral blocks such as pectoralis block, serratus block and ESP were proposed with the aim of facilitating recovery [36]. One of the underlying ideas is that, at the doses achieved, central blocks most often require hospitalization with continuous monitoring or hospitalization in ICU, which could slow down recovery, despite the less-invasive nature of the surgery (in the case of VATS in particular). In our study, as expected, patients who had an ESP were most of the time patients who had a VATS (not converted to thoracotomy) and we confirmed that their hospital length of stay was shorter than in the other groups. Interestingly, the inclusion of both VATS and thoracotomies in the same center allowed us to observe that patients who had a VATS experienced the most pain at Day 0 (vs. patients who had thoracotomy), despite a lower number of drains. This observation calls into question the use of ESP in this indication in comparison with other blocks such as the paravertebral block currently recommended in this indication [17]. In addition, when we compared TEA and IA groups, patients who had an IA had less severe pain on Day 3, but also a shorter ICU length of stay, including in the subgroup of patients who only had a thoracotomy. While studies have already compared IA with TEA in thoracic surgery [37], new, prospective and randomized controlled studies now seem necessary to verify whether intrathecal analgesia could allow an earlier recovery than epidural analgesia, especially since we know that early recovery can improve postoperative morbidity in this context.

Additionally, and interestingly, we did not observe any differences between IA and TEA using respiratory recovery criteria such as pain during chest physiotherapy, removal of drains, and early patient mobilization. On the other hand, this strategy made it possible, as desired, to obtain good results in patients who had an ESP, i.e., those who mainly had a VATS surgery, as already observed in previous studies [38,39].

Our study has some limitations, linked in part to its observational nature and the relatively low number of patients (number of patients over one year in our center). This design had the advantage of assessing in real practice the impact of our protocol on pain and recovery. Its limited duration made it possible to observe these results with similar anesthetic and surgical techniques, same anesthesiologists and surgeons, and with similar postoperative pain and rehabilitation managements. Moreover, the study included all types of surgical approaches, i.e., VATS, VATS converted to thoracotomies, and thoracotomies. This design resulted in the inclusion of patients with different postoperative conditions and an uneven number of patients between groups. However, this imbalance between the groups is likely consistent with the proportions of patients with a VATS or a thoracotomy in centers performing pulmonary resections. In addition, this choice allowed us to verify under similar conditions if this strategy, which included three possible RA techniques, was

relevant for the management of all of these patients who were to undergo lung resection in our department. These results now encourage an exploration of the value of this strategy, or of strategies using other blocks, in controlled and multicentric trials.

5. Conclusions

In our institution, a regional anesthesia strategy based on the risk of conversion to thoracotomy—combining an erector spinae plane block for video-assisted thoracoscopic surgery, thoracic epidural analgesia for thoracotomy, and intrathecal analgesia as a possible alternative—allowed for adequate postoperative analgesia and rapid recovery. Interestingly, in the subgroup of patients who underwent a thoracotomy, some of these parameters were better in patients who received intrathecal analgesia, in comparison with epidural analgesia. These results need to be confirmed by stronger prospective and controlled studies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11051376/s1, Figure S1: Flow chart of the study; Table S1: Post-operative complications; Table S2: Post hoc analysis in patients who underwent a thoracotomy.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee "CHU d'Angers" (reference number 2019/97, date of approval 9 October 2019). It was registered in the French National Technologies and Civil Liberties Commission (number: ar19-0061v0) and in the ClinicalTrials registry (number: NCT04147754). Patients were informed during anesthesia consultation, and we obtained a patient agreement before inclusion to record their data.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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References

1. Kalso, E.; Perttunen, K.; Kaasinen, S. Pain after thoracic surgery. *Acta Anaesthesiol. Scand.* **1992**, *36*, 96–100. [CrossRef] [PubMed]
2. Katz, J.; Jackson, M.; Kavanagh, B.P.; Sandler, A.N. Acute Pain after Thoracic Surgery Predicts Long-Term Post-Thoracotomy Pain. *Clin. J. Pain* **1996**, *12*, 50–55. [CrossRef] [PubMed]
3. Lederman, D.; Easwar, J.; Feldman, J.; Shapiro, V. Anesthetic considerations for lung resection: Preoperative assessment, intraoperative challenges and postoperative analgesia. *Ann. Transl. Med.* **2019**, *7*, 356. [CrossRef] [PubMed]
4. Batchelor, T.J.P.; Rasburn, N.J.; Abdelnour-Berchtold, E.; Brunelli, A.; Cerfolio, R.; Gonzalez, M.; Ljungqvist, O.; Petersen, R.H.; Popescu, W.M.; Slinger, P.D.; et al. Guidelines for enhanced recovery after lung surgery: Recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur. J. Cardio-Thorac. Surg.* **2019**, *55*, 91–115. [CrossRef] [PubMed]
5. Kehlet, H.; Rung, G.W.; Callesen, T. Postoperative opioid analgesia: Time for a reconsideration? *J. Clin. Anesth.* **1996**, *8*, 441–445. [CrossRef]
6. Gottschalk, A.; Cohen, S.P.; Yang, S.; Ochroch, E.A.; Warltier, D.C. Preventing and Treating Pain after Thoracic Surgery. *Anesthesiology* **2006**, *104*, 594–600. [CrossRef] [PubMed]
7. Yoshioka, M.; Mori, T.; Kobayashi, H.; Iwatani, K.; Yoshimoto, K.; Terasaki, H.; Nomori, H. The efficacy of epidural analgesia after video-assisted thoracoscopic surgery: A randomized control study. *Ann. Thorac. Cardiovasc. Surg.* **2006**, *12*, 313–318. [PubMed]
8. Schultz, A.-M.; Werba, A.; Ulbing, S.; Gollmann, G.; Lehofer, F. Peri-operative thoracic epidural analgesia for thoracotomy. *Eur. J. Anaesthesiol.* **1997**, *14*, 600–603. [CrossRef] [PubMed]

9. Zoumprouli, A.; Chatzimichali, A.; Papadimitriou, S.; Papaioannou, A.; Xynos, E.; Askitopoulou, H. Gastrointestinal motility following thoracic surgery: The effect of thoracic epidural analgesia. A randomised controlled trial. *BMC Anesthesiol.* **2017**, *17*, 139. [CrossRef]
10. Scherer, R.; Schmutzler, M.; Giebler, R.; Erhard, J.; Stöcker, L.; Kox, W. Complications related to thoracic epidural analgesia: A prospective study in 1071 surgical patients. *Acta Anaesthesiol. Scand.* **1993**, *37*, 370–374. [CrossRef] [PubMed]
11. Manassero, A.; Bossolasco, M.; Carrega, M.; Coletta, G. Postoperative Thoracic Epidural Analgesia: Adverse Events from a Single-Center Series of 3126 Patients. *Local Reg. Anesth.* **2020**, *13*, 111–119. [CrossRef]
12. Boisen, M.L.; Sardesai, M.P.; Kolarczyk, L.; Rao, V.K.; Owsiak, C.P.; Gelzinis, T.A. The Year in Thoracic Anesthesia: Selected Highlights From 2017. *J. Cardiothorac. Vasc. Anesth.* **2018**, *32*, 1556–1569. [CrossRef]
13. Okajima, H.; Tanaka, O.; Ushio, M.; Higuchi, Y.; Nagai, Y.; Iijima, K.; Horikawa, Y.; Ijichi, K. Ultrasound-guided continuous thoracic paravertebral block provides comparable analgesia and fewer episodes of hypotension than continuous epidural block after lung surgery. *J. Anesth.* **2015**, *29*, 373–378. [CrossRef]
14. Yeung, J.; Gates, S.; Naidu, B.V.; A Wilson, M.J.; Smith, F.G. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. *Cochrane Database Syst. Rev.* **2016**, *2*, CD009121. [CrossRef] [PubMed]
15. Vogt, A.; Stieger, D.S.; Theurillat, C.; Curatolo, M. Single-injection thoracic paravertebral block for postoperative pain treatment after thoracoscopic surgery. *Br. J. Anaesth.* **2005**, *95*, 816–821. [CrossRef] [PubMed]
16. Marret, E.; Bazelly, B.; Taylor, G.; Lembert, N.; Deleuze, A.; Mazoit, J.-X.; Bonnet, F.J. Paravertebral Block With Ropivacaine 0.5% Versus Systemic Analgesia for Pain Relief After Thoracotomy. *Ann. Thorac. Surg.* **2005**, *79*, 2109–2113. [CrossRef] [PubMed]
17. Berna, P.; Quesnel, C.; Assouad, J.; Bagan, P.; Etienne, H.; Fourdrain, A.; Le Guen, M.; Leone, M.; Lorne, E.; Nguyen, Y.-L.; et al. Guidelines on enhanced recovery after pulmonary lobectomy. *Anaesth. Crit. Care Pain Med.* **2021**, *40*, 100791. [CrossRef] [PubMed]
18. Forero, M.; Adhikary, S.; Lopez, H.; Tsui, C.; Chin, K.J. The Erector Spinae Plane Block: A Novel Analgesic Technique in Thoracic Neuropathic Pain. *Reg. Anesth. Pain Med.* **2016**, *41*, 621–627. [CrossRef] [PubMed]
19. Tsui, B.C.H.; Fonseca, A.; Munshey, F.; McFadyen, G.; Caruso, T.J. The erector spinae plane (ESP) block: A pooled review of 242 cases. *J. Clin. Anesth.* **2019**, *53*, 29–34. [CrossRef] [PubMed]
20. Pirsaharkhiz, N.; Comolli, K.; Fujiwara, W.; Stasiewicz, S.; Boyer, J.M.; Begin, E.V.; Rubinstein, A.J.; Henderson, H.R.; Lazar, J.F.; Watson, T.J.; et al. Utility of erector spinae plane block in thoracic surgery. *J. Cardiothorac. Surg.* **2020**, *15*, 1–6. [CrossRef] [PubMed]
21. Forero, M.; Rajarathinam, M.; Adhikary, S.; Chin, K.J. Erector spinae plane (ESP) block in the management of post thoracotomy pain syndrome: A case series. *Scand. J. Pain* **2017**, *17*, 325–329. [CrossRef] [PubMed]
22. Liu, N.; Kuhlman, G.; Dalibon, N.; Moutafis, M.; Levron, J.-C.; Fischler, M. A Randomized, Double-Blinded Comparison of Intrathecal Morphine, Sufentanil and their Combination versus IV Morphine Patient-Controlled Analgesia for Postthoracotomy Pain. *Anesth. Analg.* **2001**, *92*, 31–36. [CrossRef] [PubMed]
23. Madi-Jebara, S.; Adaimé, C.; Yazigi, A.; Haddad, F.; Hayek, G.; Sleilaty, G.; Antakly, M.-C. Thoracic epidural and intrathecal analgesia have similar effects on pain relief and respiratory function after thoracic surgery. *Can. J. Anaesth.* **2005**, *52*, 710–716. [CrossRef] [PubMed]
24. Mason, N.; Gondret, R.; Junca, A.; Bonnet, F. Intrathecal sufentanil and morphine for post-thoracotomy pain relief. *Br. J. Anaesth.* **2001**, *86*, 236–240. [CrossRef]
25. Meylan, N.; Elia, N.; Lysakowski, C.; Tramèr, M.R. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: Meta-analysis of randomized trials. *Br. J. Anaesth.* **2009**, *102*, 156–167. [CrossRef] [PubMed]
26. Block, B.M.; Liu, S.S.; Rowlingson, A.J.; Cowan, A.R.; Cowan, J.J.A.; Wu, C.L. Efficacy of Postoperative Epidural Analgesia: A meta-analysis. *JAMA* **2003**, *290*, 2455–2463. [CrossRef] [PubMed]
27. Pöpping, D.M.; Elia, N.; Marret, E.; Remy, C.; Tramèr, M.R. Protective Effects of Epidural Analgesia on Pulmonary Complications After Abdominal and Thoracic Surgery: A meta-analysis. *Arch. Surg. Chic. Ill* **2008**, *143*, 990–999. [CrossRef] [PubMed]
28. Bendixen, M.; Jørgensen, O.D.; Kronborg, C.; Andersen, C.; Licht, P.B. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: A randomised controlled trial. *Lancet Oncol.* **2016**, *17*, 836–844. [CrossRef]
29. Chin, K.J. Thoracic wall blocks: From paravertebral to retrolaminar to serratus to erector spinae and back again – A review of evidence. *Best Pract. Res. Clin. Anaesthesiol.* **2019**, *33*, 67–77. [CrossRef]
30. Júnior, A.d.P.J.; Erdmann, T.R.; dos Santos, T.V.; Brunharo, G.M.; Filho, C.T.B.; Losso, M.J.; Filho, G.R.D.O. Comparison between Continuous Thoracic Epidural and Paravertebral Blocks for Postoperative Analgesia in Patients Undergoing Thoracotomy: Systematic Review. *Braz. J. Anesthesiol.* **2013**, *63*, 433–442. [CrossRef]
31. Hill, S.E.; Keller, R.A.; Stafford-Smith, M.; Grichnik, K.; White, W.D.; D'Amico, T.A.; Newman, M.F. Efficacy of Single-dose, Multilevel Paravertebral Nerve Blockade for Analgesia after Thoracoscopic Procedures. *Anesthesiology* **2006**, *104*, 1047–1053. [CrossRef] [PubMed]
32. Park, M.H.; Kim, J.A.; Ahn, H.J.; Yang, M.K.; Son, H.J.; Seong, B.G. A randomised trial of serratus anterior plane block for analgesia after thoracoscopic surgery. *Anaesthesia* **2018**, *73*, 1260–1264. [CrossRef] [PubMed]
33. Fang, B.; Wang, Z.; Huang, X. Ultrasound-guided preoperative single-dose erector spinae plane block provides comparable analgesia to thoracic paravertebral block following thoracotomy: A single center randomized controlled double-blind study. *Ann. Transl. Med.* **2019**, *7*, 174. [CrossRef]

34. Van Der Ploeg, A.P.T.; Ayez, N.; Akkersdijk, G.P.; Van Rossem, C.C.; De Rooij, P.D. Postoperative pain after lobectomy: Robot-assisted, video-assisted and open thoracic surgery. *J. Robot. Surg.* **2020**, *14*, 131–136. [CrossRef]
35. Pitre, L.; Garbee, D.; Tipton, J.; Schiavo, J.; Pitt, A. Effect of intrathecal morphine plus patient-controlled analgesia with morphine versus patient-controlled analgesia with morphine alone on total morphine dosage 24 hours after surgery: A systematic review. *JBI Evid. Synth.* **2020**. [CrossRef]
36. Helander, E.M.; Webb, M.P.; Kendrick, J.; Montet, T.; Kaye, A.J.; Cornett, E.M.; Kaye, A.D. PECS, serratus plane, erector spinae, and paravertebral blocks: A comprehensive review. *Best Pract. Res. Clin. Anaesthesiol.* **2019**, *33*, 573–581. [CrossRef]
37. Dango, S.; Harris, S.; Offner, K.; Hennings, E.; Priebe, H.-J.; Buerkle, H.; Passlick, B.; Loop, T. Combined paravertebral and intrathecal vs thoracic epidural analgesia for post-thoracotomy pain relief. *Br. J. Anaesth.* **2012**, *110*, 443–449. [CrossRef] [PubMed]
38. Ciftci, B.; Ekinci, M.; Celik, E.C.; Tukac, I.C.; Bayrak, Y.; Atalay, Y.O. Efficacy of an Ultrasound-Guided Erector Spinae Plane Block for Postoperative Analgesia Management After Video-Assisted Thoracic Surgery: A Prospective Randomized Study. *J. Cardiothorac. Vasc. Anaesth.* **2020**, *34*, 444–449. [CrossRef]
39. Zhao, H.; Xin, L.; Feng, Y. The effect of preoperative erector spinae plane vs. paravertebral blocks on patient-controlled oxycodone consumption after video-assisted thoracic surgery: A prospective randomized, blinded, non-inferiority study. *J. Clin. Anaesth.* **2020**, *62*, 109737. [CrossRef]

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Effects of Iloprost on Oxygenation during One-Lung Ventilation in Patients with Low Diffusing Capacity for Carbon Monoxide: A Randomized Controlled Study

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Abstract: The protective mechanism of hypoxic pulmonary vasoconstriction during one-lung ventilation (OLV) is impaired in patients with a low diffusing capacity for carbon monoxide (DL_{CO}). We hypothesized that iloprost inhalation would improve oxygenation and lung mechanics in patients with low DL_{CO} who underwent pulmonary resection. Forty patients with a DL_{CO} < 75% were enrolled. Patients were allocated into either an iloprost group (ILO group) or a control group (n = 20 each), in which iloprost and saline were inhaled, respectively. The partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio, pulmonary shunt fraction, alveolar dead space, dynamic compliance, and hemodynamic parameters were assessed 20 min after the initiation of OLV and 20 min after drug administration. Repeated variables were analyzed using a linear mixed model between the groups. Data from 39 patients were analyzed. After iloprost inhalation, the ILO group exhibited a significant increase in the PaO_2/FiO_2 ratio and a decrease in alveolar dead space compared with the control group (p = 0.025 and p = 0.042, respectively). Pulmonary shunt, dynamic compliance, hemodynamic parameters, and short-term prognosis were comparable between the two groups. Selective iloprost administration during OLV reduced alveolar dead space and improved oxygenation while minimally affecting hemodynamics and short-term prognosis.

Keywords: one-lung ventilation; diffusing capacity for carbon monoxide; iloprost; oxygenation

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1. Introduction

One-lung ventilation (OLV) is required for operative procedures in the thoracic cavity. However, OLV aggravates ventilation–perfusion (V/Q) mismatch and commonly results in hypoxemia, which has an incidence of 5–10% [1]. Hypoxemia of the nonventilated lung triggers hypoxic pulmonary vasoconstriction (HPV), an autoregulatory mechanism that decreases the shunt fraction by diverting total pulmonary blood flow from the nonventilated lung to the ventilated lung [2,3].

The diffusing capacity for carbon monoxide (DL_{CO}) measures the ability of the gas to diffuse across the alveolar–capillary membrane [4]. Reduced DL_{CO} is an independent risk factor for increased mortality and perioperative complications related to hypoxia [5,6]. The risk of hypoxia is further increased when patients with low DL_{CO} undergo surgeries requiring OLV because the protective mechanism of HPV is impaired owing to altered compliance of the pulmonary artery [7].

Pharmacological modulation of pulmonary perfusion to reduce V/Q mismatch is gaining interest, and inhaled iloprost is recognized to enhance oxygenation in patients with acute respiratory distress syndrome (ARDS), pulmonary arterial hypertension, and chronic obstructive pulmonary disease [8,9]. Yet, limited evidence exists regarding the

use of iloprost in pulmonary resections, especially in patients with low DL_{CO}. Hence, we hypothesized that despite impaired HPV in these patients, iloprost administration would reduce V/Q mismatch by inducing favorable modulation of pulmonary perfusion. This study aimed to investigate the effects of iloprost on oxygenation and lung mechanics in patients with low DL_{CO} who underwent OLV.

2. Materials and Methods

2.1. Study Population

This prospective, randomized controlled study included patients who were scheduled for videoscope-assisted thoracoscopic single pulmonary lobectomy between September 2015 and June 2017 and adhered to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was approved by the Institutional Review Board (IRB, no. 4-2015-0706) of Severance Hospital, Yonsei University Health System (Seoul, Republic of Korea), and was registered at Clinicaltrials.gov (NCT 02784899). After IRB approval, informed consent was obtained from all subjects involved in the study, and the study methods were performed in accordance with the relevant guidelines and regulations. The inclusion criteria were as follows: (1) DL_{CO} < 75%, (2) age between 40 and 80 years, (3) American Society of Anesthesiologists physical status class between II and III. The exclusion criteria were heart failure (New York Heart Association class III or IV), anemia, arrhythmia, severe hepatic or renal disease, and history of chemotherapy or radiation therapy prior to the surgery. Anemia was defined as hemoglobin concentration <12.0 g/dL in women and <13.0 g/dL in men [10].

2.2. Anesthetic Management

Anesthesia was induced with propofol (1.0–2.0 mg/kg), remifentanil (0.5–1.0 μg/kg), and rocuronium (0.8–1.0 mg/kg). All patients were intubated with left-sided double-lumen tubes (Shiley double-lumen endobronchial tube (DLT); Covidien, Mansfield, MA, USA). The correct positioning of the DLT was confirmed using a fiberoptic bronchoscope before OLV was provided. The radial artery was cannulated, and a 7-Fr central venous catheter (Arrow; Teleflex Inc., Wayne, PA, USA) was placed in the right internal jugular vein. Mechanical ventilation was provided using autoflow pressure-controlled ventilation mode (Primus; Dräger Medical, Lubeck, Germany). Anesthesia was maintained with 1.0–2.0 vol% sevoflurane and 0.1–0.3 μg/kg/min remifentanil targeted at bispectral index (BIS VISTA; Aspect Medical Systems, Norwood, MA, USA) between 40 and 60. Intraoperatively, balanced crystalloids were administered at a rate of 3 mL/kg/h, and additional crystalloids were administered to compensate for blood loss. Vasoactive drugs, such as ephedrine, were administered if systolic blood pressure (SBP) fell below 80 mmHg.

After turning a patient into the lateral decubitus position, OLV was initiated. The tidal volume was set at 6 mL/kg, and the inspiratory–expiratory ratio was set at 1:2. The fraction of inspired oxygen (FiO_2) level was initially set at 0.6. In cases of desaturation (SpO_2 < 95%), the FiO_2 level was increased by 0.2, up to 1.0, and positive end-expiratory pressure (PEEP) of 5 mmHg was applied if $SpO_2 \geq 95\%$ was still not achieved.

2.3. Study Design and Outcome Measurements

All enrolled patients were allocated to the study groups using a randomized sequence, and the surgeon and anesthesiologist were blinded to the group allocation. Patients were randomly allocated to either an iloprost group (ILO group) or a control group. Twenty minutes after the initiation of OLV, iloprost (20 μg (2 mL), Ventavis; Bayer AG, Leverkusen, Germany) was administered to patients allocated to the ILO group. Iloprost was mixed with normal saline (3 mL) and aerosolized using an ultrasonic nebulizer (PARI BOY SX; PARI GmbH, Starnberg, Germany) connected to the inspiratory limb of the ventilator system. A comparable volume (5 mL) of normal saline was aerosolized to the patients in the control group. Interventional medications were administered for 20 min.

The study time points were as follows: (1) 20 min after the initiation of OLV in the lateral decubitus position (T1) and (2) 20 min after iloprost or normal saline administration (T2). During each study period, respiratory and hemodynamic parameters were recorded, and arterial and venous blood samples were collected. Respiratory parameters included FiO_2, end-tidal carbon dioxide ($etCO_2$), the ratio of partial pressure of arterial oxygen to FiO_2 (PaO_2/FiO_2), partial pressure of arterial oxygen (PaO_2), arterial oxygen saturation (SaO_2), pulmonary shunt (Qs/Qt), alveolar dead space, and dynamic compliance. Hemodynamic parameters included heart rate, arterial blood pressure, and central venous pressure. A blood gas analyzer (GEM Premier 4000; Instrumentation Laboratory, Lexington, MA, USA) was used to assess hemoglobin (Hb), PaO_2, SaO_2, partial pressure of arterial carbon dioxide ($PaCO_2$), partial pressure of venous oxygen (PvO_2), and venous oxygen saturation (SvO_2).

The shunt fraction (Qs/Qt) was calculated using the following formula: $(Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$, where $CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$, $CvO_2 = (1.34 \times Hb \times SvO_2) + (0.0031 \times PvO_2)$, and $CcO_2 = (1.34 \times Hb) + (0.0031 \times [FiO_2 \times (P_{atm} - P_{H2O}) - PaCO_2/RQ])$, where CcO_2, pulmonary capillary blood oxygen content; CaO_2, arterial oxygen content; CvO_2, venous oxygen content; P_{atm}, atmospheric pressure (760 mmHg at sea level); P_{H2O}, partial pressure of water (45 mmHg); RQ, respiratory quotient (0.8). The dead space ventilation was calculated according to the Hardman and Aitkenhead equation $(1.135 \times (PaCO_2 - EtCO_2)/PaCO_2 - 0.005)$ [11]. Dynamic compliance was calculated using the following equation: [tidal volume/(plateau airway pressure-PEEP)]. The incidences of intraoperative hypotension (SBP < 80 mmHg) and hypoxia (SpO_2 < 90%) were recorded. Short-term prognosis, including hospital stay, and postoperative complications, such as air leak requiring chest tube insertion, pneumonia, and in-hospital mortality, were assessed.

2.4. Statistical Analysis

The primary outcome was the change in PaO_2/FiO_2 at 20 min after iloprost inhalation (T2), and the secondary outcome was the change in other respiratory mechanics, such as alveolar dead space, shunt fraction, and dynamic compliance. A previous study reported that the standard deviation of the PaO_2/FiO_2 ratio was 60 mmHg for an inhaled-iloprost group [9]. A mean difference of 60 mmHg for the PaO_2/FiO_2 ratio between the ILO and control groups was considered clinically significant in the preliminary data for the first 10 patients after iloprost administration. Hence, 17 patients were required in each group with a power of 80% and a significance level of 0.05. Considering a 10% dropout rate, 20 patients were included in each group. The unpaired Student's *t*-test was used to analyze continuous variables, and the Wilcoxon signed-rank test was used to analyze variables that did not meet normality. Chi-square or Fisher's exact test was used to compare categorical variables between the groups. Repeated variables were analyzed using a linear mixed model with the group and time and the interaction between groups and time as a fixed effect. Post hoc analysis with Bonferroni correction for within-group comparisons versus T1 and between-group comparisons versus T2 was performed for multiple comparisons. The results were expressed as mean (standard deviation), median (interquartile range), or number (percentage). Statistical analyses were performed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA), and $p < 0.05$ was considered statistically significant.

3. Results

Forty patients scheduled to undergo video-assisted thoracoscopic single pulmonary lobectomy were enrolled in this study. As OLV could not be achieved during the measurement period owing to persistent hypoxia in one patient, data from the remaining 39 patients were assessed (Figure 1).

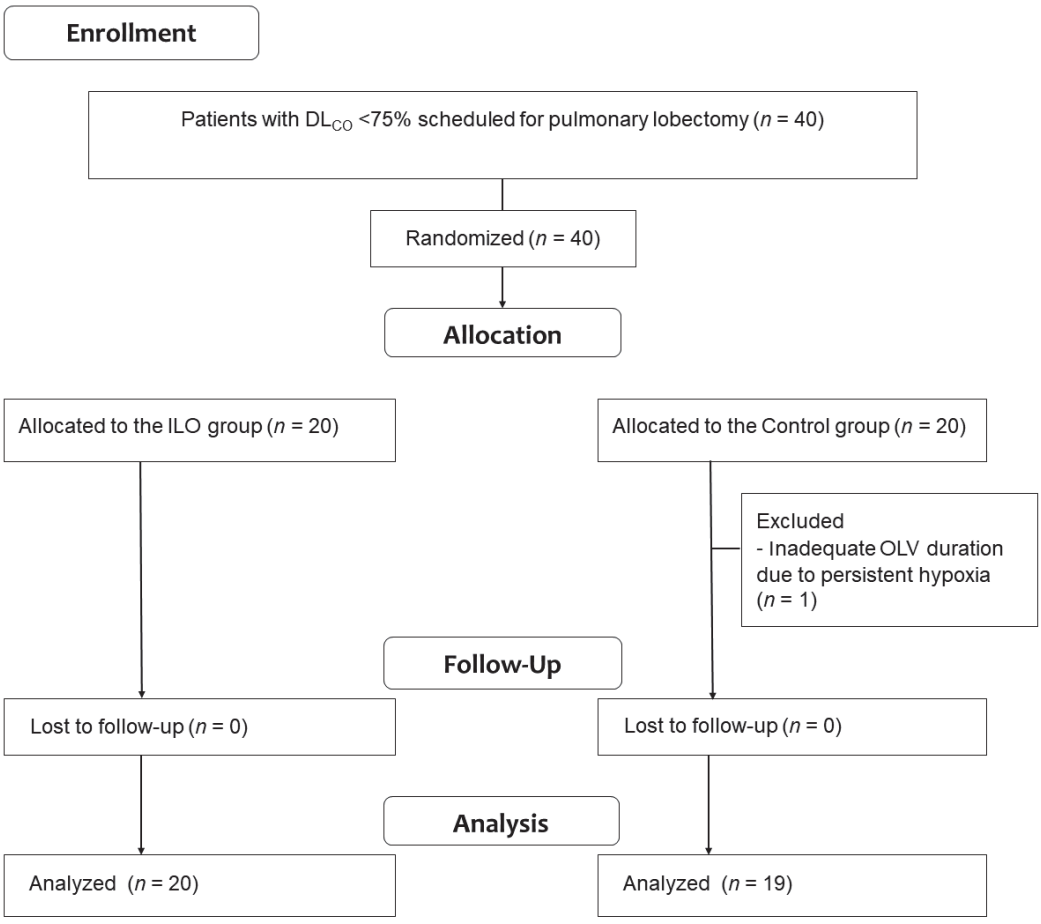

Figure 1. Patient enrollment.

Intergroup comparisons of the preoperative variables between the ILO and control groups are presented in Table 1. Age, sex, height, weight, body mass index, and ASA classification were comparable between the groups. Incidence of hypertension and diabetes mellitus, history of cigarette smoking, incidence of pulmonary abnormalities according to preoperative computed tomography, variables derived from preoperative spirometry, and DL_{CO} were also similar between the groups. None of the patients were associated with cardiac diseases such as heart failure.

Table 2 shows intergroup comparisons of the intraoperative data. All variables, including initial SpO_2 measured at patients' arrival at the operating room, side of the operation, anesthesia time, operation time, OLV time, incidence of intraoperative hypotension, intake fluid, urine output, and estimated blood loss during surgery, were comparable between the two groups with the exception of incidence of hypoxia requiring anesthetic intervention, which was more frequent in the control group ($p = 0.031$). Mean blood pressure, heart rate, and central venous pressure were also similar between the two groups (Figure 2).

Table 1. Preoperative data.

	ILO Group (n = 20)	Control Group (n = 19)	p-Value
Age (years)	68 ± 9	63 ± 10	0.173
Women (n)	10 (50)	6 (31.6)	0.242
Height (cm)	159.3 ± 10.4	164.2 ± 9.5	0.125
Weight (kg)	63.8 ± 11.9	68.1 ± 12.8	0.280
Body mass index (kg/m^2)	24.7 ± 4.4	25.0 ± 3.6	0.674
ASA classification 2/3 (n)	11 (55)/9 (45)	9 (47.4)/10 (52.6)	0.634
Hypertension (n)	6 (30)	7 (37)	0.651
Diabetes mellitus (n)	4 (20)	4 (21)	0.935
Smoking history			0.113
Ex-smoker or current smoker (n)	11 (55)	15 (78.9)	
Nonsmoker (n)	9 (45)	4 (21.1)	
Smoking index (pack × years)	10 (0–50)	31 (3–41)	0.398
Preoperative chest CT			
Atelectasis (n)	2 (10)	0 (0)	0.157
Bronchiectasis (n)	2 (10)	0 (0)	0.157
Pleural effusion (n)	1 (5)	2 (11)	0.517
Emphysema (n)	10 (50)	7 (36.8)	0.408
Interstitial lung disease (n)	3 (15)	5 (26.3)	0.382
Preoperative spirometry			
FEV_1 (L)	1.9 ± 0.6	2.6 ± 2.3	0.173
FEV_1 (% predicted)	88.9 ± 20.7	83.3 ± 17.7	0.368
FVC (L)	2.8 ± 0.9	3.1 ± 1.0	0.320
FVC (% predicted)	89.5 ± 15.6	84.7 ± 19.0	0.388
FEV_1/FVC (%)	69.6 ± 11.1	71.5 ± 13.6	0.517
DL_{CO} (% predicted)	65.5 ± 6.1	61.1 ± 10.6	0.117

Data are presented as mean ± standard deviation, number (%), or median (interquartile range). ASA, American Society of Anesthesiologists; CT, computed tomography; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; DL_{CO}, diffusion capacity of the lung for carbon monoxide.

Table 2. Intraoperative data.

	ILO Group (n = 20)	Control Group (n = 19)	p-Value
Initial SpO_2 at room air (%)	98 (97–99)	96.0 (95–99)	0.918
Lobectomy (right/left) (n)	11 (55)/9 (45)	9 (47)/10 (53)	0.634
Anesthesia time (min)	200 (180–225)	183 (151–233)	0.473
Operation time (min)	138 (120–161)	118 (100–175)	0.336
OLV time (min)	115 (95–135)	103 (81–149)	0.603
Hypotension (n)	8 (40.0)	12 (63.2)	0.206
Hypoxia (n)	1 (5.0) *	6 (31.6)	0.031
Intake fluid (mL)	1315.8 ± 316.9	1454.0 ± 581.3	0.356
Urine output (mL)	241.3 ± 161.1	256.4 ± 152.3	0.768
Estimated blood loss (mL)	102.5 ± 63.8	136.0 ± 110.6	0.248

Data are presented as mean ± standard deviation, number (%), or median (interquartile range). SpO_2, oxygen saturation (pulse oximetry); OLV, one-lung ventilation; hypotensive event defined as the incidence of systolic blood pressure < 80 mmHg; hypoxic event defined as the incidence of SpO_2 < 90% requiring anesthetic intervention. * $p < 0.05$ vs. control group.

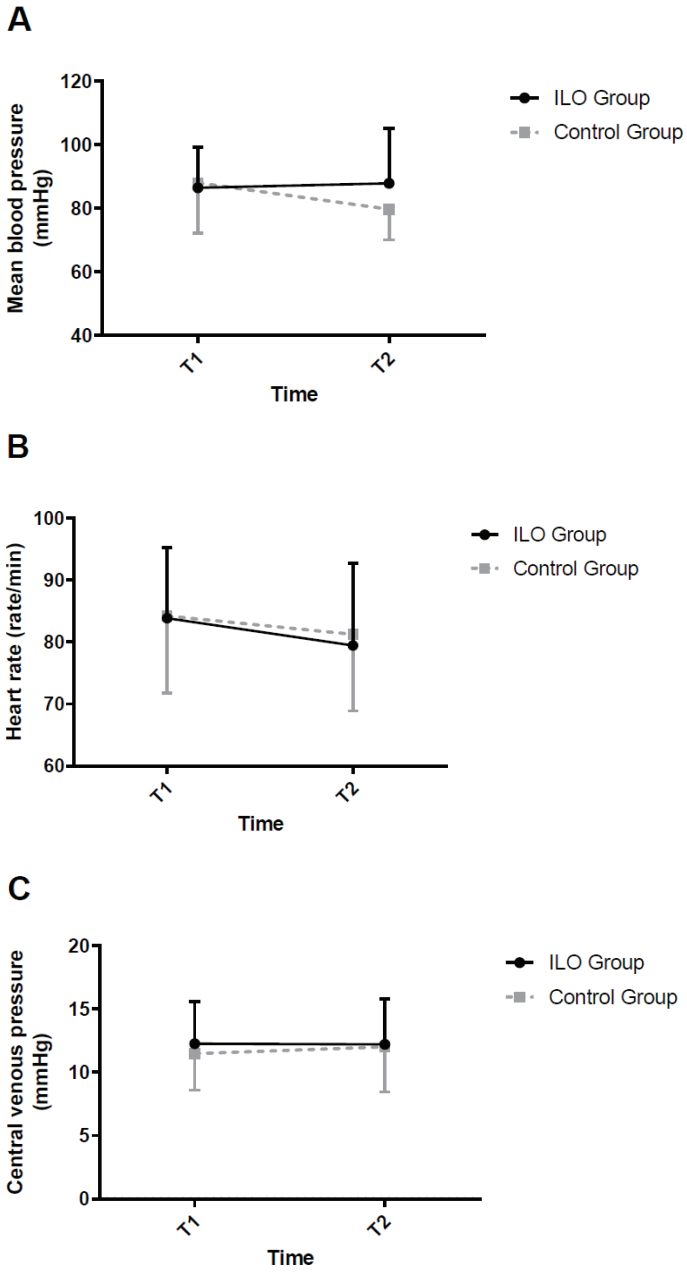

Figure 2. Effects of iloprost on hemodynamics. (**A**) Mean blood pressure, (**B**) heart rate, and (**C**) central venous pressure. Error bars represent standard deviation. No significant differences were observed between the two groups. T1, 20 min after initiation of one-lung ventilation in the lateral decubitus position; T2, 20 min after iloprost or saline administration.

The oxygenation parameters, lung mechanics, and hemodynamic data are shown in Table 3. No clinically relevant differences were observed between the two groups at T1. After iloprost administration, the ILO group showed a significant increase in the

PaO_2/FiO_2 ratio, PaO_2, and SaO_2 and a decrease in alveolar dead space when compared with T1 ($p = 0.044$, $p = 0.044$, $p = 0.024$, and $p < 0.001$, respectively), which also resulted in significant differences compared with the control group. The pulmonary shunt at T2 was significantly decreased when compared with T1 in the ILO group ($p = 0.014$), but the difference compared with that of the control group was insignificant. Changes in dynamic compliance were insignificant among the groups.

Table 3. Effects of iloprost on hemodynamics, oxygenation, and lung mechanics.

	ILO Group (n = 20)	Control Group (n = 19)	p-Value
FiO_2			0.157
T1	0.6 (0.6–0.9)	0.6 (0.6–0.7)	
T2	0.6 (0.6–0.8)	0.8 (0.6–0.8)	
PaO_2/FiO_2 ratio (mmHg)			0.025
T1	125.9 (100.1–222.0)	138.3 (110.0–191.7)	
T2	141.4 (120.8–247.7) *†	128.3 (100.0–161.8)	
PaO_2 (mmHg)			0.044
T1	84.8 (70.3–139.7)	83.0 (74.0–116.0)	
T2	104.7 (82.3–148.6) *†	81.0 (81.0–110.3)	
SaO_2 (%)			0.026
T1	95.0 (92.8–98.5)	94.2 (92.8–97.3)	
T2	97.1 (95.5–99.8) *†	95.3 (92.2–97.3)	
Pulmonary shunt (%)			0.027
T1	27.0 ± 17.9	25.1 ± 17.8	
T2	18.4 ± 11.8 *	26.6 ± 14.4	
Alveolar dead space			0.042
T1	16.4 ± 5.0	19.2 ± 11.6	
T2	10.8 ± 7.3 *†	19.2 ± 11.0	
Dynamic compliance ($mL/cm\ H_2O$)			0.055
T1	20.0 ± 5.3	21.4 ± 4.7	
T2	21.5 ± 7.9	20.2 ± 4.5	

Data are presented as the median (interquartile range) or mean ± standard deviation. FiO_2, fraction of inspired oxygen; T1, 20 min after initiation of OLV (one-lung ventilation) in the lateral decubitus position; T2, 20 min after iloprost or saline administration; PaO_2/FiO_2 ratio, the ratio of partial pressure of arterial oxygen to FiO_2; PaO_2, partial pressure of arterial oxygen; SaO_2, arterial oxygen saturation. Group × time, linear mixed model analysis as a random effect; and group, time, and group-by-time as fixed effects, * $p < 0.05$, vs. T1; † $p < 0.05$, vs. control group.

The short-term prognosis of the patients is presented in Table 4. No significant differences in the duration of hospital stay or the incidence of postoperative complications, such as air leak, postoperative pneumonia, and in-hospital mortality, were observed between the two groups.

Table 4. Short-term prognosis.

	ILO Group (n = 20)	Control Group (n = 19)	p-Value
Hospital days	6 (5–8)	7 (4–9)	0.540
Postoperative complications	3 (15.0)	6 (31.6)	0.219
Air leak	1 (5.0)	3 (15.8)	0.267
Pneumonia	2 (10.0)	4 (21.1)	0.339
In-hospital mortality	1 (5.0)	2 (5.3)	0.970

Data are presented as median (interquartile range) or number (%).

4. Discussion

In this study, we demonstrated that the selective administration of iloprost to ventilated lungs during OLV significantly reduced alveolar dead space and improved oxygenation in patients with low DL_{CO}.

Reduced DL_{CO} is associated with the loss of alveolar membrane surface area and vascular remodeling, resulting in a reduced alveolar–capillary membrane diffusing capacity [12–14]. All patients exhibited mild to moderate decreases in DL_{CO} in the context of normal spirometry. A preoperative CT scan indicated early stages of diffuse interstitial lung disease or emphysema in most of the patients. Although all patients maintained $SpO_2 \geq 95\%$ at the end of the surgery, transient declines of $SpO_2 < 90\%$ were observed in seven patients during OLV despite the application of increased FiO_2 or PEEP. The incidence of hypoxia in our study surpassed that of healthy patients (18% vs. 5–10% [1]), indicating that impaired HPV, expressed as low DL_{CO} [7], aggravated V/Q mismatch during OLV.

The favorable effect of inhaled iloprost on oxygenation is well-described in patients with ARDS [15]. A similar mechanism would be favorable in patients undergoing OLV; however, evidence regarding the effect of iloprost administration in such a cohort is scarce. Choi et al. reported improved oxygenation and decreased intrapulmonary shunts with iloprost use in pulmonary resections; however, their study excluded patients with abnormalities in preoperative spirometry [16]. Our results suggested that consistent outcomes were observed in patients with low DL_{CO} and that iloprost significantly reduced alveolar dead space, which contributed to an increased PaO_2/FiO_2 ratio. In addition, the incidence of hypoxia was significantly less frequent in the ILO group.

However, contradictory results have been reported regarding inhaled iloprost and oxygenation [17,18]. A potential explanation is that the nonselective delivery of iloprost in awake patients may have led to conflicting results in those studies. We presume that to improve oxygenation using iloprost, the administration of the drug should be restricted to well-ventilated areas of the lung. Therefore, the use of a lung separation device, such as DLT, provides an ideal environment for iloprost administration in thoracic surgeries as it strictly confines the delivery of iloprost to the ventilated lung, which favorably redistributes the pulmonary perfusion from the nonventilated lung to the ventilated lung.

Concerns may arise regarding the safety of iloprost use in pulmonary resection. Although a previous study demonstrated that iloprost did not induce systemic adverse events in patients with ARDS [9], it may still be associated with a significant decrease in systemic blood pressure [19]. However, our results indicated that the incidence of intraoperative hypotension was comparable between the two groups. Another concern is that iloprost may be associated with the inhibition of platelet activation [9]; however, estimated blood loss was comparable between the two groups, and none of the patients in the ILO group required intraoperative transfusion. The incidence of postoperative complications and the duration of hospital stay were also similar between the two groups, which supports the notion that acute inhalation of iloprost (20 μg) is less likely to be associated with adverse events during the intraoperative and postoperative periods.

This study had some limitations. First, our patients rarely exhibited a decrease in $DL_{CO} < 40\%$ preoperatively, which limits the efficacy of inhaled iloprost in patients with a mild to moderate severity grade of low DL_{CO}. However, because a very low DL_{CO} greatly increases the risk of morbidity and mortality after pulmonary resection [20,21], such patients are rarely introduced to the operating room. Second, the initiation of PEEP was delayed until hypoxia occurred despite elevated FiO_2 to demonstrate the effect of iloprost because PEEP may compress the small interalveolar vessels of the ventilated lung [22], which hinders the vasodilation effect of iloprost and aggravates V/Q mismatch. Third, because a pulmonary artery catheter is not routinely used in single pulmonary lobectomy, we were unable to acquire blood samples from the pulmonary artery. Instead, right atrial blood samples were used to calculate the shunt fraction, although evidence supports that pulmonary arterial blood samples can be substituted for right atrial blood samples [23]. In addition, we could not exclude the presence of intraoperative pulmonary hypertension in the absence of the pulmonary artery catheter, although even a mild grade of chronic obstructive pulmonary disease may be associated with increased pulmonary arterial stiffness [7].

In conclusion, the results of this study support the use of iloprost inhalation as a possible rescue strategy against hypoxia during OLV. Selective iloprost administration during OLV reduced alveolar dead space and improved oxygenation while minimally affecting intraoperative hemodynamics and short-term prognosis in patients with low DL_{CO}.

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References

1. Karzai, W.; Schwarzkopf, K. Hypoxemia during one-lung ventilation: Prediction, prevention, and treatment. *Anesthesiology* **2009**, *110*, 1402–1411. [CrossRef] [PubMed]
2. Lumb, A.B.; Slinger, P. Hypoxic pulmonary vasoconstriction: Physiology and anesthetic implications. *Anesthesiology* **2015**, *122*, 932–946. [CrossRef] [PubMed]
3. Campos, J.H.; Peacher, D. Application of Continuous Positive Airway Pressure During Video-Assisted Thoracoscopic Surgery. *Curr. Anesth. Rep.* **2021**, *11*, 446–456. [CrossRef] [PubMed]
4. Neder, J.A.; Berton, D.C.; Muller, P.T.; O'Donnell, D.E. Incorporating Lung Diffusing Capacity for Carbon Monoxide in Clinical Decision Making in Chest Medicine. *Clin. Chest Med.* **2019**, *40*, 285–305. [CrossRef] [PubMed]
5. Cerfolio, R.J.; Bryant, A.S. Different diffusing capacity of the lung for carbon monoxide as predictors of respiratory morbidity. *Ann. Thorac. Surg.* **2009**, *88*, 405–410; discussion 401–410. [CrossRef]
6. Pieretti, P.; Alifano, M.; Roche, N.; Vincenzi, M.; Forti Parri, S.N.; Zackova, M.; Boaron, M.; Zanello, M. Predictors of an appropriate admission to an ICU after a major pulmonary resection. *Respiration* **2006**, *73*, 157–165. [CrossRef]
7. Ertan, C.; Tarakci, N.; Ozeke, O.; Demir, A.D. Pulmonary artery distensibility in chronic obstructive pulmonary disease. *Echocardiography* **2013**, *30*, 940–944. [CrossRef]
8. Dernaika, T.A.; Beavin, M.; Kinasewitz, G.T. Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. *Respiration* **2010**, *79*, 377–382. [CrossRef] [PubMed]
9. Sawheny, E.; Ellis, A.L.; Kinasewitz, G.T. Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. *Chest* **2013**, *144*, 55–62. [CrossRef]
10. Blanc, B. Nutritional anemias. Report of a WHO Scientific Group. *WHO Tech. Rep. Ser.* **1968**, *405*, 1–40.
11. Hardman, J.G.; Aitkenhead, A.R. Estimation of alveolar deadspace fraction using arterial and end-tidal CO_2: A factor analysis using a physiological simulation. *Anaesth. Intensive Care* **1999**, *27*, 452–458. [CrossRef] [PubMed]
12. Zou, R.H.; Wallace, W.D.; Nouraie, S.M.; Chan, S.Y.; Risbano, M.G. Lower DLco% identifies exercise pulmonary hypertension in patients with parenchymal lung disease referred for dyspnea. *Pulm. Circ.* **2020**, *10*, 2045894019891912. [CrossRef] [PubMed]
13. Farha, S.; Asosingh, K.; Xu, W.; Sharp, J.; George, D.; Comhair, S.; Park, M.; Tang, W.H.; Loyd, J.E.; Theil, K.; et al. Hypoxia-inducible factors in human pulmonary arterial hypertension: A link to the intrinsic myeloid abnormalities. *Blood* **2011**, *117*, 3485–3493. [CrossRef] [PubMed]
14. Macintyre, N.; Crapo, R.O.; Viegi, G.; Johnson, D.C.; van der Grinten, C.P.; Brusasco, V.; Burgos, F.; Casaburi, R.; Coates, A.; Enright, P.; et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur. Respir J.* **2005**, *26*, 720–735. [CrossRef] [PubMed]
15. van Heerden, P.V.; Barden, A.; Michalopoulos, N.; Bulsara, M.K.; Roberts, B.L. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. *Chest* **2000**, *117*, 819–827. [CrossRef]
16. Choi, H.; Jeon, J.; Huh, J.; Koo, J.; Yang, S.; Hwang, W. The Effects of Iloprost on Oxygenation During One-Lung Ventilation for Lung Surgery: A Randomized Controlled Trial. *J. Clin. Med.* **2019**, *8*, 982. [CrossRef]
17. Boeck, L.; Tamm, M.; Grendelmeier, P.; Stolz, D. Acute effects of aerosolized iloprost in COPD related pulmonary hypertension—A randomized controlled crossover trial. *PLoS ONE* **2012**, *7*, e52248. [CrossRef]

18. Wang, L.; Jin, Y.Z.; Zhao, Q.H.; Jiang, R.; Wu, W.H.; Gong, S.G.; He, J.; Liu, J.M.; Jing, Z.C. Hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension. *Int. J. Chronic. Obstr. Pulm. Dis.* **2017**, *12*, 3353–3360. [CrossRef]
19. Aren, C.; Blomstrand, C.; Wikkelso, C.; Radegran, K. Hypotension induced by prostacyclin treatment during cardiopulmonary bypass does not increase the risk of cerebral complications. *J. Thorac. Cardiovasc. Surg.* **1984**, *88*, 748–753. [CrossRef]
20. Wang, J.S. Relationship of carbon monoxide pulmonary diffusing capacity to postoperative cardiopulmonary complications in patients undergoing pneumonectomy. *Kaohsiung J. Med. Sci* **2003**, *19*, 437–446. [CrossRef]
21. Datta, D.; Lahiri, B. Preoperative evaluation of patients undergoing lung resection surgery. *Chest* **2003**, *123*, 2096–2103. [CrossRef] [PubMed]
22. Battaglini, D.; Ball, L.; Wittenstein, J.; Cohen, E.; Gama, D.E.A.M.; Pelosi, P. PEEP in thoracic anesthesia: Pros and cons. *Minerva Anestesiol.* **2021**, *87*, 223–229. [CrossRef] [PubMed]
23. Turnaoglu, S.; Tugrul, M.; Camci, E.; Cakar, N.; Akinci, O.; Ergin, P. Clinical applicability of the substitution of mixed venous oxygen saturation with central venous oxygen saturation. *J. Cardiothorac. Vasc. Anesth.* **2001**, *15*, 574–579. [CrossRef] [PubMed]

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The Association between Two-Stage Tourniquet Application during Total Knee Replacement and Blood Loss: A Retrospective Cohort Study

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Abstract: Tourniquet use during total knee arthroplasty improves the surgical field, but is associated with several complications. The medical records of 506 patients who underwent elective total knee arthroplasty or total knee replacement from January 2017 to December 2020 were reviewed. A total of 331 patients who had undergone total knee arthroplasty were included. In the first half course group, the tourniquet was inflated with a pressure of 300 mmHg after manual banding before the incision and deflated after cement insertion. In the two-stage group, the tourniquet was inflated and deflated at the same stages of the procedure as in the first half course group. However, in this second group, the tourniquet was deflated for 15 min and then inflated again, and, finally, it was deflated after skin closure. The estimated blood loss, the number of patients who needed medications to control their blood pressure, and opioid usage at the post-anesthesia care unit were similar in both groups. The two-stage tourniquet technique was not related to reduced total blood loss in total knee arthroplasty.

Keywords: total knee replacement; arthroplasty; tourniquet; transfusion; vital stability

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1. Introduction

With a growing population of older adults in Korea, the number of knee arthroplasty procedures is increasing annually. The number of joint arthroplasty operations increased from 64,515 in 2010 to 85,592 in 2020. Tourniquet use during total knee arthroplasty (TKA) or total knee replacement (TKR) improves the surgical field of view [1,2] and facilitates cement injection. Additionally, it has the advantage of reducing the amount of bleeding [3] during and after surgery, and shortening operation times [4]. However, it can sometimes cause damage to nerves [5], blood vessels, and muscles, causing swelling or restrictions to the postoperative range of motion [6,7]. Several studies have demonstrated that pain and swelling after surgery can be reduced by reducing the tourniquet application time or lowering the tourniquet pressure [8], but this is still a controversial topic [2]. The typical duration of tourniquet application in TKA is from the beginning to the end of the procedure [9]. However, this tends to destabilize the patient's vital signs [10–12] and increase the amount of fluid or blood administered. Sudden restoration of blood flow after long-term tourniquet application may impair the circulation of blood to the cardiovascular system or cerebrovascular system, thereby worsening the patient's prognosis [13]. Reducing the tourniquet time or lowering the pressure may disturb the surgeon's field of view, increase the operation time, or reduce the accuracy of the operation [14]. Recently, during TKA at our hospital, we have been implementing a two-stage application process, involving tourniquet re-application after 15 min of tourniquet off-time after cement injection. In the past, the tourniquet was only applied until the injection of cement, but we switched to

the method of applying the tourniquet again after a 15 min tourniquet off-time, until skin closure. As the duration of uninterrupted tourniquet inflation increased the likelihood of neural dysfunction [15], it was expected that this method would reduce the amount of bleeding by applying the tourniquet until the end of skin closure, but would not increase the complications due to the 15 min resting period. In previous studies, the outcomes have been compared with a lack of tourniquet use [6], loosening the tourniquet after cement injection, or even after the skin incision [16,17]. However, to the best of our knowledge, no published studies have investigated the risks and benefits associated with tourniquet reapplication after an intra-operative rest period. This study analyzed differences in estimated blood volume loss, blood transfusion requirements, medications during and after surgery, and analgesic usage in the recovery room between patients who underwent TKA with tourniquet application until cement insertion (during the first 2 years in which we used this protocol) and patients who underwent TKA with two-stage tourniquet application (during the final 2 years in which our hospital used this protocol).

2. Materials and Methods

2.1. Patients

This retrospective, single-center cohort study was approved by Hanyang University Seoul Hospital's Institutional Review Board (HYUH 2021-08-041-003), which waived the requirement for written informed consent. The medical records of 506 patients who underwent elective TKA from January 2017 to December 2020 were assessed for eligibility, and 414 patients were enrolled. Eligible patients underwent unilateral TKA for the first time or contralateral TKA during one hospitalization. The exclusion criteria were revision operation, surgery on both legs at one time, and surgery under spinal anesthesia. All patients included in the study were operated on by a single senior orthopedic surgeon during this period.

The following two groups were compared according to the duration of tourniquet application: the first half (FH) course group versus the two-stage (TS) group. In the FH group, the tourniquet was inflated with a pressure of 300 mmHg after manual banding before the incision, and was deflated after cement insertion. After cement fixation, bleeding control, and muscle and skin closure were started. In the TS group, tourniquet inflation began and deflated at the same stage of the procedure as in the FH group. However, the tourniquet was deflated for 15 min (if the cement was fixed within 15 min, bleeding control was started) and then inflated again during muscle and skin closure; the tourniquet was deflated after skin closure.

2.2. Perioperative Anesthetic Care

After entering the operating room, all patients were monitored for blood pressure, heart rate, oxygen saturation, and anesthesia depth. Anesthesia induction was performed with 1–1.5 mg/kg propofol, along with 0.1 μg/kg/min remifentanil and sevoflurane. Anesthesia was maintained with inhalational anesthetic gas and remifentanil. Mechanical ventilation was delivered at a tidal volume of 6–8 mL/kg using a mixture of oxygen and medical air at a flow rate of 2–3 L/min. Arterial blood pressure was monitored via the right or left radial artery to evaluate the hemoglobin level. A 16 G large-bore angiocatheter was placed in the external jugular vein to infuse fluid and blood products. The target perioperative systolic arterial pressure was 80 to 160 mmHg, and, if necessary, cardiovascular agents, such as calcium channel blockers, beta-blockers, ephedrine, and phenylephrine, were used. After induction and during muscle closure, hemoglobin levels were checked via arterial blood analysis. Tranexamic acid was not used. If hemoglobin was less than 8 g/dL, packed red blood cells (RBCs) were transfused. One unit of packed RBCs was approximately 320 mL in volume, of which the red blood cell volume was 180 to 200 mL. Hemovac drain was placed under the skin at the end of the surgery.

2.3. Outcome Variables

The following variables were further evaluated: (1) pre-operative factors (age, sex, weight, height, and comorbidities); (2) intra-operative factors (perioperative hemoglobin level, tourniquet time, and use of cardiovascular agents); (3) post-operative factors (post-operative hemoglobin level, transfusion of packed RBCs, and use of analgesics).

2.4. Statistical Analysis

All statistical analyses were performed using SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as numbers and percentages. Continuous variables are reported as means ± standard deviations. Normally distributed data were evaluated with the Shapiro–Wilk test or the Kolmogorov–Smirnov test.

Primary outcomes (hemoglobin and estimated blood loss) were evaluated with the Mann–Whitney U test or independent *t*-test.

Demographic data, peri-operative data, and clinical outcomes between the two groups were analyzed using the chi-square test for categorical variables, and an independent samples *t*-test or Mann–Whitney U test for continuous variables. For skewed data, the Mann–Whitney U test was used. Differences in categorical variables were compared by the chi-square test or Fisher's exact test. A two-sided alpha of 0.05 was used for all statistical tests.

3. Results

A total of 414 cases of unilateral TKA surgery were reviewed. Among the 414 patients, one patient who underwent spinal anesthesia was excluded. There were 209 patients in the FH group and 204 patients in the TS group. In each group, we excluded 12 and 7 patients, respectively, for whom it was impossible to calculate the amount of bleeding, and 9 and 32 patients, respectively, with missing hemoglobin levels because laboratory tests were not performed in the recovery room immediately after surgery. We also excluded 11 patients from each group with outlying values of blood volume loss. Finally, data were analyzed for 331 operations (Figure 1).

There were no significant differences in age, height, or weight between the groups. There was no significant intergroup difference resulting from the independent samples *t*-test analysis. Cardiovascular diseases, such as hypertension, were more prevalent in the TS group. There were no significant differences between the groups in terms of patients who stopped taking anticoagulants that could affect the bleeding volume (Table 1). There was no significant intergroup difference in pre-operative hemoglobin level.

Intra-operative blood loss was calculated using the hemoglobin balance formula [3,18]. The FH group had a mean blood loss of 542.90 mL, and the TS group had a mean bleeding volume of 514.66 mL (Table 2).

$$\text{Hbloss total} = \text{BV} \times (\text{Hbi} - \text{Hbe}) \times 0.001 + \text{Hbt}.$$
$$\text{Vloss total} = 1000 \times \text{Hbloss total}/\text{Hbi}.$$
$$\text{Generally, 1 U banked blood is considered to contain } 52 \pm 5.4 \text{ g Hb}.$$
$$\text{BV} = \text{k1} \times \text{H3} + \text{k2} \times \text{W} + \text{k3}.$$
$$\text{For males, k1} = 0.3669, \text{ k2} = 0.03219, \text{ and k3} = 0.6041;$$
$$\text{For females, k1} = 0.3561, \text{ k2} = 0.03308, \text{ and k3} = 0.1833.$$

Vloss total (mL): the total volume of RBC loss;
Hbloss total (g): the loss volume of Hb;
Hbi (g/L): the Hb value before surgery;
Hbe (g/L): the Hb value after surgery;
Hbt (g): the total volume of blood transfusion.

There was no significant difference between the two groups in the proportions of patients who used antihypertensive drugs while using tourniquets, or those who used antihypertensive drugs after tourniquet removal (Table 3).

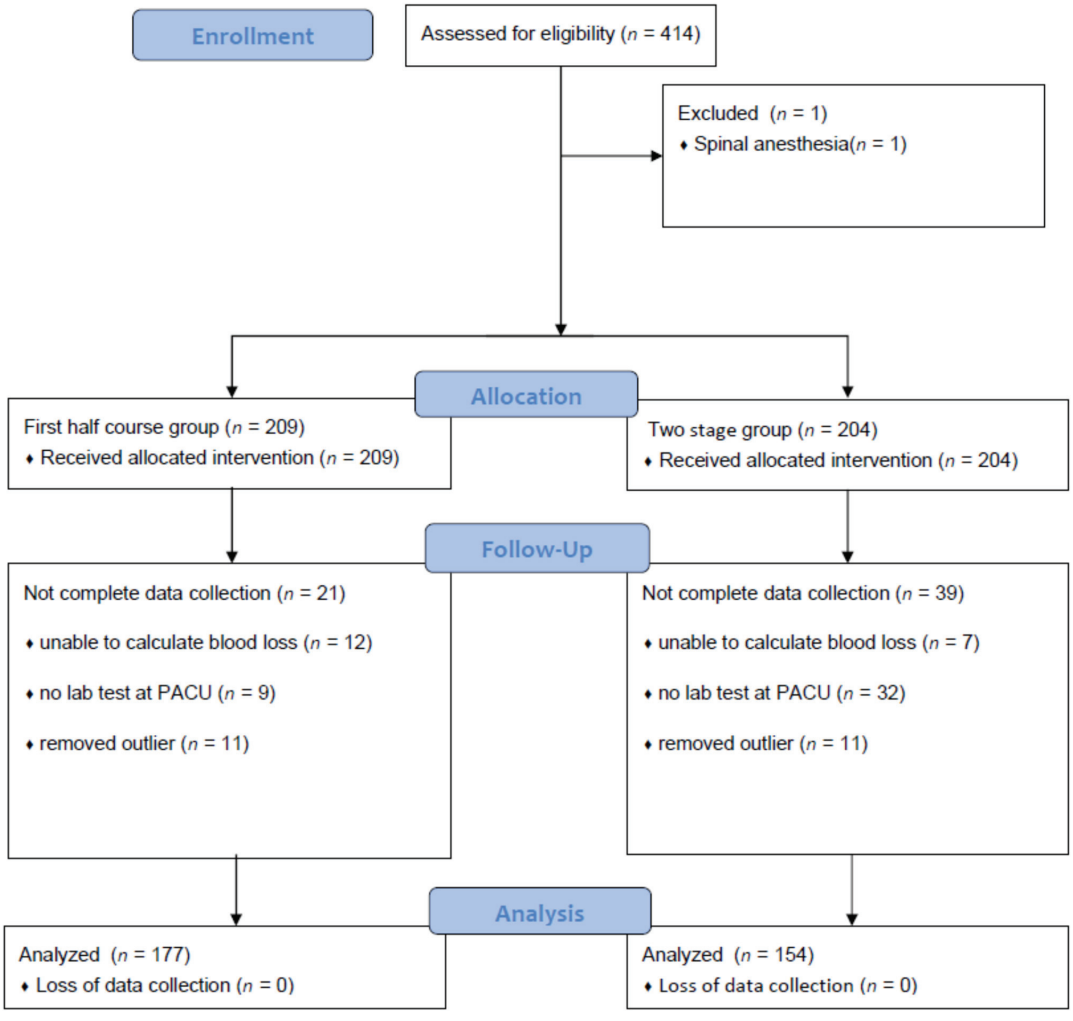

Figure 1. Flow diagram of patient selection.

Table 1. Characteristics of patients.

Variables	FH Group (*n* = 177)	TS Group (*n* = 154)	*p*-Value
Patient Characteristics			
Age	69.5 ± 8.3	69.9 ± 7.2	0.622
Height (cm)	155.1 ± 6.4	154.9 ± 7.7	0.756
Weight (kg)	62.0 ± 9.7	62.1 ± 9.2	0.899
Disease characteristics			
Hypertension	97	103	0.025
Diabetes Mellitus	39	35	0.880
Stroke	6	1	0.084
Chronic kidney disease	6	6	0.806
Angina, myocardial infarction	7	13	0.087
Taking anticoagulants	42	45	0.258
Pre-operative hemoglobin (g/dL)	12.9 ± 1.2	13.0 ± 1.1	0.589

Table 2. Estimated blood loss by hemoglobin balance formula.

Estimated Blood Loss	FH Group	TS Group
Volume (mL)	542.90 ± 274.77	514.66 ± 228.54

$p = 0.314$.

Table 3. The number of patients who needed medications.

Medications	FH Group (*n* = 177)	TS Group (*n* = 154)	*p*-Value
Type of Drugs			
Antihypertensive drug [1]	38	26	0.292
Vasopressor [2]	28	21	0.577

[1] nicardipine, labetalol, and esmolol; [2] phenylephrine and ephedrine.

Intra-operative transfusions were lower in the TS group. There was no statistically significant intergroup difference in transfusion volume in the recovery room, or in transfusion requirement in the ward after the surgery (Table 4). However, although not statistically significant, the transfusion volume in the ward was generally lower in the TS group than in the FH group.

Table 4. Transfused blood units during and after the surgery.

Transfused Blood (Number of Patients)	FH Group	TS Group	*p*-Value
Intra-operatively	0(149) 1(26) 2(2)	0(151) 1(3) 2(0)	0.000
In the post-anesthesia care unit	0(174) 1(3)	0(153) 1(1)	0.385
In the ward post-operatively	0(153) 1(12) 2(12)	0(140) 1(11) 2(3)	0.108

The hemoglobin values were compared intra-operatively and in the post-anesthesia care unit. The hemoglobin values were similar in both groups (Table 5).

Table 5. Hemoglobin values during and after the surgery.

Hemoglobin Values (g/dL)	FH Group	TS Group	*p*-Value
Intra-operatively (initial)	11.8 ± 1.1	11.8 ± 1.0	0.435
Intra-operatively (last)	10.5 ± 1.0	10.4 ± 1.0	0.403
In the post-anesthesia care unit	11.3 ± 1.0	11.2 ± 1.0	0.246

Since the estimated blood loss and hemoglobin values do not differ significantly between the two groups, an analysis of the intergroup differences was performed on data for transfused patients and non-transfused patients (Table 6).

Table 6. Hemoglobin values of transfused and non-transfused patients.

Hemoglobin Values (g/dL)	Non-Transfused Group (*n* = 300)	Transfused Group (*n* = 31)	*p*-Value
Pre-operative	13.1 ± 1.0	11.7 ± 1.0	0.000
Intra-operatively (initial)	11.9 ± 1.0	10.5 ± 0.8	0.000

Pre-operative hemoglobin and initial intra-operative hemoglobin were significantly lower in transfused patients. Lower hemoglobin values were related to intra-operative transfusion.

The total opioid usage was compared in terms of fentanyl dose (Table 7). Pethidine 25 mg was converted to fentanyl 25 μg equivalents. The analgesic demand was relatively larger in the TS group, but the intergroup difference was not statistically significant.

Table 7. Opioid usage at post-anesthesia care unit.

Opioid Use (μg)	FH Group	TS Group
Fentanyl Equivalent	76.2 ± 43.9	84.4 ± 56.1

$p = 0.147$.

There was no significant difference between the ischemic time from the first tourniquet in the TS group versus the total tourniquet time in the FH group (Table 8).

Table 8. Durations of tourniquet applications.

Time (min)	FH Group (*n* = 177)	TS Group (*n* = 154)	*p*-Value
Tourniquet applied			
1st	89.0 ± 17.2	89.6 ± 16.6	0.747
2nd	-	25.4 ± 8.2	

4. Discussion

Intra-operative tourniquet use has been studied extensively. Tourniquets are used in most operations because it is thought that they help secure the field of view and shorten operation times accordingly. However, it is known that skin blistering, wound hematoma, wound oozing, muscle injury, rhabdomyolysis, nerve palsy, postoperative stiffness, deep vein thrombosis, and pulmonary embolism [6] may be associated with tourniquet use. At our hospital, we investigated associations between the method of tourniquet use in TKA operations and blood loss, need for medication, and opioid consumption.

The reason we first introduced this method was that events such as a gradual decrease in the patient's blood pressure sometimes occurred at the time of suture. Therefore, we assumed that if the tourniquet was applied again, the amount of bleeding at the time of muscle and skin suturing could be reduced, even if only a little.

In a previous study [16], a significantly reduced bleeding volume was associated with prolonged tourniquet application. In our study, there was no significant difference in the amount of intra-operative bleeding between the FH and TS groups, despite a slightly lower amount of blood loss in the TS group. Significantly, lower levels of intra-operative bleeding have been associated with tourniquet application compared with when tourniquets are not used [6]. In previous studies, the mean blood loss volumes when using tourniquets have varied from 25.6 mL to 350 mL. In our study, the estimated mean blood loss was 542.90 mL in the FH group, compared with 514.66 mL in the TS group.

Blood loss estimates vary greatly from study to study because of differences between studies in the formulas used to calculate the amount of bleeding. According to one study [18], the different mean values obtained ranged from 971 mL to 1699 mL, depending on which of the four formulas was used to calculate the bleeding volume. In this study, the amount of bleeding was estimated using the hemoglobin balance formula.

As for transfusion requirements, the proportion of patients who underwent intra-operative transfusion was statistically significantly higher in the FH group. There was no statistically significant intergroup difference in post-operative blood transfusion requirements in the post-anesthesia care unit or ward, but, on average, they were lower in the TS group. As can be observed from the results, the pre-operative hemoglobin and initial intra-operative hemoglobin were significantly lower in transfused patients. The reason that the proportion of patients who needed transfusion was higher in the FH group might be related to the incidence of patients who had lower hemoglobin levels. Although additional research is needed to determine what levels of pre-operative hemoglobin increase the possibility of transfusion, if the patient's hemoglobin is not high, preparing packed red blood cells in advance might be a better option.

In a comparative study of tourniquet application versus non-application, the amount of bleeding during surgery was small in the tourniquet group, but the amount of bleeding after surgery showed mixed results [19]. However, if blood transfusions could be reduced, even during surgery, this might help to reduce the complications associated with blood transfusions, such as urticaria, anaphylaxis, transfusion-related acute lung injury, and hypothermia [20].

In this study, the total operation time was around 130 min. In previous studies [19], the operation time varies greatly from 73 to 163 min.

Prolonged tourniquet use increases the patient's blood pressure and pulse rate, which, in turn, causes severe hypotension after turning the tourniquets off. It is known that the relative mortality risk increases by 3.6% for every minute of hypotension, which is defined as an SBP of less than 80 mmHg [21]. Despite the fact that about 20 min of tourniquet time was added, in this study, the need for anti-hypertensive drugs, such as nicardipine or beta-blockers, to lower the blood pressure during tourniquet use, or the need for vasopressors, such as ephedrine or phenylephrine, after tourniquet release, were not significantly different between the two groups. The rest period in the middle is thought to be helpful for preventing hemodynamic insults that blunt the sympathetic activity [22] of tourniquet use throughout an entire operation. As this was a retrospective study, the blood pressure and heart rate at the exact time before and after tourniquet removal were not recorded. Usually, the anesthetic record is completed every 5 min, so the exact time of vital signs could not be determined.

In addition, there was no significant intergroup difference in the amount of analgesic used in the recovery room after surgery, so it is thought that there was no significant difference in the pain felt by the patients. The relationship between the initial visual analog scale score and subsequent opioid requirement is depicted by a sigmoid curve [23].

Through this retrospective study, we could not find a significant correlation between the method of tourniquet use and the amount of bleeding in TKA. However, it is widely thought that tourniquet use is associated with small volumes of blood transfusion.

There were some limitations to this study.

First, this study was not a randomized controlled trial. However, there was no statistically significant difference in age or body mass index between the two patient groups, and there was no significant difference between the two groups in the number of patients who used anticoagulants that could affect the amount of bleeding.

Second, since this was a retrospective study, it was not possible to set standards for the use of vasopressors or transfusions during or after surgery. However, the groups did not significantly differ in this regard.

A well-designed randomized controlled trial is needed to further investigate the two-stage application of tourniquets.

5. Conclusions

The two-stage tourniquet technique was not related to reduced total blood loss in total knee replacement.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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References

1. Zak, S.G.; Yeroushalmi, D.; Long, W.J.; Meftah, M.; Schnaser, E.; Schwarzkopf, R. Does the Use of a Tourniquet Influence Outcomes in Total Knee Arthroplasty: A Randomized Controlled Trial. *J. Arthroplast.* **2021**, *36*, 2492–2496. [CrossRef]
2. Cao, Q.; He, Z.; Fan, Y.; Meng, J.; Yuan, T.; Zhao, J.; Bao, N. Effects of tourniquet application on enhanced recovery after surgery (ERAS) and ischemia-reperfusion post-total knee arthroplasty: Full- versus second half-course application. *J. Orthop. Surg.* **2020**, *28*, 1–8. [CrossRef]
3. Hamawandi, S.A.; Amin, H.I.; Al-Humairi, A.K. Effects of the Use of Tourniquet in Total Knee Arthroplasty on the Clinical and Functional Outcomes with 5 Years of Follow-up: A Randomized Controlled Trial. *J. Knee Surg.* **2021**, *1*. [CrossRef]
4. Cai, D.F.; Fan, Q.H.; Zhong, H.H.; Peng, S.; Song, H. The effects of tourniquet use on blood loss in primary total knee arthroplasty for patients with osteoarthritis: A meta-analysis. *J. Orthop. Surg. Res.* **2019**, *14*, 348. [CrossRef]
5. Olivecrona, C.; Blomfeldt, R.; Ponzer, S.; Stanford, B.R.; Nilsson, B.Y. Tourniquet cuff pressure and nerve injury in knee arthroplasty in a bloodless field: A neurophysiological study. *Acta Orthop.* **2013**, *84*, 159–164. [CrossRef]
6. Ahmed, I.; Chawla, A.; Underwood, M.; Price, A.J.; Metcalfe, A.; Hutchinson, C.E.; Warwick, J.; Seers, K.; Parsons, H.; Wall, P.D.H. Time to reconsider the routine use of tourniquets in total knee arthroplasty surgery. *Bone Jt. J.* **2021**, *103*, 830–839. [CrossRef]
7. Olivecrona, C.; Lapidus, L.J.; Benson, L.; Blomfeldt, R. Tourniquet time affects postoperative complications after knee arthroplasty. *Int. Orthop.* **2013**, *37*, 827–832. [CrossRef]
8. Olivecrona, C.; Ponzer, S.; Hamberg, P.; Blomfeldt, R. Lower tourniquet cuff pressure reduces postoperative wound complications after total knee arthroplasty: A randomized controlled study of 164 patients. *JBJS* **2012**, *94*, 2216–2221. [CrossRef]
9. Migliorini, F.; Maffulli, N.; Aretini, P.; Trivellas, A.; Tingart, M.; Eschweiler, J.; Baroncini, A. Impact of tourniquet during knee arthroplasty: A bayesian network meta-analysis of peri-operative outcomes. *Arch. Orthop. Trauma Surg.* **2021**, *141*, 1007–1023. [CrossRef]
10. Kim, K.S.; Min, H.K.; Youn, H.J.; Cheong, M.A.; Jun, J.H. The Hemodynamic Effects of a Tourniquet Application during Knee Surgery in Elderly Patients with Hypertension. *Korean J. Anesth.* **2006**, *51*, 695–700. [CrossRef]
11. Girardis, M.; Milesi, S.; Donato, S.; Raffaelli, M.; Spasiano, A.; Antonutto, G.; Pasqualucci, A.; Pasetto, A. The Hemodynamic and Metabolic Effects of Tourniquet Application during Knee Surgery. *Anesth. Analg.* **2000**, *91*, 727–731. [CrossRef]

12. Song, I.; Kim, D.Y.; Kim, Y.J. The effect of tourniquet deflation on hemodynamics and regional cerebral oxygen saturation in aged patients undergoing total knee replacement surgery. *Korean J. Anesthesiol.* **2012**, *63*, 425–430. [CrossRef]
13. Huh, I.Y.; Kim, D.-Y.; Lee, J.-H.; Shin, S.J.; Cho, Y.W.; Park, S.E. Relation between preoperative autonomic function and blood pressure change after tourniquet deflation during total knee replacement arthroplasty. *Korean J. Anesthesiol.* **2012**, *62*, 154–160. [CrossRef]
14. Pinsornsak, P.; Pinitchanon, P.; Boontanapibul, K. Effect of Different Tourniquet Pressure on Postoperative Pain and Complications After Total Knee Arthroplasty: A Prospective, Randomized Controlled Trial. *J. Arthroplast.* **2021**, *36*, 1638–1644. [CrossRef]
15. Horlocker, T.T.; Hebl, J.R.; Gali, B.; Jankowski, C.J.; Burkle, C.M.; Berry, D.J.; Zepeda, F.A.; Stevens, S.R.; Schroeder, D.R. Anesthetic, Patient, and Surgical Risk Factors for Neurologic Complications After Prolonged Total Tourniquet Time during Total Knee Arthroplasty. *Anesth. Analg.* **2006**, *102*, 950–955. [CrossRef]
16. Vaishya, R.; Agarwal, A.K.; Vijay, V.; Tiwari, M.K. Short term outcomes of long duration versus short duration tourniquet in primary total knee arthroplasty: A randomized controlled trial. *J. Clin. Orthop. Trauma* **2018**, *9*, 46–50. [CrossRef]
17. Wang, C.; Zhou, C.; Qu, H.; Yan, S.; Pan, Z. Comparison of tourniquet application only during cementation and long-duration tourniquet application in total knee arthroplasty: A meta-analysis. *J. Orthop. Surg. Res.* **2018**, *13*, 1–10. [CrossRef]
18. Gao, F.Q.; Li, Z.J.; Zhang, K.; Sun, W.; Zhang, H. Four methods for calculating blood-loss after total knee arthroplasty. *Chin. Med. J.* **2015**, *128*, 2856–2860. [CrossRef]
19. Zhang, W.; Li, N.; Chen, S.; Tan, Y.; Al-Aidaros, M.; Chen, L. The effects of a tourniquet used in total knee arthroplasty: A meta-analysis. *J. Orthop. Surg. Res.* **2014**, *9*, 13. [CrossRef]
20. Sahu, S.; Hemlata; Verma, A. Adverse events related to blood transfusion. *Indian J. Anaesth.* **2014**, *58*, 543–551. [CrossRef]
21. Monk, T.G.; Saini, V.; Weldon, B.C.; Sigl, J.C. Anesthetic Management and One-Year Mortality after Noncardiac Surgery. *Anesth. Analg.* **2005**, *100*, 4–10. [CrossRef]
22. Kim, E.; Cho, M.R.; Byun, S.H.; Lim, J.A.; Chae, S.; Choi, W.K.; Kim, I.; Kim, J. Sympathetic predominance before tourniquet deflation is associated with a reduction in arterial blood pressure after tourniquet deflation during total knee arthroplasty. *Physiol. Res.* **2021**, *70*, 401–412. [CrossRef]
23. Aubrun, F.; Langeron, O.; Quesnel, C.; Coriat, P.; Riou, B. Relationships between Measurement of Pain Using Visual Analog Score and Morphine Requirements during Postoperative Intravenous Morphine Titration. *Anesthesiology* **2003**, *98*, 1415–1421. [CrossRef]

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Perioperative Supplemental Oxygen and Plasma Catecholamine Concentrations after Major Abdominal Surgery—Secondary Analysis of a Randomized Clinical Trial

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Abstract: Perioperative stress is associated with increased sympathetic activity that leads to increases in heart rate and blood pressure, which are associated with the development of perioperative myocardial ischemia. In healthy volunteers, it was shown that the administration of supplemental oxygen attenuated sympathetic nerve activity and subsequently led to lower plasma catecholamine concentrations. We therefore tested the hypothesis that perioperative supplemental oxygen attenuates sympathetic nerve in patients at risk for cardiovascular complications undergoing major abdominal surgery. We randomly assigned 81 patients to receive either 80% or 30% inspired oxygen concentration throughout surgery and the first two postoperative hours. We assessed noradrenaline, adrenaline, and dopamine plasma concentrations before the induction of anesthesia, two hours after surgery and on the third postoperative day. There was no significant difference in postoperative noradrenaline (effect estimated: −41.5 ng·L^{-1}, 95%CI −134.3, 51.2; p = 0.38), adrenaline (effect estimated: 11.2 ng·L^{-1}, 95%CI −7.6, 30.1; p = 0.24), and dopamine (effect estimated: −1.61 ng·L^{-1}, 95%CI −7.2, 3.9; p = 0.57) concentrations between both groups. Based on our results, it seems unlikely that supplemental oxygen influences endogenous catecholamine release in the perioperative setting.

Keywords: catecholamines; supplemental oxygen; major abdominal surgery; cardiovascular risk; MINS

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1. Introduction

Surgery is associated with an increased stress response that triggers sympathetic nerve activity, leading to an increased release of endogenous plasma catecholamines [1,2]. This causes a significant increase in heart rate and blood pressure, which has been shown to be associated with a higher risk of developing myocardial injury after non-cardiac surgery (MINS) [2–4]. Moreover, in the non-operating setting, elevated endogenous plasma catecholamine levels are associated with the development and progression of cardiac related diseases [5,6].

The effect of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE-1) trial has shown that perioperative sympathetic nerve blockade with metoprolol significantly decreased the incidence of postoperative myocardial infarction in patients undergoing noncardiac surgery [3]. The authors suggested that a decrease of heart rate and blood pressure is associated with a simultaneous decrease in myocardial oxygen

consumption that consequently resulted in a lower incidence of myocardial perfusion-related complications [3]. Additionally, higher plasma catecholamine levels stimulate platelet aggregation, which is another trigger factor for the development of acute coronary stenosis [2,7,8]. Moreover, another study has shown that hypertension causes endovascular shear stress that might further be a contributing factor for the development and progression of myocardial ischemia [2].

Higher oxygen concentrations are still commonly administered during surgery and recommended by the WHO to reduce the risk of postoperative wound infections [9]. Therefore, it is still of clinical interest if the perioperative administration of supplemental oxygen also attenuates the effect of sympathetic nerve activity, specifically in patients at risk for cardiovascular complications undergoing major abdominal surgery.

In this context, we tested the hypothesis that the perioperative administration of 80% oxygen leads to a significant decrease in postoperative sympathetic nerve activity, which was assessed with consecutive plasma adrenaline, noradrenaline, and dopamine concentration measurements, as compared to the administration of 30% oxygen in patients at risk for cardiovascular complications undergoing major abdominal surgery. Moreover, to evaluate the association between plasma catecholamine concentrations and the incidence of MINS, we compared the plasma catecholamine concentrations between patients who developed MINS and patients who did not develop MINS in the first three postoperative days.

2. Materials and Methods

2.1. Study Design and Participants

This is a pre-planned secondary analysis of a single-center, double-blinded, randomized clinical trial, which investigated the effect of supplemental oxygen on maximum postoperative NT-proBNP concentrations in patients at risk for cardiovascular complications undergoing major abdominal surgery. The trial was conducted at the Medical University of Vienna [10]. The trial was approved by the local Institutional Review Board and was registered at ClinicalTrials.gov (NCT 03366857) and at the European Clinical Trial Database (EudraCT 2017-003714-68). The study protocol was published previously [11]. In our main trial, we did not observe a significant difference in maximum postoperative NT-proBNP concentrations between patients receiving 80% and 30% oxygen for the duration of surgery and the first two postoperative hours [10]. We also did not observe a significant difference in the incidence of MINS between both groups [10].

We obtained written informed consent from all patients before randomization. We included 82 consecutive patients for serum catecholamine measurements, who were enrolled into the main study and scheduled for major abdominal surgery expected to last at least 2 h. Eligible patients were over 45 years of age and underwent major abdominal surgery under general anesthesia. For study inclusion, patients had to meet at least one of the following criteria: 1. history of coronary disease; 2. history of peripheral arterial disease; 3. history of stroke; OR 4. any three of the following six criteria (a–f): (a) age over 70 years; (b) undergoing major surgery; (c) history of congestive heart failure; (d) history of transient ischemic attack; (e) diabetes and currently taking an oral hypoglycemic agent or insulin; (f) history of hypertension. Patients meeting the following criteria were excluded from this study: 1. sepsis; 2. preoperative inotropic therapy; 3. oxygen dependent patients; 4. history of severe heart failure (defined as ejection fraction <30%).

2.2. Randomization

We randomized patients using a web-based randomization program (Randomizer, Medical University of Graz, Graz, Austria, https://www.meduniwien.ac.at/randomizer/web; last accessed on 5 November 2019). The randomization sequence was generated by the study statistician using permutated blocks. Each block had a size of six numbers, of which all investigators were unaware. There was no stratification of randomization.

Shortly before the induction of anesthesia, we randomized patients to receive either 80% or 30% inspired oxygen concentration throughout surgery and for two hours post-

operatively. After endotracheal intubation, patients in the 80% oxygen group received an inspired oxygen fraction of 0.8 throughout surgery and 8 L/min oxygen via facemask with reservoir for the first two postoperative hours. Patients in the 30% oxygen group received an inspired oxygen fraction of 0.3 throughout surgery and 3 L/min oxygen via facemask without a reservoir for the first two postoperative hours. If needed, oxygen fraction was increased at the discretion of the attending anesthetist according to a predefined algorithm [11].

The trial was conducted according to the original protocol [11]. The protocol for the induction and maintenance of anesthesia was published previously [11]. During the perioperative period, pain was treated according to our local clinical standard. In detail, all patients received metamizole or another non-steroid anti-inflammatory drug in the recovery room. If the visual analogue pain score (VAS) was over 4, we additionally administered piritramide.

2.3. Measurements

We recorded demographic data, including age, sex, BMI, the American Society of Anesthesiologists (ASA) physical status, comorbidities, long-term medication, type of surgery, and preoperative laboratory values. We also recorded routine intraoperative variables, including the duration of anesthesia and surgery, fluid and anesthesia management, and hemodynamic parameters and blood gas analysis. We performed blood gas analysis hourly. Blood pressure and oxygen saturation were recorded intraoperatively and for the first two postoperative hours. Intraoperative core temperature was measured at the distal esophagus. We also recorded the amount of piritramide and fluids administered during the first three postoperative days on the ward.

Blinded research personnel drew all study specific pre- and postoperative blood samples. In all patients, noradrenaline, adrenaline, and dopamine plasma concentrations were assessed shortly before the induction of anesthesia, within two hours after the end of surgery and on the third postoperative day. Troponin T concentrations for MINS diagnosis were measured shortly before the induction of anesthesia, within two hours after the end of surgery, on the first, and on the third postoperative day.

All laboratory measurements were performed by the department for laboratory medicine at the Medical University of Vienna.

2.4. Data Management

Blinded research personnel obtained all postoperative data. All data were recorded and stored in the data management system 'Clincase', v2.7.0.12 hosted by IT Systems & Communications, Medical University of Vienna, Vienna, Austria.

2.5. Statistical Analysis

We performed intention-to-treat analysis according to the allocated randomization. Statistical analyses were performed with SPSS (Version 26, IBM SPSS Statistic, Armonk, NY, USA). The continuous variables were summarized using mean, standard deviation (SD), median, quartiles (25th percentile; 75th percentile), as well as minimum and maximum values. Descriptive statistics are given for randomized groups separately. Categorical variables were summarized using absolute and percent values.

2.6. Plasma Catecholamines

For each plasma catecholamine, we performed a repeated-measure mixed linear model to calculate the estimates and confidence intervals for the effect of 80% versus 30% oxygen concentration on postoperative noradrenaline, adrenaline, and dopamine plasma concentrations. Oxygen concentrations were defined as fixed effects. Furthermore, values per time point were compared between groups using two-tailed Mann-Whitney U tests.

2.7. Post-Hoc Analysis

To evaluate, if patients with MINS had higher stress levels represented by significantly increased plasma catecholamines concentrations, we further stratified our patients into patients with MINS and no-MINS. Therefore, we evaluated differences in maximum plasma catecholamine concentrations between MINS and no-MINS using a Mann-Whitney U test. Maximum plasma catecholamine concentrations were used to reflect the impact of MINS on the stress response. MINS was defined as an elevated postoperative high-sensitivity Troponin T concentration of 20–65 ng/L with an absolute change of at least 5 ng/L from the preoperative value or a concentration exceeding 65 ng/L regardless of the baseline value, in the absence of nonischemic causes (sepsis, atrial fibrillation, pulmonary embolism) [12].

2.8. Sample Size

This is a secondary analysis of a randomized controlled clinical trial [10]. The estimated number of patients required for this secondary analysis was based on a previous study that evaluated the effect of surgery on postoperative plasma catecholamine concentrations [1]. The study showed that postoperative plasma noradrenaline increased on the second postoperative day to 676 ng·L^{-1} (±210 ng·L^{-1}) as compared to preoperative baseline values [1]. We assumed a similar postoperative increase in our 30% oxygen group and anticipated a clinically meaningful lower increase of 20% in our 80% oxygen group. Thus, we calculated that at least 39 patients per group are necessary to have 80% power to detect a significant difference at an alpha of 0.05. To compensate for potential dropouts, we included 41 patients per group.

3. Results

We enrolled 82 consecutive patients, who were enrolled in the main trial, undergoing major abdominal surgery at risk for cardiovascular complications from December 2017 to July 2018. One patient in the 30% oxygen group was excluded after randomization because surgery was postponed. Overall, 41 patients were randomly assigned to receive 80% inspired oxygen concentration and 40 patients to receive 30% inspired oxygen concentration throughout surgery and for two hours postoperatively (Figure 1).

The patient characteristics, ASA physical status, comorbidities, long-term medication, type of surgery, and baseline laboratory parameters were similar between both groups (Table 1). Similarly, intraoperative and postoperative variables, such as duration of anesthesia and surgery, fluid management, anesthesia management, hemodynamic parameters, and arterial blood gas analysis, were balanced between both groups. The number of patients requiring intraoperative vasopressors, as well as the overall amount of vasopressors administered were similar between both study groups (Table 2). Postoperative heart rate did not differ between the groups. Postoperative mean arterial pressure was significantly higher in the 30% oxygen group. There was also no significant difference in fluid and opioid administration within the first three postoperative days (Table 2).

3.1. Plasma Catecholamine Concentrations

The administration of supplemental oxygen did not result in a significant difference in the postoperative plasma noradrenaline (effect estimated: −41.5 ng·L^{-1}, 95% CI −134.3, 51.2; p = 0.38), adrenaline (effect estimated: 11.2 ng·L^{-1}, 95% CI −7.6, 30.1; p = 0.24), and dopamine (effect estimated: −1.61 ng·L^{-1}, 95% CI −7.2, 3.9; p = 0.57) concentrations (Figure 2a–c) between the 80% and 30% oxygen groups within the first three postoperative days. Plasma catecholamine concentrations measured at each time point are shown in Table 3.

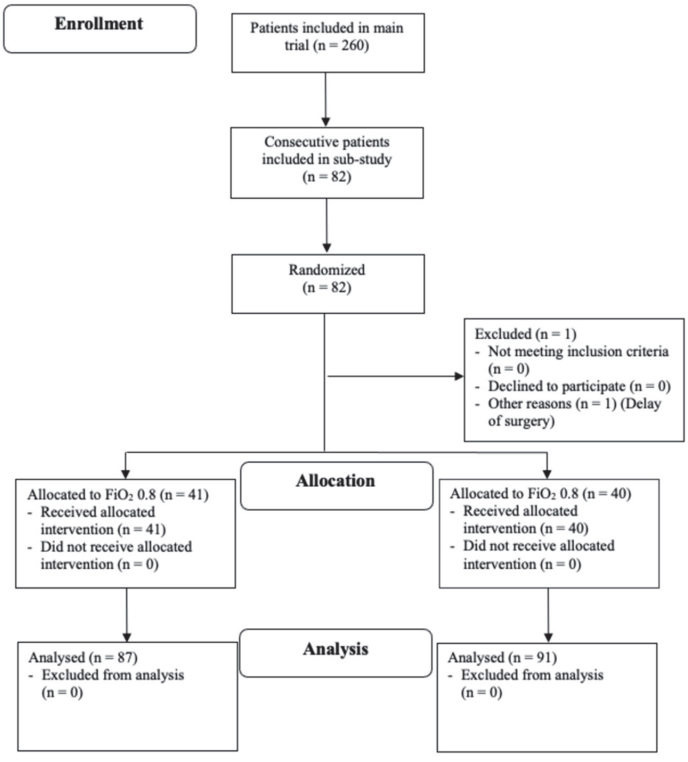


Figure 1. Patient Flow Diagram; Design and Form in Accordance with the 2010 CONSORT Guidelines [13].

Table 1. Summary characteristics are presented as counts, percentages of patients, and median (25th quartile; 75th quartile). BMI, body mass index; ASA, American Society of Anesthesiologists physical status; ACI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; NT-proBNP, N-terminal brain natriuretic peptide.

Patient Characteristics				
	80% Oxygen (*n* = 41)		**30% Oxygen (*n* = 40)**	
Age, years	75	(70; 78)	73	(69; 77)
Height, cm	170	(167; 175)	174	(168; 179)
Weight, kg	80	(72; 88)	84	(77; 92)
BMI, $kg \cdot m^{-2}$	26.8	(24.1; 29.8)	27.6	(25.2; 29.9)
Sex, *n* (%)				
Women	15	(36.7)	9	(22.5)
Men	26	(63.3)	31	(77.5)
ASA physical status, *n* (%)				
II	13	(36.6)	16	(40)
III	28	(63.4)	24	(60)
Comorbidities, *n* (%)				
Hypertension	39	(95.1)	36	(90.0)
Coronary artery disease	9	(21.9)	8	(20.0)
Peripheral artery disease	6	(14.6)	5	(12.5)

Table 1. *Cont.*

Patient Characteristics				
	80% Oxygen (n = 41)		30% Oxygen (n = 40)	
Stroke	5	(12.2)	4	(10.0)
Congestive heart failure	3	(7.3)	3	(7.5)
Transient ischemic attack	1	(2.4)	6	(15.0)
Insulin use	13	(31.7)	12	(30.0)
Long-term medication, *n* (%)				
Beta blockers	17	(41.5)	16	(40.0)
ACI/ARB	24	(58.5)	21	(52.5)
Diuretics	12	(29.3)	6	(15.0)
Statins	20	(48.8)	18	(45.0)
Acetylsalicylic acid	2	(4.9)	3	(7.5)
Oral anticoagulant	18	(43.9)	15	(37.5)
Alpha 2 agonist	1	(2.4)	2	(5.0)
Type of Surgery, (%)				
Hepatobiliary	8	(19.5)	7	(17.5)
Colorectal	9	(22.0)	8	(20.0)
Pancreatic	6	(14.6)	3	(7.5)
Urological	12	(29.3)	19	(47.5)
Other	6	(14.6)	3	(7.5)
Laboratory parameters				
CRP, $mg \cdot dL^{-1}$	0.33	(0.19; 1.43)	0.26	(0.12; 0.58)
Creatinine, $mg \cdot dL^{-1}$	0.9	(0.8; 1.0)	0.9	(0.8; 1.1)
Leukocytes, $G \cdot L^{-1}$	6.61	(5.42; 8.60)	6.58	(5.03; 8.07)
NT-proBNP, $pg \cdot mL^{-1}$	280	(97; 533)	128	(69; 391)
Troponin T, $ng \cdot L^{-1}$	14	(11; 22)	15	(9; 22)

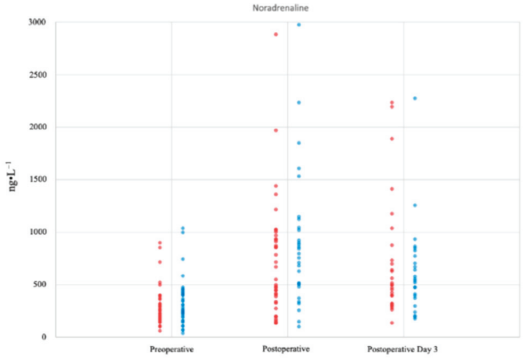
Table 2. Summary characteristics of perioperative variables are presented as medians (25th quartile; 75th quartile). All *p*-values are for two-tailed Mann-Whitney U tests or chi-square tests according to the distribution of data. etSevo, end-tidal Sevoflurane concentration; FiO_2, fraction of inspired oxygen; $etCO_2$, end-tidal carbon dioxide concentration; HR, heart rate; MAP mean arterial pressure; SV, stroke volume; CO, cardiac output; CVP, central venous pressure; pO_2, oxygen partial pressure; pCO_2, carbon dioxide partial pressure; SpO_2, peripheral oxygen saturation; BE, base excess; Hb, hemoglobin; VAS, visual analog scale.

Perioperative Variables					
	80% Oxygen (n = 41)		30% Oxygen (n = 40)		p-Value
Intraoperative					
Duration of anesthesia, min	264	(191; 403)	215	(177; 287)	0.06
Duration of surgery, min	207	(134; 329)	152	(129; 233)	0.17
Fluid management					
Crystalloid, mL	2237	(1262; 3538)	1936	(1396; 2696)	0.41
Blood loss, mL	200	(0; 500)	200	(0; 500)	0.78
Urine output, mL	245	(150; 400)	225	(285; 400)	0.83
Anesthesia management					
Fentanyl, mcg	1100	(863; 1488)	1050	(800; 1500)	0.60
Propofol, mg	145	(70; 160)	150	(100; 200)	0.15
Phenylephrine, mg	0.25	(0.10; 0.58)	0.20	(0.08; 0.52)	0.56
Noradrenaline, mg	0.0	(0.0; 1.0)	0.0	(0.0; 0.3)	0.10
etSevo, %	1.3	(1.0; 1.5)	1.2	(0.7; 1.4)	0.18
FiO_2, %	81	(80; 81)	32	(31; 68)	
$etCO_2$, mmHg	35	(34; 36)	34	(32; 36)	0.18
Core temp, °C	36.2	(35.9; 36.8)	36.4	(36.2; 36.9)	0.55

Table 2. *Cont.*

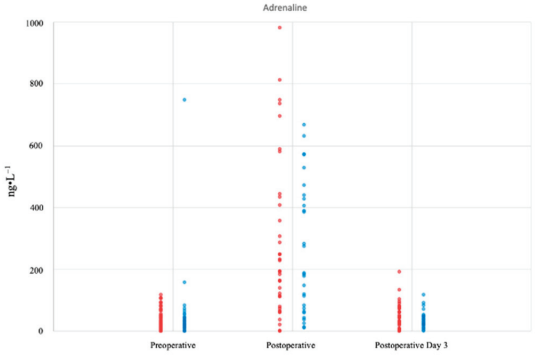
Perioperative Variables					
	80% Oxygen (n = 41)		30% Oxygen (n = 40)		p-Value
Hemodynamic Parameters					
HR, beats·min^{-1}	62	(58; 69)	73	(62; 84)	0.59
MAP, mmHg	79	(74; 90)	91	(85; 95)	0.42
SV, mL	77	(55; 81)	52	(30; 67)	0.22
CO, L·min^{-1}	4.7	(3.7; 5.4)	3.3	(1.9; 4.5)	0.12
CVP, mmHg	12	(8; 15)	11	(8; 20)	0.69
Arterial Blood Gas Analysis					
pO_2, mmHg	158	(112; 195)	91	(75; 155)	<0.05
pCO_2, mmHg	43	(39; 52)	49	(46; 60)	0.50
SpO_2, %	100	(99; 100)	98	(97; 99)	<0.001
pH	7.34	(7.28; 7.38)	7.31	(7.25; 7.34)	0.33
BE	−1.9	(−4.6; −0.7)	−1.2	(−3.3; −0.1)	0.25
Hb, g·dL^{-1}	11.8	(10.4; 12.5)	13.4	(11.1; 13.9)	0.31
Lactate, mmol·L^{-1}	0.8	(0.6; 1.0)	1.6	(0.9; 2.3)	0.53
Glucose, mg·dL^{-1}	163	(150; 184)	155	(123; 175)	0.31
2 h postoperative					
Hemodynamic Parameters					
HR, beats·min^{-1}	75	(60; 88)	82	(64; 90)	0.41
MAP, mmHg	86	(75; 103)	109	(98; 122)	<0.001
SpO_2, %	99	(97; 99)	98	(97; 99)	0.11
VAS	2	(0; 4)	2	(0; 4)	0.88
PONV					
Dexamethasone, n (%)	29	(70.7)	35	(87.5)	0.10
PONV, n (%)	4	(9.8)	5	(12.5)	0.74
Ondansetron, n (%)	10	(24.4)	12	(30.0)	0.62
Amount per capita, mg	4	(4; 5)	4	(4; 5)	0.84
Droperidol, n (%)	2	(4.9)	3	(7.5)	0.68
Amount per capita, mg	1.25	(1.25; 1.25)	1.25	(1.25; 1.25)	1.00
72 h postoperative					
Fluid, mL [a]	10,400	(7417; 12,525)	9471	(7013; 11,526)	0.58
Piritramide, mg [b]	12.0	(4.5; 22.0)	8.3	(3.0; 21.8)	0.65

[a] overall amount of fluid administered during the first 72 h after surgery. [b] overall amount of piritramide administered during the first 72 h after surgery.

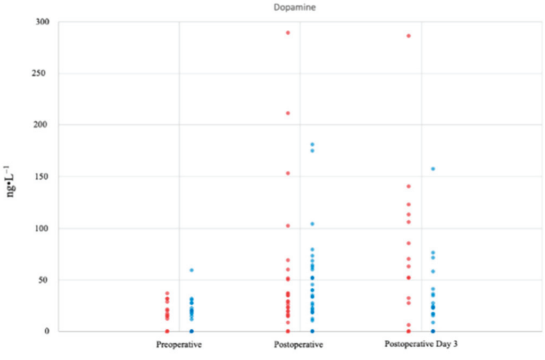


(**a**)

Figure 2. *Cont.*



(**b**)



(**c**)

Figure 2. Plots showing the perioperative course of plasma noradrenaline (**a**), adrenaline (**b**), and dopamine (**c**) concentrations between patients who received 80% oxygen (blue) and patients who received 30% oxygen (red). Each circle represents one patient at each timepoint.

Table 3. Plasma catecholamine concentrations at each timepoint are presented as median (25th quartile; 75th quartile). All *p*-values are for two-tailed Mann-Whitney U tests.

Plasma Catecholamine Concentrations					
	80% Oxygen (n = 41)		**30% Oxygen (n = 40)**		***p*-Value**
Noradrenaline, ng·L^{-1}					
Baseline	247	(147; 443)	259	(170; 369)	0.20
2 h postoperative	757	(447; 1240)	494	(318; 864)	0.13
Postoperative day 3	560	(384; 827)	493	(313; 730)	0.89
Adrenaline, ng·L^{-1}					
Baseline	27	(16; 43)	25	(14; 69)	0.59
2 h postoperative	187	(70; 539)	193	(74; 444)	0.86
Postoperative day 3	36	(18; 49)	43	(23; 75)	0.17
Dopamine, ng·L^{-1}					
Baseline	0	(0; 19)	0	(0; 15)	0.66
2 h postoperative	34	(19; 52)	19	(0; 35)	0.10
Postoperative day 3	23	(0; 37)	0	(0; 85)	0.92

3.2. Post-Hoc Analysis

A total of 26 (32.1%) of our patients developed MINS within three days after surgery. There was no significant difference in maximum postoperative concentrations of noradrenaline ($p = 0.48$), adrenaline ($p = 0.72$), and dopamine ($p = 0.94$) between patients with MINS and patients without MINS (Table 4).

Table 4. Plasma noradrenaline, adrenaline, and dopamine concentrations between patients with MINS and patients with no MINS are presented as median (25th quartile; 75th quartile). All *p*-values are for two-tailed Mann-Whitney U tests.

Post-Hoc Analysis					
	MINS ($n = 26$)		No MINS ($n = 55$)		*p*-Value
Noradrenaline, ng·L^{-1}					
Baseline	233	(121; 415)	259	(166; 380)	
2 h postoperative	672	(365; 990)	501	(349; 927)	
Postoperative day 3	505	(400; 809)	531	(311; 795)	
Maximum	782	(508; 1040)	855	(597; 1164)	0.48
Adrenaline, ng·L^{-1}					
Baseline	31	(16; 48)	21	(15; 56)	
2 h postoperative	164	(83; 585)	193	(67; 442)	
Postoperative day 3	38	(18; 87)	40	(22; 66)	
Maximum	171	(113; 571)	211	(75; 438)	0.72
Dopamine, ng·L^{-1}					
Baseline	0	(0; 19)	0	(0; 0)	
2 h postoperative	31	(0; 61)	23	(15; 36)	
Postoperative day 3	16	(0; 53)	22	(0; 67)	
Maximum	39	(11; 68)	36	(17; 71)	0.94

4. Discussion

The perioperative administration of 80% versus 30% inspired oxygen concentration showed no significant effect on postoperative plasma noradrenaline, adrenaline, and dopamine concentrations in patients at risk for cardiovascular complications undergoing major abdominal surgery. Additionally, we also found no significant difference in postoperative noradrenaline, adrenaline, and dopamine plasma concentrations between patients with and without MINS.

Evidence exists in the non-surgical setting that supplemental oxygen significantly decreased the release of plasma catecholamine concentrations [14]. Specifically, in patients with chronic heart failure, the long-term administration of two liters of oxygen significantly attenuated sympathetic nerve activity, which resulted in lower serum noradrenaline and adrenaline concentrations as compared to breathing air [14]. Supplemental oxygen was also associated with significantly decreased brain natriuretic peptide concentrations [15]. The authors concluded that oxygen administration reduced sympathetic nerve activity that finally attenuated the myocardial strain in these patients [15]. In contrast, we did not observe any effect in plasma catecholamine concentrations between both study groups. An explanation therefore might be that we investigated patients having major abdominal surgery and administered supplemental oxygen only throughout the immediate perioperative period. Thus, it might be possible that the intraoperative administration of supplemental oxygen leads to distinct physiological effects as compared to the nonsurgical setting.

A recent review has shown that the administration of supplemental oxygen has significant hemodynamic effects in healthy volunteers, septic patients, and patients undergoing cardiac surgery [16]. Specifically, it has been shown that supplemental oxygen significantly decreases heart rate, stroke volume, and cardiac output [16]. In contrast, we did not find any significant differences in intraoperative hemodynamic parameters between both groups. This is consistent with the results of a previous trial and of our main trial, in which no significant differences in intraoperative hemodynamic parameters were observed [10,17].

An explanation therefore might be that all of our patients received general anesthesia. It is well known that anesthetics and opioids blunt sympathetic nerve activity, and therefore hemodynamic effects of oxygen might play a minor role in the surgical setting.

Over 90% of our patients had a history of clinically relevant hypertension requiring medical treatment. Interestingly, it has been shown that patients with a history of hypertension have significantly higher plasma catecholamine concentrations as compared to normotensive patients [18]. Furthermore, approximately 40% of our patients also took β-blockers therapy. Since they inhibit the effect of endogenous catecholamines on receptors and not their release, there should be no influence on stress markers [3]. Moreover, the number of patients with pre-existing hypertension and patients taking β-blockers was similar between both study groups. Therefore, it seems unlikely that hypertension and β-blocker therapy influenced postoperative plasma catecholamine concentrations and, consequently, our results.

Pain and hypothermia, which are common in the perioperative period, are further trigger factors for stress and exacerbated catecholamine release [19–21]. Therefore, we actively warmed our patients during surgery. There was no difference in perioperative amounts of opioids administration between both groups.

It has previously been shown that perioperative elevated plasma catecholamine concentrations resulting from high blood pressure, relative insulin deficiency, surgical trauma, and hypothermia are trigger factors for myocardial ischemia [20]. In this context, it has been shown that patients undergoing major non-cardiac surgery, who had increased postoperative Troponin T levels, also had significantly higher plasma noradrenaline and adrenaline concentrations [1]. Thus, in a post-hoc analysis, we also evaluated if patients with MINS had higher plasma catecholamine concentrations as compared to those without MINS. We did not observe significantly higher plasma catecholamine concentrations in patients with MINS as compared to patients without MINS. Nevertheless, this was a post-hoc analysis and we did not power this study to detect a significant difference in maximum catecholamine concentrations between patients with and without MINS, and it should therefore be investigated in future trials.

Potentially adverse effects of supplemental oxygen have been described after the long-term administration of supplemental oxygen [22]. A trial in 1386 patients showed no significant difference in postoperative complications between patients receiving 80% and 30% oxygen during general anesthesia [23]. Furthermore, the most recent trial in 5000 patients also did not show a significant difference in the incidence of postoperative complications [24]. This is consistent with the results of our main trial [10].

This study has some limitations. Firstly, we did not measure plasma catecholamine concentrations on the first and second postoperative day. Therefore, it might be possible that we have missed the maximum rise in postoperative plasma catecholamine concentrations. However, it has been shown that plasma catecholamine measurements on the third postoperative day accurately represent the maximal stress response in cardiac-risk patients undergoing noncardiac surgery [1].

Some of our patients required a continuous infusion of noradrenaline to maintain mean arterial pressure (MAP) over 65 mmHg during surgery. There was no difference between the number of patients requiring noradrenaline administration and the total amount of noradrenaline administered between both groups. Furthermore, since the plasma half-life of noradrenaline is only 2.5 min and none of our patients received a continuous noradrenaline infusion in the postoperative study period, we thus did not expect a significant influence on our results.

In summary, this secondary analysis did not show a significant effect of perioperative supplemental oxygen on postoperative plasma catecholamine concentrations in patients at risk for cardiovascular complications undergoing major abdominal surgery. Our study period was limited to the immediate perioperative period. As we observed a significant increase in plasma catecholamine concentrations within the third postoperative day, further

studies should focus on postoperative treatment options in order to attenuate sympathetic nerve activity.

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Data Availability Statement: The data presented in this secondary analysis are available on request from the corresponding author.

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References

1. Sametz, W.; Metzler, H.; Gries, M.; Porta, S.; Sadjak, A.; Supanz, S.; Juan, H. Perioperative catecholamine changes in cardiac risk patients. *Eur. J. Clin. Investig.* **1999**, *29*, 582–587. [CrossRef] [PubMed]
2. Parker, S.D.; Breslow, M.J.; Frank, S.M.; Rosenfeld, B.A.; Norris, E.J.; Christopherson, R.; Rock, P.; Gottlieb, S.O.; Raff, H.; Perler, B.A.; et al. Catecholamine and cortisol responses to lower extremity revascularization: Correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Crit. Care Med.* **1995**, *23*, 1954–1961. [CrossRef] [PubMed]
3. Devereaux, P.J.; Yang, H.; Yusuf, S.; Guyatt, G.; Leslie, K.; Villar, J.C.; Xavier, D.; Chrolavicius, S.; Greenspan, L.; Pogue, J.; et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet* **2008**, *371*, 1839–1847. [CrossRef] [PubMed]
4. Devereaux, P.J.; Szczeklik, W. Myocardial injury after non-cardiac surgery: Diagnosis and management. *Eur. Heart J.* **2019**, *41*, 3083–3091. [CrossRef]
5. Cohn, J.N.; Levine, T.B.; Olivari, M.T.; Garberg, V.; Lura, D.; Francis, G.S.; Simon, A.B.; Rector, T. Plasma norepinephrine as a Guide to Prognosis in Chronic Congestive Heart Failure. *N. Engl. J. Med.* **1984**, *311*, 819–823. [CrossRef]
6. Lamba, S.; Abraham, W.T. Alterations in adrenergic receptor signaling in heart failure. *Heart Fail. Rev.* **2000**, *5*, 7–16. [CrossRef]
7. Priebe, H.J. Triggers of perioperative myocardial ischaemia and infarction. *Br. J. Anaesth.* **2004**, *93*, 9–20. [CrossRef]
8. Wu, K.K. Platelet activation mechanisms and markers in arterial thrombosis. *J. Intern. Med.* **1996**, *239*, 17–34. [CrossRef]
9. Allegranzi, B.; Zayed, B.; Bischoff, P.; Kubilay, N.Z.; de Jonge, S.; de Vries, F.; Gomes, S.M.; Gans, S.; Wallert, E.D.; Wu, X.; et al. Surgical site infections 2 New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: An evidence-based global perspective. *Lancet Infect. Dis.* **2016**, *16*, e288–e303. [CrossRef]
10. Reiterer, C.; Kabon, B.; Taschner, A.; von Sonnenburg, M.F.; Graf, A.; Adamowitsch, N.; Starlinger, P.; Goshin, J.; Fraunschiel, M.; Fleischmann, E. Perioperative supplemental oxygen and NT-proBNP concentrations after major abdominal surgery—A prospective randomized clinical trial. *J. Clin. Anesth.* **2021**, *73*, 110379. [CrossRef]
11. Reiterer, C.; Kabon, B.; von Sonnenburg, M.F.; Starlinger, P.; Taschner, A.; Zotti, O.; Goshin, J.; Drlicek, G.; Fleischmann, E. The effect of supplemental oxygen on perioperative brain natriuretic peptide concentration in cardiac risk patients—A protocol for a prospective randomized clinical trial. *Trials* **2020**, *21*, 400. [CrossRef] [PubMed]
12. Devereaux, P.J.; Biccard, B.M.; Sigamani, A.; Xavier, D.; Chan, M.T.; Srinathan, S.K.; Walsh, M.; Abraham, V.; Pearse, R.; Wang, C.Y.; et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA—J. Am. Med. Assoc.* **2017**, *317*, 1642–1651. [CrossRef]
13. Schulz, K.F.; Altman, D.G.; Moher, D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Int. J. Surg.* **2011**, *9*, 672–677. [CrossRef] [PubMed]
14. Staniforth, A.D.; Kinnear, W.J.M.; Starling, R.; Hetmanski, D.J.; Cowley, A.J. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyn-Stokes respiration. *Eur. Heart J.* **1998**, *19*, 922–928. [CrossRef]
15. Shigemitsu, M.; Nishio, K.; Kusuyama, T.; Itoh, S.; Konno, N.; Katagiri, T. Nocturnal oxygen therapy prevents progress of congestive heart failure with central sleep apnea. *Int. J. Cardiol.* **2007**, *115*, 354–360. [CrossRef]
16. Smit, B.; Smulders, Y.M.; van der Wouden, J.C.; Oudemans-van Straaten, H.M.; Spoelstra-de Man, A.M.E. Hemodynamic effects of acute hyperoxia: Systematic review and meta-analysis. *Crit. Care* **2018**, *22*, 40. [CrossRef]

17. Greif, R.; Akca, O.; Horn, E.-P.; Kurz, A.; Sessler, D.I. Supplemental Perioperative Oxygen to reduce the Incidence of Surgical-Wound Infection. *N. Engl. J. Med.* **2000**, *342*, 161–167. [CrossRef]
18. Bühler, F.R.; Amann, F.W.; Bolli, P.; Hulthén, L.; Kiowski, W.; Landmann, R.; Bürgisser, E. Elevated adrenaline and increased alpha-adrenoceptor-mediated vasoconstriction in essential hypertension. *J. Cardiovasc. Pharmacol.* **1982**, *4* (Suppl. 1), S134–S138. [CrossRef]
19. Møller, I.W.; Dinesen, K.; Søndergård, S.; Knigge, U.; Kehlet, H. Effect of patient-controlled analgesia on plasma catecholamine, cortisol and glucose concentrations after cholecystectomy. *Br. J. Anaesth.* **1988**, *61*, 160–164. [CrossRef]
20. Devereaux, P.J.; Goldman, L.; Cook, D.J.; Gilbert, K.; Leslie, K.; Guyatt, G.H. Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *CMAJ* **2005**, *173*, 627–634. [CrossRef]
21. Frank, S.M.; Higgins, M.S.; Breslow, M.J.; Fleisher, L.A.; Gorman, R.B.; Sitzmann, J.V.; Raff, H.; Beattle, C. The Catecholamine, Cortisol, and Hemodynamic Responses to Mild Perioperative Hypothermia. *Anesthesiology* **1995**, *82*, 83–93. [CrossRef]
22. Chu, D.K.; Kim, L.H.; Young, P.J.; Zamiri, N.; Almenawer, S.A.; Jaeschke, R.; Szczeklik, W.; Schünemann, H.J.; Neary, J.D.; Alhazzani, W. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): A systematic review and meta-analysis. *Lancet* **2018**, *391*, 1693–1705. [CrossRef]
23. Meyhoff, C.S.; Wetterslev, J.; Jorgensen, L.N.; Henneberg, S.W.; Høgdall, C.; Lundvall, L.; Svendsen, P.E.; Mollerup, H.; Lunn, T.H.; Simonsen, I.; et al. Effect of High Perioperative Oxygen Fraction on Surgical Site Infection and Pulmonary Complications after Abdominal Surgery. *JAMA* **2009**, *302*, 1543–1550. [CrossRef] [PubMed]
24. Kurz, A.; Kopyeva, T.; Suliman, I.; Podolyak, A.; You, J.; Lewis, B.; Vlah, C.; Khatib, R.; Keebler, A.; Reigert, R.; et al. Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. *Br. J. Anaesth.* **2018**, *120*, 117–126. [CrossRef] [PubMed]

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Perioperative Supplemental Oxygen and Postoperative Copeptin Concentrations in Cardiac-Risk Patients Undergoing Major Abdominal Surgery—A Secondary Analysis of a Randomized Clinical Trial

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Abstract: Noncardiac surgery is associated with hemodynamic perturbations, fluid shifts and hypoxic events, causing stress responses. Copeptin is used to assess endogenous stress and predict myocardial injury. Myocardial injury is common after noncardiac surgery, and is often caused by myocardial oxygen demand-and-supply mismatch. In this secondary analysis, we included 173 patients at risk for cardiovascular complications undergoing moderate- to high-risk major abdominal surgery. Patients were randomly assigned to receive 80% or 30% oxygen throughout surgery and the first two postoperative hours. We evaluated the effect of supplemental oxygen on postoperative Copeptin concentrations. Copeptin concentrations were measured preoperatively, within two hours after surgery, on the first and third postoperative days. In total, 85 patients received 0.8 FiO_2, and 88 patients received 0.3 FiO_2. There was no significant difference in postoperative Copeptin concentrations between both study groups ($p = 0.446$). Copeptin increased significantly within two hours after surgery, compared with baseline in the overall study population (estimated effect: -241.7 pmol·L^{-1}; 95% CI -264.4, -219.1; $p < 0.001$). Supplemental oxygen did not significantly attenuate postoperative Copeptin release. Copeptin concentrations showed a more immediate postoperative increase compared with previously established biomarkers. Nevertheless, Copeptin concentrations did not surpass Troponin T in early determination of patients at risk for developing myocardial injury after noncardiac surgery.

Keywords: supplemental oxygen; perioperative stress; Copeptin; MINS; major abdominal surgery; cardiovascular risk

1. Introduction

During recent years, the prevalence of cardiovascular risk factors and comorbidities in patients undergoing noncardiac surgery has significantly increased [1]. As a consequence, the incidence of postoperative major cardiovascular complications has risen to approximately 8% among this patient population [2,3].

Surgery and anesthesia are associated with trauma, hemodynamic perturbations, fluid shifts, stress and hypoxic events [4,5]. These are trigger factors for endogenous

stress, reflected by increased catecholamine and cortisol release, and myocardial injury [6]. Elevated stress levels are associated with increased sympathetic nerve activity leading to tachycardia and hypertension [7]. This might lead to an imbalance in myocardial oxygen supply and demand, and finally result in myocardial injury [7–9]. It is very well known that perioperative hypoxic events caused by hypovolemia, hypotension, tachycardia and hypoxemia significantly increase the risk for myocardial injury after noncardiac surgery (MINS) [9,10]. A previous study has shown that preoperative Copeptin concentrations might be able to predict myocardial injury in the immediate perioperative period [11].

Copeptin is a relatively novel biomarker and reflects plasma concentrations of arginine-vasopressin (AVP) [12]. AVP is an antidiuretic hormone released from the hypothalamus in response to changes in plasma osmolality and blood pressure, and its main function is homeostasis of fluid balance, vascular tonus and regulation of the endocrine stress response [13]. In detail, an increase in blood osmolality and hypovolemia leads to increased plasma AVP and Copeptin concentrations [14]. In contrast to AVP, plasma concentrations of Copeptin are very stable and simple to measure, and are therefore used to indirectly assess plasma AVP concentration [13]. Copeptin concentrations significantly correlate with physiologic as well as pathophysiologic endogenous stress, such as that caused by surgery [13,15]. In detail, Copeptin concentrations are significantly increased in patients who have suffered from myocardial infarction, heart failure, shock, stroke and traumatic brain injury [16–19]. Elevated concentrations are explained by exacerbated endogenous stress associated with cardiovascular complications [11]. Furthermore, preoperative elevated Copeptin values are strong predictors for MINS [11]. Copeptin concentrations accurately reflect myocardial strain and injury as well as endogenous stress, and could therefore be of high value in properly reflecting perioperative stress.

In our main trial, we investigated the effect of 80% versus 30% perioperative oxygen administration on postoperative maximum NT-proBNP concentrations and MINS [20]. We observed no significant difference between both study groups [21]. Because there is limited data in regard to perioperative Copeptin concentrations, specifically on the subject of supplemental oxygen, we evaluated in this secondary analysis if supplemental oxygen influences perioperative Copeptin concentrations. Thus, we evaluated the hypothesis if perioperative administration of 80% oxygen leads to a significant decrease in postoperative Copeptin concentrations as compared to perioperative administration of 30% oxygen in patients at risk for cardiovascular complications undergoing moderate- to high-risk major abdominal surgery. Furthermore, we evaluated the effect of surgery per se as well as MINS on perioperative Copeptin concentrations in the overall study population. In a post-hoc analysis, we evaluated the predictive values of Copeptin concentrations in the perioperative time course for the development of MINS.

2. Materials and Methods

2.1. Study Design

This is a pre-planned secondary analysis of a prospective, randomised, double-blinded, single-centre clinical trial conducted at the Medical University of Vienna, which primarily investigated the effect of 80% versus 30% inspired oxygen concentration on postoperative maximum NT-proBNP concentrations [21]. This study was approved by the University's Ethics Committee (Ethikkomission Medizinische Universität Wien; Borschkegasse 8b/6, 1090, Vienna, Austria; EK-Number 1744/2017; Chairperson Prof. Martin Brunner) on 13 November 2017. Written informed consent was obtained from all patients participating in the study. The trial was registered prior to patient enrolment at ClinicalTrials.gov (NCT03366857, Principal Investigator: Edith Fleischmann, Date of registration: 2 December 2017) and the European Trial Database (EudraCT 2017-003714-68), and was conducted according to the Declaration of Helsinki and Good Clinical Practice. This manuscript adheres to the applicable CONSORT guidelines. The study protocol was published previously [20]. The additional measurement of Copeptin concentrations for this secondary analysis was amended on 19 July 2018 after 87 patients had already been included. Patients of at least

45 years of age and undergoing major abdominal surgery for ≥2 h were eligible for the trial. Detailed inclusion and exclusion criteria were published previously [20].

2.2. Randomisation

For patient randomisation of the main study, a web-based randomisation programme (Randomizer, Medical University of Graz, Graz, Austria, https://www.meduniwien.ac.at/randomizer/web) (last accessed on 5 November 2019) was used. Randomisation sequence was generated by the study statistician using permutated blocks with a size of six numbers. We did not use stratification of randomisation.

Patients were randomised to receive either 80% or 30% inspired oxygen concentration throughout surgery, and for the first two postoperative hours. We randomised patients shortly before induction of anesthesia. The trial was conducted in accordance with the original protocol [20]. Protocol for induction and maintenance of anesthesia was published previously [20]. Intraoperative fluid management in all patients was performed in an esophageal-Doppler-guided manner according to a previously published algorithm [22,23]. As per study protocol, all patients received a 2 $mL \cdot kg^{-1} \cdot BW^{-1}$ baseline infusion of balanced crystalloids. A bolus of 250 mL balanced crystalloids was administered when stroke volume decreased by ≥20% from baseline. In case of acute bleeding or systemic inflammatory response during surgery, volume was administered according to fluid requirements to maintain hemodynamic stability. Blood and blood products were administered as per clinical judgement [20]. Copeptin concentrations were measured preoperatively, within two hours after surgery, and on the first and third postoperative day. All data were recorded and stored in the data management system 'Clincase', v2.7.0.12 hosted by IT Systems & Communications, Medical University of Vienna, Vienna, Austria.

2.3. Statistical Analysis

We performed an intention-to-treat analysis according to allocated randomisation. Continuous variables were summarised using mean, standard deviation (SD), median, quartiles [25th percentile; 75th percentile] as well as minimum and maximum values. Descriptive statistics are given for randomised groups separately. Categorical variables were summarised using absolute and percent values. Continuous intraoperative values were compared between groups using Mann–Whitney U tests. To investigate a difference in the time course of Copeptin concentrations between the two study groups, first a linear regression model for Copeptin accounting for time, study group and the interaction between time and group as fixed factors as well as accounting for subject ID as random factor was performed. Univariable linear regression models (with random factor subject) were performed for the possible influence factors of time (without interaction term time), type of surgery (open or laparoscopic), age, BMI, sex, ASA physical status, history of coronary artery disease, peripheral artery disease, stroke, heart failure, diabetes, and hypertension. All factors significant (with a $p < 0.05$) in the simple models were then included in a multivariable regression model (with random factor patient). All analyses were performed using R version 3.3.3 and SAS version 9.4 (SAS Institute, Cary, NC, USA).

2.4. Post-Hoc Analysis

We compared the perioperative time-course of Copeptin concentrations between patients who developed MINS and patients who did not develop MINS. We measured Troponin T concentrations in all patients preoperatively, within 2 h after surgery, on the first and third postoperative days. MINS was defined as a postoperative Troponin T concentration of 20–65 $ng \cdot L^{-1}$ with an absolute change of at least 5 $ng \cdot L^{-1}$ or a postoperative Troponin T concentration > 65 $ng \cdot L^{-1}$. Patients in whom Troponin T concentration was adjudicated for nonischemic etiology (e.g., sepsis, pulmonary embolism) were not considered as having MINS [24]. We performed a Mann–Whitney U test to compare Copeptin values at each time point. We further performed a receiver-operating characteristics (ROC) curve to evaluate the predictive value of Copeptin and Troponin T concentrations at baseline and

within two hours after surgery on the occurrence of postoperative MINS. Furthermore, we performed a ROC curve to investigate the predictive value of Copeptin concentrations in the perioperative period on the occurrence of a composite of postoperative cardiovascular complications, including cardiac failure, myocardial infarction, new onset of cardiac arrhythmias and death.

2.5. Sample Size Considerations

Out of the 260 patients planned for the primary aim of the main study, we included 173 patients in our secondary analysis.

We re-estimated the sample size for this secondary analysis based on previous data on Copeptin to get an evaluation of the available sample size. Previous data showed that postoperative Copeptin concentrations in patients undergoing vascular surgery and developing myocardial injury increased up to 100 ± 80 pmol·L^{-1} compared with Copeptin concentrations of 65 ± 80 pmol·L^{-1} in patients without myocardial injury [25]. Therefore, we assumed a difference of 35% in postoperative Copeptin concentrations as clinically meaningful. Using a two-sided t-test, we calculated that at least 82 patients per group are needed to detect a significant difference between both study groups at a significance level of 0.05 with 80% power. Thus, the given sample size of 173 (85 vs. 88) may be adequate to detect the assumed clinically relevant effect.

3. Results

A total of 173 consecutive patients, who were enrolled in the main trial from August 2018 to May 2019, were included in this secondary analysis. Eighty-five patients received 80% inspired oxygen and eighty-eight patients received 30% inspired oxygen throughout surgery and for the first two postoperative hours (Figure 1).

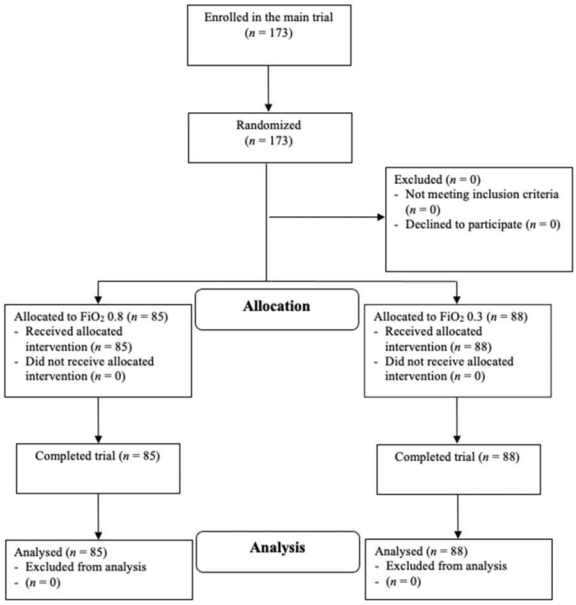

Figure 1. Patient Flow Diagram; Design and Form in Accordance with the 2010 CONSORT Guidelines [26].

Baseline characteristics, including age, weight, ASA physical status, cardiovascular comorbidities, long-term medications and baseline laboratory parameters, were balanced between the two study groups (Table 1). The duration of anesthesia and surgery, anaesthet-

ics, fluid, and vasopressors administered, hemodynamic parameters, and arterial blood gas analyses were balanced between both study groups (Table 2).

Table 1. Patient Characteristics.

	80% Oxygen (n = 85)	30% Oxygen (n = 88)
Age, years	73 (70; 78)	74 (70; 79)
Height, cm	172 (165; 176)	172 (167; 178)
Weight, kg	80 (67; 93)	75 (67; 90)
BMI, $kg \cdot m^{-2}$	26.6 (23.8; 30.7)	24.9 (23.2; 27.7)
Sex, *n* (%)		
Women	31 (36.5)	28 (31.8)
Men	54 (63.5)	60 (68.2)
ASA physical status, *n* (%)		
II	16 (18.8)	30 (34.1)
III	67 (78.8)	58 (65.9)
IV	2 (2.4)	0 (0)
Comorbidities, *n* (%)		
Hypertension	79 (92.9)	82 (93.2)
Coronary artery disease	24 (28.2)	23 (26.1)
Peripheral artery disease	13 (15.3)	15 (17.0)
Stroke	7 (8.2)	5 (5.7)
Congestive heart failure	5 (5.9)	6 (6.8)
Transient ischemic attack	2 (2.4)	2 (2.3)
Diabetes	26 (30.6)	19 (21.6)
Insulin use	7 (8.2)	2 (2.3)
Long-term medication, *n* (%)		
Beta blockers	44 (51.8)	47 (53.4)
ACI/ARB	45 (52.9)	50 (56.8)
Diuretics	31 (36.5)	26 (29.5)
Statins	33 (38.8)	38 (43.2)
Acetylsalicylic acid	24 (28.2)	30 (34.1)
Oral anticoagulant	31 (36.5)	21 (23.9)
Alpha 2 agonist	3 (3.5)	3 (3.4)
Type of Surgery, (%)		
Hepatobiliary	6 (7.1)	6 (6.8)
Colorectal	18 (21.2)	18 (20.5)
Pancreatic	11 (12.9)	14 (15.9)
Urological	37 (42.1)	34 (40.0)
Gynaecological	6 (7.1)	3 (3.4)
Other	10 (11.8)	10 (11.6)
Open vs. Laparoscopic Surgery, (%)		
Open	51 (60.0)	53 (60.2)
Laparoscopic	30 (35.3)	30 (34.1)
Both [1]	4 (4.7)	5 (5.7)
Laboratory parameters		
CRP, $mg \cdot dL^{-1}$	0.33 (0.10; 0.82)	0.27 (0.10; 0.91)
Creatinine, $mg \cdot dL^{-1}$	0.9 (0.7; 1.1)	0.9 (0.8; 1.1)
Hemoglobin, $g \cdot dL^{-1}$	12.2 (10.7; 13.2)	12.6 (10.8; 13.9)
Leukocytes, $G \cdot L^{-1}$	5.96 (5.03; 7.72)	5.73 (4.85; 7.76)
NT-proBNP, $pg \cdot ml^{-1}$	205 (88; 486)	218 (102; 796)
Troponin T, $ng \cdot L^{-1}$	13 (8; 19)	13 (9; 21)

Summary characteristics are presented as counts, percentages of patients, and median [25th quartile; 75th quartile]. BMI, body mass index; ASA, American Society of Anaesthesiologists physical status; ACI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; NT-proBNP, N-terminal brain natriuretic peptide. [1] Defined as conversion from laparoscopic to open procedure.

Table 2. Perioperative variables.

	80% Oxygen (n = 85)	30% Oxygen (n = 88)	p-Value
Intraoperative			
Duration of anesthesia, min	272 (186; 355)	259 (205; 352)	0.622
Duration of surgery, min	221 (141; 307)	200 (142; 292)	0.711
Fluid management			
Crystalloid, mL	2160 (1508; 3386)	2578 (1683; 3339)	0.304
Blood loss, mL	300 (0; 600)	275 (0; 725)	0.610
Urine output, mL	300 (150; 475)	300 (200; 500)	0.417
Anesthesia management			
Fentanyl, mcg	1013 (800; 1463)	1100 (838; 1513)	0.459
Propofol, mg	120 (93; 150)	125 (50; 200)	0.536
Phenylephrine, mg	0.28 (0.09; 0.46)	0.21 (0.08; 0.42)	0.717
Noradrenaline, mg	0.25 (0.00; 0.60)	0.20 (0.00; 0.08)	0.491
etSevo, %	1.3 (1.0; 1.3)	1.2 (1.0; 1.3)	0.556
FiO_2, %	80 (80; 80)	31 (30; 32)	
$etCO_2$, mmHg	34 (32; 36)	34 (31; 35)	0.531
Core temp, °C	36.5 (36.1; 36.8)	36.5 (36.2; 36.9)	0.210
Hemodynamic Parameters			
HR, beats·min^{-1}	70 (58; 86)	65 (56; 73)	0.845
MAP, mmHg	80 (76; 84)	81 (76; 88)	0.549
SV, mL	71 (63; 84)	66 (57; 83)	0.821
CO, L·min^{-1}	4.1 (3.7; 5.6)	4.6 (3.7; 5.3)	0.615
CVP, mmHg	12 (10; 15)	10 (9; 12)	0.086
Arterial Blood Gas Analysis			
pO_2, mmHg	314 (270; 361)	131 (109; 158)	<0.001
pCO_2, mmHg	42 (40; 44)	41 (39; 43)	0.015
pH	7.38 (7.35; 7.41)	7.39 (7.35; 7.42)	0.169
BE	−0.6 (−1.9; 0.9)	−0.3 (−1.9; 0.9)	0.765
Hemoglobin, g·dL^{-1}	11.7 (9.9; 12.8)	11.7 (10.2; 12.9)	0.745
Lactate, mmol·L^{-1}	0.9 (0.7; 1.2)	0.9 (0.7; 1.1)	0.745
Glucose, mmol·L^{-1}	7.3 (6.4; 8.9)	7.0 (6.2; 8.1)	0.071
2 h postoperative			
Hemodynamic Parameters			
HR, beats·min^{-1}	75 (61; 91)	69 (63; 77)	0.450
MAP, mmHg	82 (76; 100)	81 (77; 100)	0.431
72 h postoperative			
Fluid, mL [a]	9852 (6845; 11,989)	9506 (7200; 12,137)	0.900
Piritramide, mg [b]	8.0 (3.0; 20.3)	10.0 (3.0; 21.0)	0.903

Summary characteristics of perioperative variables are presented as medians [25th quartile; 75th quartile]. All p-values are for two-tailed Mann–Whitney U tests. etSevo, end-tidal Sevoflurane concentration; FiO_2, Fraction of inspired oxygen; $etCO_2$, end-tidal carbon dioxide concentration; HR, heart rate; MAP, mean arterial pressure; SV, stroke volume; CO, cardiac output; CVP, central venous pressure; pO_2, oxygen partial pressure; pCO_2, carbon dioxide partial pressure; BE, base excess. [a] Overall amount of fluid administered during the first 72 h after surgery. [b] Overall amount of piritramide administered during the first 72 h after surgery.

3.1. Primary Outcome

We did not observe a significant difference in Copeptin concentrations in the overall perioperative time course (p = 0.446) between both study groups (Figure 2). Furthermore, at none of the time points was a significant difference in Copeptin concentrations between the 80% oxygen and 30% oxygen group found (2 h postoperative: p = 0.090; postoperative day 1: p = 0.936; postoperative day 3: p = 0.935) (Table 3).

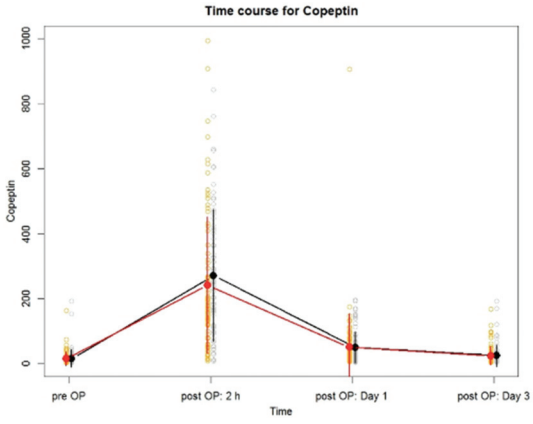

Figure 2. Plot showing the perioperative trend of Copeptin concentrations between patients who received 0.8 FiO_2 (red) and patients who received 0.3 FiO_2 (black). Dots represent mean values, vertical lines represent standard deviations of each group. The blank dots give the values of the observed individuals separately for the two groups.

Table 3. Univariable regression model Copeptin.

Variable	Comparison	Effect	Lower CI	Upper CI	*p*-Value
Time	pre vs. 2 h post	−241.740	−264.440	−219.050	<0.001
	pre vs. POD 1	−35.206	−58.245	−12.168	0.003
	pre vs. POD 3	−7.976	−31.470	15.519	0.505
Time × Group	Group 30% vs. 80% pre	−0.087	−35.119	34.944	0.996
	Group 30% vs. 80% 2 h post	29.838	−4.614	64.291	0.090
	Group 30% vs. 80% POD 1	−1.453	−36.794	33.888	0.936
	Group 30% vs. 80% POD 3	−1.514	−38.053	35.025	0.935
	Group 30% pre vs. 2 h post	−256.380	−288.210	−224.550	<0.001
	Group 30% pre vs. POD 1	−34.513	−66.983	−2.042	0.037
	Group 30% pre vs. POD 3	−7.259	−40.295	25.778	0.666
	Group 80% pre vs. 2 h post	−226.450	−258.820	−194.080	<0.001
	Group 80% pre vs. POD 1	−35.878	−68.582	−3.175	0.032
	Group 80% pre vs. POD 3	−8.685	−42.115	24.744	0.610
Type of surgery	Laparoscopic vs. Open	−31.164	−55.866	−6.463	0.014
Time × Type of surgery	Overall Interaction				<0.001
Age		0.559	−0.937	2.055	0.464
BMI		0.194	−2.136	2.523	0.871
Sex	Female vs. Male	15.426	−9.309	40.161	0.221
ASA	III, IV vs. I, II	−3.227	−29.836	23.383	0.812
Coronary Artery Disease	Yes vs. No	5.535	−20.697	31.767	0.679
Peripheral Artery Disease	Yes vs. No	19.548	−12.763	51.859	0.235
Stroke	Yes vs. No	1.759	−44.601	48.118	0.941
Heart Failure	Yes vs. No	22.391	−24.925	69.707	0.353
Diabetes	Yes vs. No	−1.582	−28.143	24.980	0.907
Hypertension	Yes vs. No	−4.915	−51.273	41.443	0.835

The estimated effect sizes, confidence intervals (CI) and *p*-values were calculated using univariable regression models. pre, preoperative; 2 h post, within two hours after surgery; POD, postoperative day; BMI, body mass index; ASA, American Society of Anesthesiologists.

Copeptin concentrations increased significantly within two hours after surgery, compared with baseline values in the overall study population (estimated effect pre vs. post: −241.7 pmol·L^{-1}; 95% CI −264.4 to −219.1; $p < 0.001$) as well as in each study group (each $p < 0.001$). Similarly, Copeptin concentrations on the first postoperative day were elevated significantly from baseline values in the overall study population (estimated effect pre vs. post: −35.2 pmol·L^{-1}; 95% CI −58.2 to −12.2; $p = 0.003$) as well as in each study group (80% oxygen group: $p = 0.032$; 30% oxygen group: $p = 0.037$). There was no significant difference

found in Copeptin concentrations on the third postoperative day compared with baseline values in the overall study population ($p = 0.505$), or the 80% oxygen group ($p = 0.610$) or the 30% oxygen group ($p = 0.666$) separately.

Baseline patient characteristics, including age, sex, BMI, ASA physical status, history of coronary artery disease, history of peripheral artery disease, history of stroke, heart failure, diabetes or hypertension, did not significantly affect perioperative Copeptin concentrations in the univariable regression model (all $p > 0.05$). On an average over all time points, significantly larger Copeptin concentrations were found for open as compared to laparoscopic surgery ($p = 0.014$). A larger increase in Copeptin concentrations from baseline to two hours after surgery was found for open surgeries as compared to laparoscopic surgeries ($p = 0.001$).

In the multivariable regression model, Copeptin values within two hours after surgery were significantly higher in patients receiving open as compared to laparoscopic surgery ($p < 0.001$).

No significant difference was observed in postoperative Copeptin concentrations from baseline to the first or third postoperative day between open or laparoscopic surgeries (Appendix A, Table A1).

3.2. Post-Hoc Analysis

We observed significantly higher Copeptin concentrations in patients with MINS as compared to patients without MINS before surgery (14.1 [IQR 8.1 to 22.4] versus 7.7 [IQR 4.5 to 14.2]; $p = 0.002$), on the first postoperative day (49.0 [IQR 29.7 to 116.0] versus 26.7 [IQR 11.9; 53.6]; $p = 0.002$) and on the third postoperative day (24.3 [IQR 16.1 to 46.3] versus 12.5 [IQR 7.2 to 21.5]; $p = 0.002$). Copeptin concentrations within two hours after surgery were similar between patients with MINS (190.3 [IQR 118.2 to 376.9]) and patients without MINS (196.8 [IQR 109.0 to 362.9]) ($p = 0.840$) (Appendix A, Figure A1). Figure A2 in Appendix A shows ROC curves for preoperative Copeptin concentrations and MINS (Area under the curve (AUC) = 0.686; 95% CI 0.586 to 0.926) as well as for preoperative Troponin T concentrations and MINS (AUC = 0.908; 95% CI 0.849 to 0.967) (Appendix A). The area under the ROC curve for Copeptin concentrations within two hours after surgery and MINS was 0.514 (95% CI 0.400 to 0.628) and for Troponin T within two hours after surgery and MINS was 0.480 (95% CI 0.368 to 0.592) (Appendix A, Figure A2).

Overall, 10 patients in this secondary analysis developed a postoperative cardiovascular complication within 30 days after surgery. Copeptin concentrations at baseline (AUC = 0.666; 95% CI 0.445 to 0.886) or within 2 h after surgery (AUC = 0.611; 95% CI 0.432 to 0.789) did not show a predictive value for the occurrence of cardiovascular complications within 30 days after surgery. The area under the ROC curve for Copeptin concentrations on the first postoperative day and cardiovascular complications was 0.819 (95% CI 0.688 to 0.950) and for Copeptin concentrations on the third postoperative day and cardiovascular complications was 0.866 (95% CI 0.743 to 0.988) (Appendix A, Figure A3).

4. Discussion

The administration of perioperative supplemental oxygen did not significantly attenuate the release of postoperative Copeptin concentrations in patients at risk for cardiovascular complications undergoing moderate- to high-risk major abdominal surgery. However, we observed a significant increase in postoperative Copeptin concentrations compared with preoperative baseline values in both study groups as well as in the overall study population.

In contrast to the non-surgical setting, we did not observe significant stress reduction in patients who received perioperative supplemental oxygen [27]. One explanation could be that in the study performed in the non-surgical setting, supplemental oxygen was administered for four weeks during the night [27]. Furthermore, only patients with stable heart failure and documented Cheyne–Stokes respiration, who have a high risk for nocturnal desaturation, were included [27]. In this context, the authors suggested that the

administration of supplemental oxygen leads to a reduction in episodes of desaturation, which finally leads to reduction in stress [27]. Thus, it might be possible that the duration of oxygen administration in our study was too short to show the same effects. Furthermore, patients undergoing surgery are closely monitored, which makes episodes of desaturation very unlikely. Therefore, our patients might have not been exposed to stress caused by hypoxic events.

An in vitro study has shown that hyperoxia leads to a significant increase in cytotoxicity in adult cardiac myocytes [28]. A retrospective analysis of the PROXI trial has shown that supplemental oxygen increases the risk of myocardial complications after noncardiac surgery [29]. However, a further retrospective sub-analysis of a more recent prospective trial, which investigated the effect of 80% versus 30% oxygen on wound-related complications, did not observe a negative effect of intraoperative supplemental oxygen on cardiovascular complications [30]. More importantly, the most recent trial also showed no negative effects of supplemental oxygen on the incidence of MINS in patients with cardiovascular risk factors undergoing major noncardiac surgery [31]. These findings are consistent with the results of our main trial [21]. Similar to postoperative Troponin T concentrations, the administration of supplemental oxygen also did not result in a significant difference in postoperative Copeptin concentrations.

It has been shown recently that preoperative Copeptin values > 14 ng/L have a high predictive value for the development of myocardial injury after surgery [11]. However, the trend of Copeptin concentrations in the postoperative period was only investigated in a relatively small study on 30 patients undergoing major vascular surgery [25]. In our post-hoc analysis, we observed significantly increased Copeptin concentrations in patients with MINS as compared to patients with no MINS on the first and third postoperative days. Copeptin concentrations within 2 h after surgery did not differ significantly between those groups. Interestingly, we found that Copeptin concentrations before surgery and two hours after surgery were not superior to Troponin T at these time points for predicting MINS. Therefore, it seems likely that Copeptin concentrations in the preoperative and immediate postoperative period do not surpass Troponin T concentrations in the early stratification of patients at risk of developing MINS.

Several studies have shown that noncardiac surgery is associated with a significant postoperative increase in cardiac and stress markers [21,32]. The time after surgery remains a very decisive period associated with cardiovascular complication [2,33]. Troponin T and NT-proBNP concentrations in the first postoperative days are strong predictors for myocardial injury and myocardial strain [2,34]. In contrast to NT-proBNP and Troponin T, which increase approximately 48 h after major abdominal surgery [21,35], we observed that Copeptin concentrations peak within two hours after surgery. Nevertheless, only Copeptin concentrations on the first and third postoperative days were predictive for the development of MINS. Copeptin concentrations have been shown to be significantly elevated in patients experiencing cardiovascular morbidities, including myocardial infarction, stroke and heart failure. Postoperative atherosclerotic complications are the leading cause of postoperative deaths in patients undergoing major noncardiac surgery [24]. Nevertheless, while several risk factors for the development of cardiovascular complications have been established, a clear pathophysiologic explanation has not been determined yet [36]. In our secondary analysis we found a significant increase in postoperative Copeptin concentrations, which highlights the fact that noncardiac surgery is associated with a significant postoperative stress response. Furthermore, we observed a predictive value of preoperative Copeptin concentrations for the development of MINS as well as a predictive value of Copeptin concentrations on the first and third postoperative days for the development of cardiovascular complications. Based on our results, further studies should investigate the impact of perioperative stress on the occurrence of postoperative cardiovascular complications in patients undergoing major noncardiac surgery.

We observed significantly higher postoperative Copeptin concentrations in the overall study population compared with baseline values. Surgery is associated with significantly

higher cortisol concentrations, inflammatory response and oxidative stress [37–39]. Similar postoperative responses in oxidative stress were also observed in another secondary analysis of our main trial [40]. In detail, we have shown that oxidative stress, assessed via oxidation–reduction potential, which is a reliable marker for oxidative stress [41], significantly increased in the overall study population [40]. Furthermore, there was a simultaneous decrease in the oxidation–reduction capacity [40].

Our study has some limitations. This is a secondary analysis of our main trial [21]. The primary study was powered to detect the effect of supplemental oxygen on postoperative maximum NT-proBNP concentrations [21]. Nevertheless, the given sample size may be adequate to detect clinically relevant effects of supplemental oxygen on Copeptin concentrations. We did not measure further biomarkers to assess perioperative stress such as catecholamines or cortisol concentrations in our study population. The additional assessment of other biomarkers might have provided more substantial information on the effect of supplemental oxygen on perioperative stress response.

5. Conclusions

In summary, we showed that the administration of supplemental oxygen has no significant effect on postoperative Copeptin concentrations, which has been used as a surrogate parameter for surgical stress response and myocardial injury. However, we found that Copeptin increased earlier as compared to other biomarkers. Based on our results and previous literature, it is becoming more evident that surgical trauma is a very stressful event, which was reflected by a significant increase in postoperative Copeptin concentrations. In this context, supplemental oxygen might play a negligible role in the postoperative stress response, which could be predominantly caused by surgery.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Ethikkommission Medizinische Universität Wien (protocol code 1744/2017; Date of approval 13 November 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this secondary analysis are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Multivariable regression model Copeptin.

Variable	Comparison	Effect	Lower CI	Upper CI	*p*-Value
Time × OP Type	Overall Interaction Test				<0.001
	Laparoscopic vs. Open: 2 h post—pre	−100.940	−147.280	−54.589	<0.001
	Laparoscopic vs. Open: POD 1—pre	−12.263	−59.370	34.845	0.609
	Laparoscopic vs. Open: POD 3—pre	−10.150	−58.725	38.425	0.682
	Laparoscopic vs. Open: pre	−1.973	−37.623	33.676	0.914

Table A1. *Cont.*

Variable	Comparison	Effect	Lower CI	Upper CI	*p*-Value
	Laparoscopic vs. Open: 2 h post	−102.910	−138.100	−67.715	<0.001
	Laparoscopic vs. Open: POD 1	−14.236	−50.421	21.949	0.440
	Laparoscopic vs. Open: POD 3	−12.123	−50.204	25.957	0.532
	Laparoscopic: pre vs. 2 h post	−176.100	−213.39	−138.810	<0.001
	Laparoscopic: pre vs. POD 1	−27.172	−65.203	10.859	0.161
	Laparoscopic: pre vs. POD 3	−1.508	−41.303	38.287	0.941
	Open: pre vs. 2 h post	−277.030	−304.550	−249.520	<0.001
	Open: pre vs. POD 1	−39.435	−67.232	−11.637	0.006
	Open: pre vs. POD 3	−11.658	−39.512	16.197	0.411

The estimated effect sizes, confidence intervals (CI) and *p*-values were calculated using multivariable regression models (with random factor patient); POD, postoperative day.

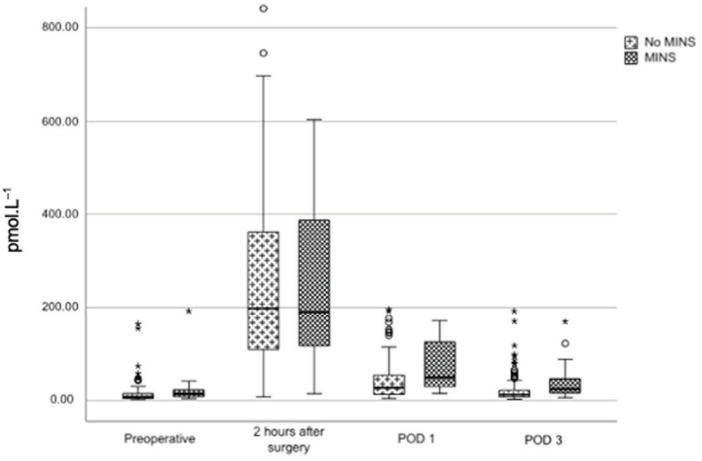

Figure A1. Boxplots showing the perioperative trend of Copeptin concentrations between patients with MINS and patients without MINS. Boxplots demonstrate medians and interquartile ranges; circles represent outliers; stars represent extreme outliers; MINS, myocardial injury after noncardiac surgery; POD, postoperative day.

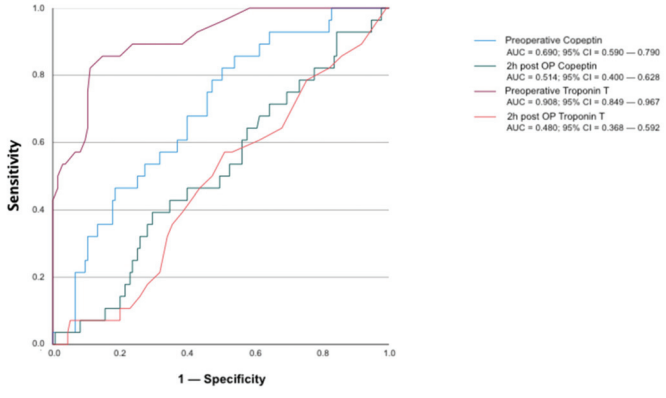

Figure A2. Receiver–operator characteristic curves for MINS and Copeptin concentrations at baseline (blue) and within two hours after surgery (green) and Troponin T concentrations at baseline (red) and within two hours after surgery (orange). 2 h post OP, within two hours after surgery; AUC, area under the curve; CI, confidence interval.

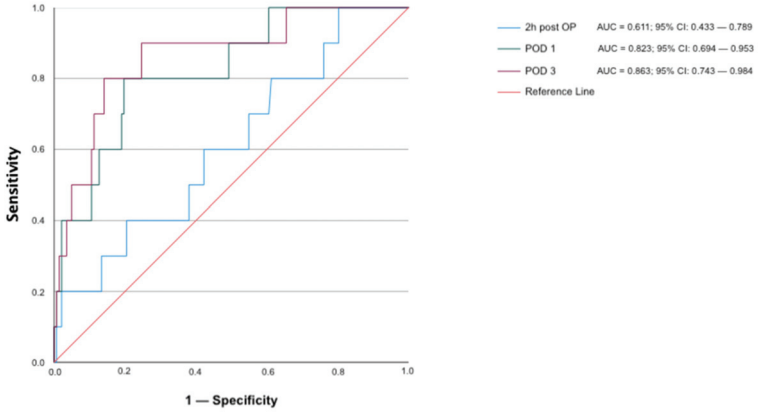

Figure A3. Receiver–operator characteristic curves for cardiovascular complications within 30 days after surgery and Copeptin concentrations at baseline (blue), within two hours after surgery (green), on the first postoperative day (red) and on the third postoperative day (orange). 2 h post OP, within two hours after surgery; AUC, area under the curve; CI, confidence interval.

References

1. Weiser, T.G.; Haynes, A.B.; Molina, G.; Lipsitz, S.R.; Esquivel, M.M.; Uribe-Leitz, T.; Fu, R.; Azad, T.; Chao, T.E.; Berry, W.R.; et al. Estimate of the global volume of surgery in 2012: An assessment supporting improved health outcomes. *Lancet* **2015**, *385*, S11. [CrossRef]
2. Devereaux, P.J.; Duceppe, E.; Guyatt, G.; Tandon, V.; Rodseth, R.; Biccard, B.M.; Xavier, D.; Szczeklik, W.; Meyhoff, C.S.; Vincent, J.; et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA-J. Am. Med. Assoc.* **2017**, *317*, 1642–1651. [CrossRef]
3. Smilowitz, N.R.; Gupta, N.; Ramakrishna, H.; Guo, Y.; Berger, J.S.; Bangalore, S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol.* **2017**, *2*, 181–187. [CrossRef]
4. Turan, A.; Chang, C.; Cohen, B.; Saasouh, W.; Essber, H.; Yang, D.; Ma, C.; Hovsepyan, K.; Khanna, A.K.; Vitale, J.; et al. Incidence, Severity, and Detection of Blood Pressure Perturbations after Abdominal Surgery—A prospective blinded observational study. *Anesthesiology* **2019**, *130*, 550–559. [CrossRef] [PubMed]
5. Shoemaker, W.C.; Appel, P.L.; Kram, H.B. Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. *Crit. Care Med.* **1988**, *16*, 1117–1120. [CrossRef] [PubMed]
6. Chernow, B.; Alexander, H.R.; Smallridge, R.C.; Thompson, W.R.; Cook, D.; Beardsley, D.; Fink, M.P.; Lake, C.R.; Fletcher, J.R. Hormonal Responses to Graded Surgical Stress. *Arch. Intern. Med.* **1987**, *147*, 1273–1278. [CrossRef]
7. Parker, S.D.; Breslow, M.J.; Frank, S.M.; Rosenfeld, B.A.; Norris, E.J.; Christopherson, R.; Rock, P.; Gottlieb, S.O.; Raff, H.; Perler, B.A.; et al. Catecholamine and cortisol responses to lower extremity revascularization: Correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group. *Crit. Care Med.* **1995**, *23*, 1954–1961. [CrossRef]
8. Devereaux, P.J.; Yang, H.; Yusuf, S.W.; Guyatt, G.H.; Leslie, K.; Villar, J.C.; Xavier, D.; Chrolavicius, S.; Greenspan, L.; Pogue, J.; et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. *Lancet* **2008**, *371*, 1839–1847. [CrossRef]
9. Devereaux, P.J.; Szczeklik, W. Myocardial injury after non-cardiac surgery: Diagnosis and management. *Eur. Heart J.* **2019**, *41*, 3083–3091. [CrossRef]
10. Gill, N.P.; Wright, B.; Reilly, C.S. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. *Br. J. Anaesth.* **1992**, *68*, 471–473. [CrossRef]
11. Mauermann, E.; Bolliger, D.; Seeberger, E.; Puelacher, C.; Corbiere, S.; Filipovic, M.; Seeberger, M.; Mueller, C.; Buse, G.L. Incremental value of preoperative copeptin for predicting myocardial injury. *Anesth. Analg.* **2016**, *123*, 1363–1371. [CrossRef] [PubMed]
12. Lipinski, M.J.; Escárcega, R.O.; D'Ascenzo, F.; Magalhães, M.A.; Baker, N.C.; Torguson, R.; Chen, F.; Epstein, S.E.; Miró, O.; Llorens, P.; et al. A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction. *Am. J. Cardiol.* **2014**, *113*, 1581–1591. [CrossRef] [PubMed]
13. Christ-Crain, M. Vasopressin and Copeptin in health and disease. *Rev. Endocr. Metab. Disord.* **2019**, *20*, 283–294. [CrossRef]
14. Balanescu, S.; Kopp, P.; Gaskill, M.B.; Morgenthaler, N.G.; Schindler, C.; Rutishauser, J. Correlation of plasma copeptin and vasopressin concentrations in hypo-, iso-, and hyper-osmolar states. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 1046–1052. [CrossRef] [PubMed]

15. Bolignano, D.; Cabassi, A.; Fiaccadori, E.; Ghigo, E.; Pasquali, R.; Peracino, A.; Peri, A.; Plebani, M.; Santoro, A.; Settanni, F.; et al. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. *Clin. Chem. Lab. Med.* **2014**, *52*, 1447–1456. [CrossRef] [PubMed]
16. Nickel, C.H.; Bingisser, R.; Morgenthaler, N.G. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. *BMC Med.* **2012**, *10*, 7. [CrossRef]
17. Khan, S.Q.; Dhillon, O.S.; O'Brien, R.J.; Struck, J.; Quinn, P.A.; Morgenthaler, N.G.; Squire, I.B.; Davies, J.E.; Bergmann, A.; Ng, L. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester acute myocardial infarction peptide (LAMP) study. *Circulation* **2007**, *115*, 2103–2110. [CrossRef]
18. Alehagen, U.; Dahlström, U.; Rehfeld, J.F.; Goetze, J.P. Association of copeptin and N-terminal proBNP concentrations with risk of cardiovascular death in older patients with symptoms of heart failure. *JAMA-J. Am. Med. Assoc.* **2011**, *305*, 2088–2095. [CrossRef]
19. Morgenthaler, N.G.; Müller, B.; Struck, J.; Bergmann, A.; Redl, H.; Christ-Crain, M. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. *Shock* **2007**, *28*, 219–226. [CrossRef]
20. Reiterer, C.; Kabon, B.; Von Sonnenburg, M.F.; Starlinger, P.; Taschner, A.; Zotti, O.; Goshin, J.; Drlicek, G.; Fleischmann, E. The effect of supplemental oxygen on perioperative brain natriuretic peptide concentration in cardiac risk patients—A protocol for a prospective randomized clinical trial. *Trials* **2020**, *21*, 400. [CrossRef]
21. Reiterer, C.; Kabon, B.; Taschner, A.; von Sonnenburg, M.F.; Graf, A.; Adamowitsch, N.; Starlinger, P.; Goshin, J.; Fraunschiel, M.; Fleischmann, E. Perioperative supplemental oxygen and NT-proBNP concentrations after major abdominal surgery—A prospective randomized clinical trial. *J. Clin. Anesth.* **2021**, *73*, 110379. [CrossRef] [PubMed]
22. Gan, T.J.; Sooitt, A.; Maroof, M.; El-Moalem, H.; Robertson, K.M.; Moretti, E.; Dwane, P.; Glass, P.S.A. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* **2002**, *97*, 820–826. [CrossRef]
23. Feldheiser, A.; Conroy, P.; Bonomo, T.; Cox, B.; Garces, T.R.; Spies, C.; Anaesthesia Working Group of the Enhanced Recovery after Surgery (ERAS®) Society. Development and feasibility study of an algorithm for intraoperative goaldirected haemodynamic management in noncardiac surgery. *J. Int. Med. Res.* **2012**, *40*, 1227–1241. [CrossRef] [PubMed]
24. Spence, J.; LeManach, Y.; Chan, M.T.; Wang, C.Y.; Sigamani, A.; Xavier, D.; Pearse, R.; Alonso-Coello, P.; Garutti, I.; Srinathan, S.K.; et al. Myocardial injury after noncardiac surgery: A large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* **2014**, *120*, 564–578. [CrossRef]
25. Kamber, F.; Mauermann, E.; Seeberger, E.; Guerke, L.; Mueller, C.; Bolliger, D.; Buse, G.A.L. Peri-operative copeptin concentrations and their association with myocardial injury after vascular surgery: A prospective observational cohort study. *Eur. J. Anaesthesiol.* **2018**, *35*, 682–690. [CrossRef] [PubMed]
26. Schulz, K.F.; Altman, D.G.; Moher, D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *Int. J. Surg.* **2011**, *9*, 672–677. [CrossRef]
27. Staniforth, A.D.; Kinnear, W.J.M.; Starling, R.; Hetmanski, D.J.; Cowley, A.J. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyn-Stokes respiration. *Eur. Heart J.* **1998**, *19*, 922–928. [CrossRef]
28. Hafner, C.; Wu, J.; Tiboldi, A.; Hess, M.; Mitulović, G.; Kaun, C.; Krychtiuk, K.; Wojta, J.; Ullrich, R.; Tretter, E.V.; et al. Hyperoxia induces inflammation and cytotoxicity in human adult cardiac myocytes. *Shock* **2017**, *47*, 436–444. [CrossRef] [PubMed]
29. Fonnes, S.; Gögenur, I.; Søndergaard, E.S.; Siersma, V.D.; Jorgensen, L.N.; Wetterslev, J.; Meyhoff, C.S.; Søndergaard, E. Perioperative hyperoxia—Long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. *Int. J. Cardiol.* **2016**, *215*, 238–243. [CrossRef]
30. Ruetzler, K.; Cohen, B.; Leung, S.; Mascha, E.J.; Knotzer, J.; Kurz, A.; Sessler, D.I.; Turan, A. Supplemental intraoperative oxygen does not promote acute kidney injury or cardiovascular complications after noncardiac surgery: Subanalysis of an alternating intervention trial. *Anesth. Analg.* **2019**, *130*, 933–940. [CrossRef]
31. Holse, C.; Aasvang, E.K.; Vester-Andersen, M.; Rasmussen, L.S.; Wetterslev, J.; Christensen, R.; Jorgensen, L.N.; Pedersen, S.S.; Loft, F.C.; Troensegaard, H.; et al. Hyperoxia and Antioxidants for Myocardial Injury in Noncardiac Surgery: A 2 × 2 Factorial, Blinded, Randomized Clinical Trial. *Anesthesiology* **2022**, *136*, 408–419. [CrossRef] [PubMed]
32. Sametz, W.; Metzler, H.; Gries, M.; Porta, S.; Sadjak, A.; Supanz, S.; Juan, H. Perioperative catecholamine changes in cardiac risk patients. *Eur. J. Clin. Investig.* **1999**, *29*, 582–587. [CrossRef] [PubMed]
33. Devereaux, P.J.; Duceppe, E.; Guyatt, G.; Tandon, V.; Rodseth, R.; Biccard, B.M.; Xavier, D.; Szczeklik, W.; Meyhoff, C.; Vincent, J.; et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): An international, randomised, placebo-controlled trial. *Lancet* **2018**, *391*, 2325–2334. [CrossRef]
34. Rodseth, R.N.; Biccard, B.M.; Chu, R.; Buse, G.A.L.; Thabane, L.; Bakhai, A.; Bolliger, D.; Cagini, L.; Cahill, T.J.; Cardinale, D.; et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: Systematic review and individual patient meta-analysis. *Anesthesiology* **2013**, *119*, 271–283. [CrossRef] [PubMed]
35. Reiterer, C.; Kabon, B.; Taschner, A.; Zotti, O.; Kurz, A.; Fleischmann, E. A comparison of intraoperative goal-directed intravenous administration of crystalloid versus colloid solutions on the postoperative maximum N-terminal pro brain natriuretic peptide in patients undergoing moderate- To high-risk noncardiac surgery. *BMC Anesthesiol.* **2020**, *20*, 192. [CrossRef] [PubMed]
36. Devereaux, P.J.; Sessler, D.I. Cardiac complications in patients undergoing major noncardiac surgery. *N. Engl. J. Med.* **2015**, *373*, 2258–2269. [CrossRef] [PubMed]

37. Solomon, M.J.; Young, C.J.; Eyers, A.A.; Roberts, R.A. Randomized clinical trial of laparoscopic versus open abdominal rectopexy for rectal prolapse. *Br. J. Surg.* **2002**, *89*, 35–39. [CrossRef] [PubMed]
38. Arsalani-Zadeh, R.; Ullah, S.; Khan, S.; MacFie, J. Oxidative stress in laparoscopic versus open abdominal surgery: A systematic review. *J. Surg. Res.* **2011**, *169*, e59–e68. [CrossRef]
39. Obradovic, M.; Kurz, A.; Kabon, B.; Roth, G.; Kimberger, O.; Zotti, O.; Bayoumi, A.; Reiterer, C.; Stift, A.; Fleischmann, E. The effect of intraoperative goal-directed crystalloid versus colloid administration on perioperative inflammatory markers- Asubstudy of a randomized controlled trial. *BMC Anesthesiol.* **2020**, *20*, 210. [CrossRef]
40. Reiterer, C.; Fleischmann, E.; Taschner, A.; Adamowitsch, N.; von Sonnenburg, M.F.; Graf, A.; Fraunschiel, M.; Starlinger, P.; Goschin, J.; Kabon, B. Perioperative supplemental oxygen and oxidative stress in patients undergoing moderate- to high-risk major abdominal surgery—A subanalysis of randomized clinical trial. *J. Clin. Anesth.* **2022**, *77*, 110614. [CrossRef]
41. Stagos, D.; Goutzourelas, N.; Ntontou, A.M.; Kafantaris, I.; Deli, C.K.; Poulios, A.; Jamurtas, A.Z.; Bar-Or, D.; Kouretas, D. Assessment of eccentric exercise-induced oxidative stress using oxidation-reduction potential markers. *Oxid. Med. Cell. Longev.* **2015**, *2015*, 204615. [CrossRef] [PubMed]

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Systematic Review

A Comparison of McGrath Videolaryngoscope versus Macintosh Laryngoscope for Nasotracheal Intubation: A Systematic Review and Meta-Analysis

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Abstract: Background: In this study, it was shown that the routine use of McGrath videolaryngoscopy may improve intubation success rates. The benefits to using a videolaryngoscope in nasotracheal intubation were also demonstrated. However, no solid evidence concerning the effectiveness of the use of McGrath videolaryngoscopes in nasotracheal intubation has previously been reported. As a result, we questioned whether, in adult patients who underwent oral and maxillofacial surgeries with nasotracheal intubation (P), the use of a McGrath videolaryngoscope (I) compared with a Macintosh laryngoscope (C) could reduce the intubation time, improve glottis visualization to a score of classification 1 in the Cormack–Lehane classification system, and improve the first-attempt success rate (O). The secondary outcomes measured were the rate of the use of Magill forceps and the external laryngeal pressure (BURP) maneuver used. Methods: An extensive literature search was conducted using databases. Only randomized controlled trials that compared the McGrath videolaryngoscopy and Macintosh laryngoscopy techniques in nasotracheal intubation in adult patients were included. Results: Five articles met the inclusion criteria and were included in the final analysis (n = 331 patients). The results showed a significant decrease in intubation time and a higher rate of classification 1 scores in the Cormack–Lehane classification system, but no difference in the first-attempt success rates were found between the McGrath group and the Macintosh group. Decreases in the rate of the use of Magill forceps and the use of the external laryngeal pressure maneuver were also found in the pooled analysis. With regard to the overall risk of bias, the selected trials were classified to have at least a moderate risk of bias, because none of the trials could blind the operator to the type of laryngoscope used. Conclusions: Our analysis suggests that the use of a McGrath videolaryngoscope in nasotracheal intubation resulted in shorter intubation times, improved views of the glottis and similar first-success rates in adult patients who received general anesthesia for dental, oral, maxillofacial, or head and neck cancer surgery, and also reduced the use of Magill forceps and the BURP maneuver.

Keywords: McGrath; videolaryngoscope; nasotracheal intubation

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1. Introduction

McGrath videolaryngoscopes comprise a direct video laryngoscope, a battery-contained handle, and a disposable plastic blade in a single device, and anesthesiologists can perform intubation using a McGrath videolaryngoscope in patients with either normal or difficult airways. Kriege et al. revealed that the routine use of McGrath videolaryngoscopy may improve intubation success rates [1].

Hoshijima et al. completed a comprehensive systematic review and meta-analysis in which a comparison of McGrath videolaryngoscopes versus Macintosh laryngoscopes in orotracheal intubation was presented. The authors suggested that the McGrath videolaryngoscope was more suitable than the Macintosh laryngoscope in terms of glottic visualization, but the McGrath videolaryngoscope extended the intubation time, and its success rate in terms of tracheal intubation was not superior [2]. However, the study did not compare these two tools in nasotracheal intubation.

Nasotracheal intubation is largely performed during oral and maxillofacial surgeries. The benefits of this technique include the fact that it provides good accessibility and a larger surgical field [3]. The procedure involves passing an endotracheal tube through the nostril into the nasopharynx and the trachea. Several techniques are often used to enhance the success rate during nasotracheal intubation, such as the use of Magill forceps or the external laryngeal pressure maneuver [3]. A systematic review and meta-analysis by Jiang et al. compared videolaryngoscopy with direct laryngoscopy in nasotracheal intubation and concluded that the use of a videolaryngoscope did not improve the success rate of nasotracheal intubation in adult patients, but it improved the first-attempt success rate, optimized the laryngeal view, and decreased the intubation time. Additionally, the analysis showed a lower rate of the use of Magill forceps [4]. However, studies that used videolaryngoscopy included in this meta-analysis were detailed, and this study did not specifically survey the McGrath videolaryngoscopy technique.

Currently, there is no solid evidence concerning the effectiveness of McGrath videolaryngoscopes in nasotracheal intubation. As a result, we questioned whether, in adult patients who underwent oral and maxillofacial surgeries with nasotracheal intubation (P), the use of a McGrath videolaryngoscope (I) compared to a Macintosh laryngoscope (C) could reduce intubation time, improve glottis visualization to a score of classification 1 in the Cormack–Lehane classification system, and improve the rate of first-attempt success in intubation (O). The secondary outcomes were the rate of the use of Magill forceps and the use of the external laryngeal pressure (BURP) maneuver.

2. Methods

This study followed the Cochrane Handbook for Systematic Review of Interventions [5] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [6], and the study protocol was registered in the International prospective register of systematic reviews (PROSPERO) in 2022 (registration number: CRD42022293199).

2.1. Search Strategy

An extensive literature search was conducted using PubMed and Cochrane Central Register of Controlled Trials from 1 January 1980 to 10 October 2021. The last search date was 1 November 2021. The search strategy used in the two electronic databases was the use of search strings, including "McGrath, (or McGrath MAC, videolaryngoscope), and nasotracheal intubation (or NTI)" in all fields. Reviews, case reports, and studies published in abstract forms were excluded. No language restriction was imposed.

2.2. Study Selection

1. Inclusion Criteria Prospective randomized clinical trials that compared the McGrath videolaryngoscopy and Macintosh laryngoscopy techniques in nasotracheal intubation in adult patients (age $\geq$ 18 years old) who underwent operations with general anesthesia were included.
2. Exclusion Criteria We excluded manikin trials, cadaver studies, observational studies, studies that involved tracheal intubation during cardiopulmonary resuscitation, double-lumen tubes, pediatric patients (age < 18 years old), and articles that involved nasotracheal intubation with other videolaryngoscopes.

2.3. Outcomes

1. Primary outcome The primary outcomes were the intubation time (from the intranasal placement of the tube to the detection of carbon dioxide via capnography), the rate of classification 1 scores in the Cormack–Lehane classification system, and the first-attempt success rate.
2. Secondary outcome The secondary outcomes were the rate of the use of Magill forceps and the use of the external laryngeal pressure (or backward, upward, or rightward pressure) maneuver.

2.4. Data Extraction

Three authors (Ho, CH, Hsu, WH, and Chen, LC) assessed each article independently, evaluated whether it met the inclusion criteria, and used standardized data collection forms for data extraction. For continuous variables, the mean, standard deviation (SD), and sample size were extracted from each eligible article. Data such as the median and interquartile range that could not be used directly were converted to means and SDs using formulae provided in the Cochrane Handbook. For the dichotomous data, the number of events that occurred and the sample size were also extracted. If more than two comparisons were made in one study, the authors only extracted the results concerning the McGrath videolaryngoscopy and Macintosh laryngoscopy groups.

2.5. Data Synthesis

In terms of the data synthesis of the outcomes involved in the studies, three types of outcomes were observed:

1. All of the studies included shared the same methods and units when evaluating the outcomes, such as intubating time, first-attempt success rate, the Cormack–Lehane classification of the quality of the view of the glottis/vocal cord, and the use of Magill forceps during intubation (continuous outcomes needed to share the same unit);
2. When evaluating the outcomes, different terms which shared one similar meaning were used: external laryngeal manipulation. Some of the studies used the term "backward–upward–rightward pressure maneuver (BURP maneuver)" or "external laryngeal pressure" to define the same maneuver.
3. The studies included used different tools/values to evaluate the outcome of ease of intubation. This kind of outcome was not synthesized and included in our studies.

Furthermore, the data were only synthesized and evaluated when more than 50% of the studies had thoroughly included data-concerning outcomes.

Five groups of data met the criteria and were synthesized: intubation time, Cormack–Lehane grade, the use of Magill forceps, external laryngeal pressure, and first-attempt success rate. Meta-analyses were performed using RevMan 5.4 software, The Nordic Cochrane Centre, Copenhagen, Denmark (https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download, accessed on 21 October 2021). A random-effects model was applied to account for clinical and methodological heterogeneity between studies. Statistical heterogeneity was assessed with I^2, where values of 30–60% and 50–90% were considered to represent moderate and substantial heterogeneity, respectively. The risk ratios (RRs) or odds ratios (ORs) with 95% CIs were calculated for dichotomous/discrete outcomes and then pooled with the Mantel–Haenszel method. Continuous outcomes (intubation time) were calculated with the weighted mean differences (WMDs) of mean values and SDs using the inverse variance method. A p-value < 0.05 was considered statistically significant. The outcomes of intubation time and Cormack–Lehane grade were analyzed using a random-effects model, and the other three study data were analyzed using a fixed-effects model.

2.6. Risk of Bias

Two authors (Ho, CH and Hsu, WH) independently appraised the risk of bias of the selected eligible studies using the "risk of bias" assessment tool in the Cochrane Handbook

and generated a "risk of bias" summary figure using Review Manager (RevMan 5.4.1). Concerning the overall risk-of-bias judgement, if the trial was assessed to be at low risk of bias in all domains for this result, the study was classified as being "low-risk"; if the trial was assessed to raise some concerns in more than one domain without any high risk of bias in any domain, the study was classified as having "some concerns"; if the trial was assessed to be at high risk of bias in more than one domain, the study was classified as being "high-risk".

2.7. Quality Assessment

The quality of evidence concerning the outcomes that we investigated was assessed by applying the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to study the limitations, consistency of effects, imprecision, indirectness, and publication bias in our reviews [7]. After the assessment, a table concerning the GRADE evidence profile was created using GRADEpro software (https://www.gradepro.org/, accessed on 18 April 2022) to rate all outcomes, including very low, low, moderate, or high quality.

3. Results

3.1. Searching Result

Following our search strategy, 67 papers were found on PubMed, and 387 papers were found on Cochrane. Duplicated and unpublished studies were excluded initially, and the remaining 236 studies were screened carefully using their titles and abstracts. A total of 224 studies were excluded at this step, of which 164 studies were irrelevant (including studies concerning orotracheal intubation or different topics), 7 studies discussed videolaryngoscopes, 2 studies were manikin studies, and 51 studies were not RCTs. In total, 12 articles were selected for full text assessment following our inclusion and exclusion criteria. A total of seven articles were excluded, of which one article discussed airways that were predicted to be difficult and did not have adequate outcomes that we could analyze [8], one article discussed a pediatric population [9], and five articles discussed different videolaryngoscopes [10–14]. Eventually, five articles were found to meet our inclusion criteria and were included in the final analysis (n = 331 patients) [15–19] (Figure 1).

3.2. Included Studies

The characteristics of the selected studies are summarized in Table 1. In the meta-analysis, a total of 331 cases were included (165 cases that used the McGrath laryngoscope and 166 cases that used the Macintosh laryngoscope). The type of surgery performed in the selected studies included dental, oral, maxillofacial, and head and neck cancer surgery. All of the participants were classified as ASA 1~2. All five studies were carried out in patients with normal airways.

3.3. Result of Primary Outcomes

In the analysis of the five selected studies, the results showed significant decreases in intubation times in the McGrath group compared with the Macintosh group (MD, −10.98 sec; 95% CI, −18.97 to −2.98; n = 331; p = 0.007; I^2 = 88%, Figure 2). During intubation, when using McGrath videolaryngoscope, there was a greater possibility of obtaining a view of the vocal cords that was classified as classification 1 in the Cormack–Lehane classification system (RR, 2.34; 95% CI, 1.25 to 4.40; n = 331; p = 0.008; I^2 = 87%, Figure 3), which indicated that using the McGrath videolaryngoscope provided better glottis visualization during nasotracheal intubation. All of the trials separately revealed significantly better Cormack–Lehane classifications when the McGrath videolaryngoscope was used. Pooled data showed no significant differences in the first-attempt success rates between the McGrath and Macintosh laryngoscopes (RR, 1.04; 95% CI, 1.00 to 1.08; n = 331; p = 0.17; I^2 = 38%, Figure 4).

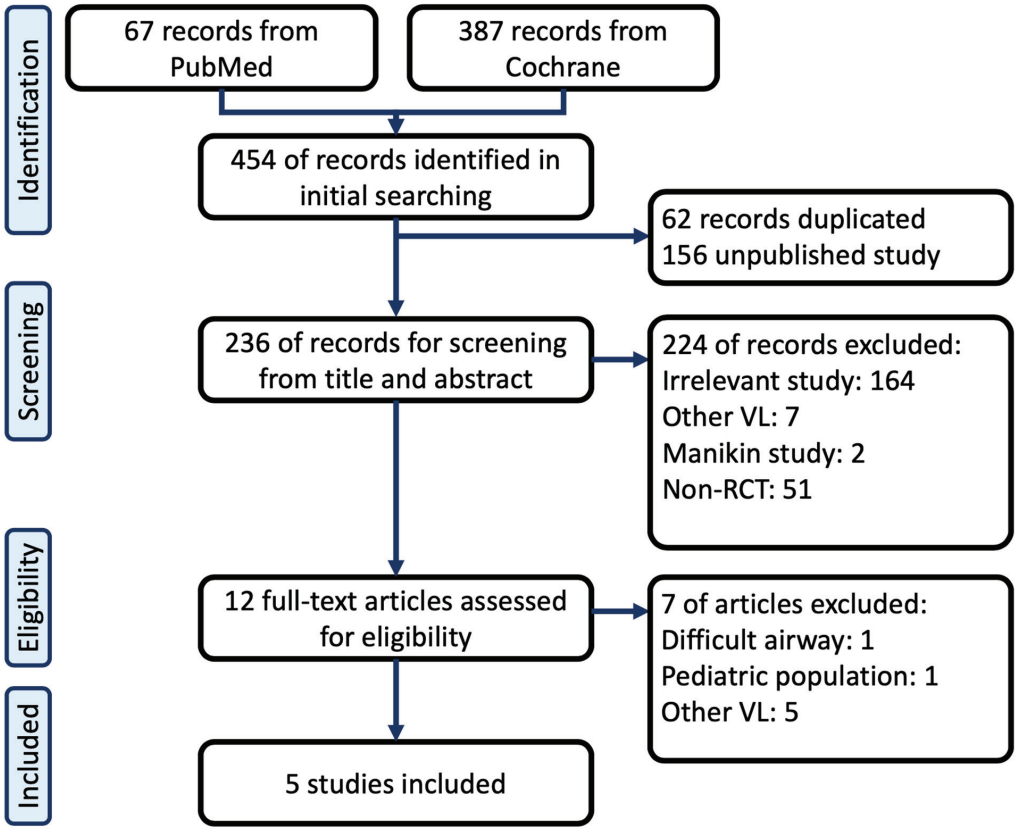

Figure 1. Flow chart of the systemic review. VL, videolaryngoscope; RCT, randomized control trial. Articles Excluded due to Difficult airway [8], Pediatric population [9], Other VL [10–14]; Included studies [15–19].

Table 1. The summary of the characteristics of included studies.

Author	Year	Participants	Case Number (MG/ML)	ASA Status	Outcomes					Other Outcomes
					Intubation Time	CL Classification 1	Successful Rate in 1st Attempt	Magill Forceps Use	BURP Maneuver	
Kwak [15]	2015	Oral and maxillofacial surgery	70 (35/35)	1~2	V	V	V	V		Ease of intubation, bleeding
Sato [16]	2017	Elective oral surgery	40 (20/20)	1~2	V	V	V	V	V	bleeding, esophageal intubation, dental injury
Chae [17]	2019	Elective oral and maxillofacial surgery	82 (41/41)	1~2	V	V	V	V	V	Nasotracheal intubation difficulty score
Roh [18]	2019	Dental or maxillofacial surgery	80 (40/40)	1~2	V	V	V	V	V	Bleeding risk, ease of intubaiton
Ambulkar [19]	2021	Elective head and neck cancer surgery	59 (29/30)	1~2	V	V	V	V	V	Difficulty of intubation

MG: McGrath laryngoscope, ML: Macintosh laryngoscope, ASA status: American Society of Anesthesiologists Classification, CL: Cormack–Lehane classification; BURP: backward, upward, right lateral pressure maneuver.

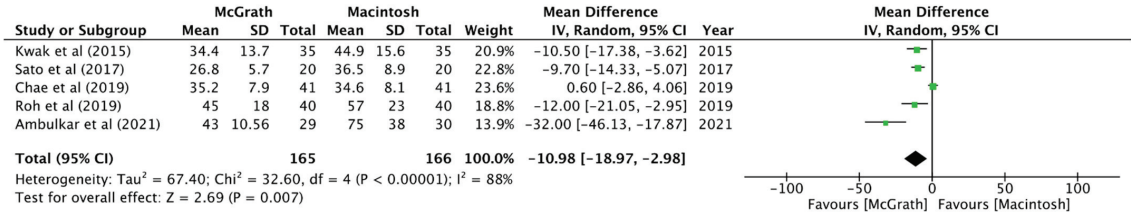

Figure 2. Forest plot of the intubation time of nasotracheal intubation (McGrath vs. Macintosh laryngoscope). The width of the horizontal line represents the 95% confidence interval (CI) of each study, and the square proportional represents the weight of each study. The rhombus represents the pooled rate and 95% CI. (same as below).

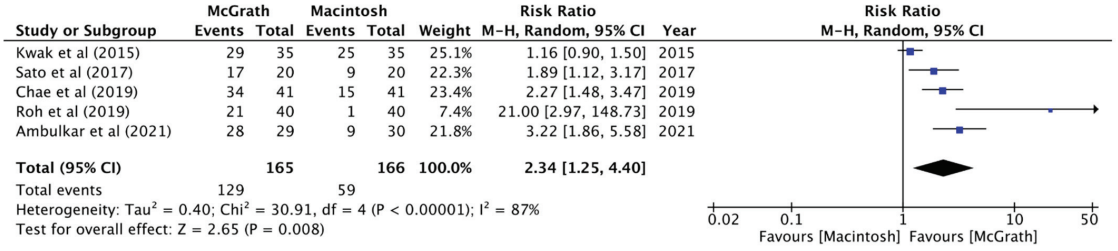

Figure 3. Forest plot of the rate of Cormack–Lehane classification 1 (McGrath vs. Macintosh laryngoscope).

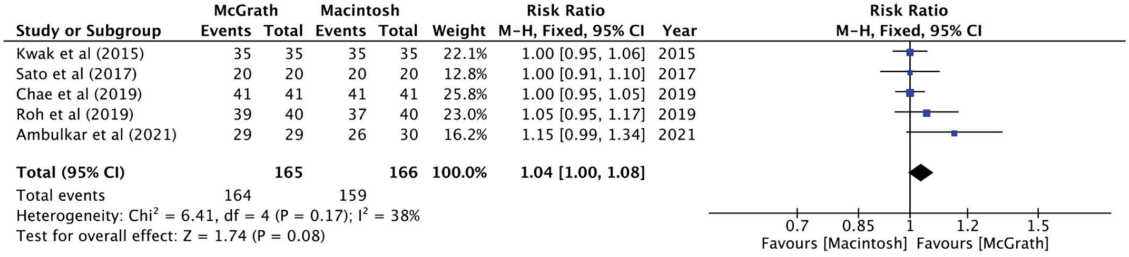

Figure 4. Forest plot of the first-attempt success rate (McGrath vs. Macintosh laryngoscope).

3.4. Result of Secondary Outcomes

All five studies reported a comparison of the rate of the use of Magill forceps. The pooled analysis showed that McGrath videolaryngoscopy compared with Macintosh laryngoscopy was associated with a reduced rate of Magill forceps use (OR, 0.08; 95% CI, 0.03 to 0.23; $n = 331$; $p < 0.00001$; $I^2 = 0\%$, Figure 5). The use of the external laryngeal pressure maneuver was compared in four studies. Kwak et al. used optimal external laryngeal manipulation despite what the Cormack–Lehane classification was and compared the quality of glottis visualization before and after optimal external laryngeal manipulation. The pooled analysis revealed a significant difference between the two groups (OR, 0.13; 95% CI, 0.07 to 0.25; $n = 261$; $p = 0.002$; $I^2 = 80\%$, Figure 6).

3.5. Risk of Bias

The risks of bias are summarized in Figure 7, and the overall risk of bias in the selected trials was classified to be at least a moderate risk of bias, because during all of the trials, blinding of the type of laryngoscope to the participants is impossible. In addition, Chae et al. did not present adequate outcomes that we could include.

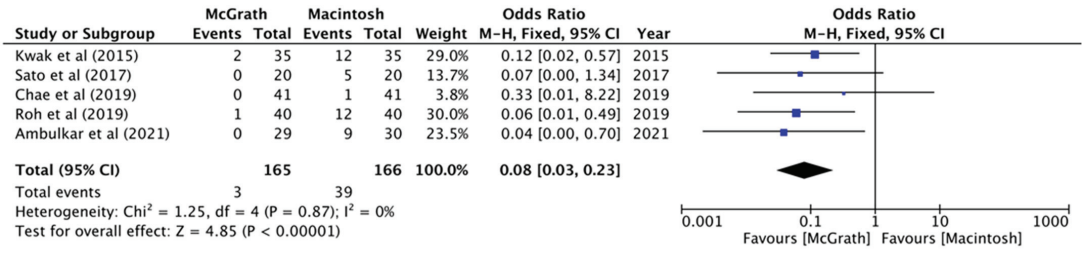

Figure 5. Forest plot of the Magill forceps used (McGrath vs. Macintosh laryngoscope).

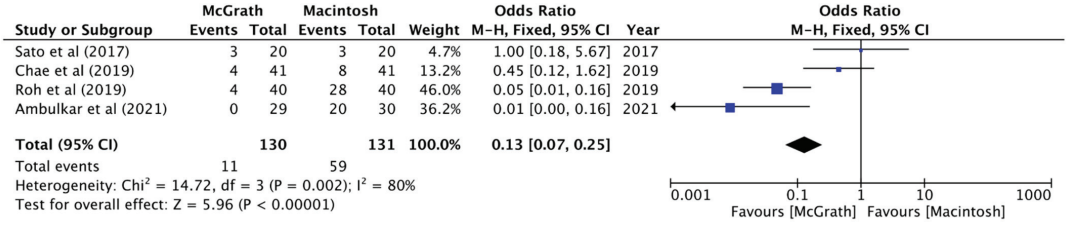

Figure 6. Forest plot of the external laryngeal pressure maneuver used (McGrath vs. Macintosh laryngoscope).

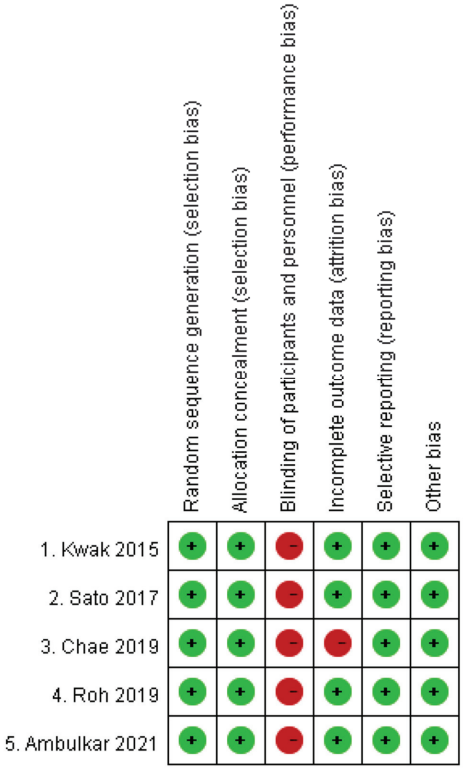

Figure 7. The summary of the risks of bias of the selected studies. Green circle with a plus symbol represents low risk of bias, and red circle with a minus symbol represents high risk of bias. All the studies face high risk of bias regarding the blinding of the participants.

3.6. GRADE Assessment

We evaluated the quality of evidence according to the GRADE assessment [7], and Table 2 displays a brief summary of the quality of evidence and the findings. Due to heterogeneity and the impossibility of blinding the participants, most of the outcomes were rated as low to very low quality, which is one of the limitations of our study.

Table 2. GRADE Evidence Profiles: McGrath for nasotracheal intubation.

Quality Assessment						Summary of Findings				
						Number of Patients (%)		Effect		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	McGrath	Macintosh	Relative Risk (95% CI)	Absolute Risk	Quality of Evidence
Intubation time										
5	No serious risk of bias *1	Serious *2	No serious limitation	No serious limitation	No Serious limitation	165	166	MD = −10.98 (−2.98~−18.97)		Low
Cormack-Lehane classification 1										
5	No serious risk of bias *1	Serious *2	No serious limitation	No serious limitation	No Serious limitation	129/165 (78.2%)	59/166 (35.5)	2.34 (1.25~4.40)	44 more per 100	Very low
First attempt successful rate										
5	No serious risk of bias *1	No serious limitation	No serious limitation	Mild limitation	No Serious limitation	164/165 (99.4%)	159/166 (95.8%)	1.04 (1.00~1.08)	Not Significant	Low
Use of Magill forceps										
5	No serious risk of bias *1	No serious limitation	No serious limitation	No serious limitation	No Serious limitation	3/165 (1.8%)	39/166 (23.5%)	OR = 0.08 (0.03–0.23)	21 less per 100	Low
Backward-upward-rightward Pressure Maneuver										
4	No serious risk of bias *1	Serious *2	No serious limitation	No serious limitation	No Serious limitation	11/130	59/131	OR = 0.13 (0.07–0.25)	36 less per 100	Very low

MD: mean difference, OR: odds ratio. *1: All the trials involved has the risk of bias due to incapability of blinding of the participants; *2: substantial heterogeneity found (I^2 between 60–90%). Quality of evidence: low means that confidence in the effects of the intervention is very likely to change with future research findings or all studies have severe limitations; very low means that uncertainty remains about the effects of the intervention.

4. Discussion

Our analysis showed that the use of the McGrath videolaryngoscope shortens the nasotracheal intubation time compared with that needed using the Macintosh laryngoscope. This result was compatible with that of the previous meta-analysis [4]. Jiang et al. reported a pooled analysis that showed shorter intubation times in nasotracheal intubation using different videolaryngoscopes. However, Hoshijima et al. reported a prolonged orotracheal intubation time when the McGrath videolaryngoscope was used compared with when the Macintosh laryngoscope was used [2]. The difference in these results may be the result of differences between the process of nasotracheal intubation and traditional orotracheal intubation. The process of nasotracheal intubation includes passing an endotracheal tube through the naris into the nasopharynx and using the laryngoscope to visualize the endotracheal tube that passes through the vocal cords. Operators were not able to adjust the shape of the endotracheal tubes using stylets. Due to the process and limitations mentioned above, the time needed for nasotracheal intubation is more unpredictable and relies more heavily on the view of the glottis using a laryngoscope. Furthermore, most of the participants in our studies underwent dental, oral, maxillofacial, and head and neck cancer surgery, which means our population was very different from that studied by Hoshijima et al. Concerning the comparison of the McGrath videolaryngoscope and other videolaryngoscopes, the McGrath videolaryngoscope allowed for a shorter orotracheal intubation time as the patients had restricted neck movement and were limited in their ability to open their mouths [20].

The results of our study also display an increase in the rate of classification 1 scores from the Cormack–Lehane classification system when using the McGrath videolaryngoscope, which suggests that the glottis can be visualized better using this technique. A previous study revealed that laryngeal grade views were superior to the McGrath vide-

olaryngoscope than the Macintosh laryngoscope in simulated difficult airways [21]. The improvement of glottic visualization provided by videolaryngoscopes may be attributed to the digital camera on the blade tip of videolaryngoscopes, which allows practitioners to access the glottis more intuitively, gain a wider visual angle, and decrease the demand of the alignment of the visual axes. In order to predict the rate of difficult intubation, the Cormack–Lehane classification system was utilized to describe the views of laryngeal structures via direct laryngoscopy. Nevertheless, it was questioned whether this classification was appropriate for predicting the success rate with videolaryngoscopy [22]. Videolaryngoscopy provides indirect views of the glottis, so practitioners should have good hand–eye coordination and the adequate experience required to perform videolaryngoscopies.

A previous study showed that the results concerning the first-attempt success rates between McGrath and Macintosh laryngoscopy in tracheal intubation were similar, and first-attempt success rates were only increased in patients with difficult airways using videolaryngoscopy in nasotracheal intubation [5]. The results of our study revealed a similar result that showed McGrath and Macintosh laryngoscopes were not statistically different in terms of the first-attempt success rates. However, a previous study that investigated the use of these techniques in patients with predicted difficult airways showed that the use of the McGrath videolaryngoscope increased the first-attempt success rate [8].

In the nasotracheal intubation procedure, practitioners often use assistive maneuvers to pass the endotracheal tube through the vocal cords, including Magill forceps, the BURP maneuver, cuff inflation, etc. In our analysis, the rates of the use of Magill forceps and external laryngeal pressure were much lower in nasotracheal intubation procedures that utilized the McGrath videolaryngoscope. Previous RCTs demonstrated the same conclusion that using videolaryngoscopes in nasotracheal intubation resulted in fewer uses of Magill forceps compared with using a conventional direct laryngoscope [23]. Fewer uses of assistive maneuvers could not only represent clearer laryngeal views but also reduce possible complications, such as direct pharyngeal injury and cuff tear [24,25]. While nasotracheal intubation is associated with numerous complications [26], anesthesiologists should be concerned about every possible complication.

There were several limitations in our analysis. First, every study that we included had a different study protocol, strategy, and endpoint, which meant that measurement biases on primary and secondary outcomes were present in our analysis. Second, all of the participants that we enrolled were adults; therefore, these results cannot be directly applied to pediatric populations. Additionally, one trial gave the contradictory suggestion that the Macintosh laryngoscope provided shorter nasotracheal intubation times, better tracheal navigation, and required less use of the cuff inflation method in a pediatric population [9]. Third, nasotracheal intubation was usually performed in patients with predicted difficult airways; however, the cases in our analysis were classified as normal airways. As a result, the conclusions would be difficult to apply to the case of predicted difficult airways. Finally, two factors decrease the quality of the evidence of our outcomes: one is the impossibility of blinding due to the different appearance of the two intubating tools, and the other is the heterogeneity of the studies included.

In conclusion, our analysis suggests that using the McGrath videolaryngoscope in nasotracheal intubation provided shorter intubation times, better glottis views, and higher first-success rates in adult patients who received general anesthesia for dental, oral, maxillofacial, or head and neck cancer surgery, and also reduced the uses of Magill forceps and the BURP maneuver. However, additional high-quality trials should be obtained to clarify the benefits of the McGrath videolaryngoscope in terms of the overall success rate, in pediatric populations and in predicted difficult airways.

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the database, assess related articles, extract and sort out the data of selected trials, correct and revise the error of the article. T.-Y.L. This author helped to supervise the progress and the program of this analysis. M.L. This author helped to re-check the article of the analysis, including methodology and grammatical error, and was also a corresponding author. C.-W.L. This author helped to supervise the progress and the program of this analysis, and was also a corresponding author. All authors have read and agreed to the published version of the manuscript.

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References

1. Kriege, M.; Alflen, C.; Tzanova, I.; Schmidtmann, I.; Piepho, T.; Noppens, R.R. Evaluation of the McGrath MAC and Macintosh laryngoscope for tracheal intubation in 2000 patients undergoing general anaesthesia: The randomised multicentre EMMA trial study protocol. *BMJ Open* **2017**, *7*, e016907. [CrossRef] [PubMed]
2. Hoshijima, H.; Mihara, T.; Maruyama, K.; Denawa, Y.; Takahashi, M.; Shiga, T.; Nagasaka, H. McGrath videolaryngoscope versus Macintosh laryngoscope for tracheal intubation: A systematic review and meta-analysis with trial sequential analysis. *J. Clin. Anesth.* **2018**, *46*, 25–32. [CrossRef] [PubMed]
3. Prasanna, D.; Bhat, S. Nasotracheal Intubation: An Overview. *J. Maxillofac. Oral Surg.* **2014**, *13*, 366–372. [CrossRef] [PubMed]
4. Jiang, J.; Ma, D.-X.; Li, B.; Wu, A.-S.; Xue, F.-S. Videolaryngoscopy versus direct laryngoscopy for nasotracheal intubation: A systematic review and meta-analysis of randomised controlled trials. *J. Clin. Anesth.* **2019**, *52*, 6–16. [CrossRef]
5. Cumpston, M.; Li, T.; Page, M.J.; Chandler, J.; Welch, V.A.; Higgins, J.P.; Thomas, J. Updated guidance for trusted systematic reviews: A new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst. Rev.* **2019**, *10*, D142. [CrossRef]
6. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 105906. [CrossRef]
7. Guyatt, G.; Oxman, A.D.; Akl, E.A.; Kunz, R.; Vist, G.; Brozek, J.; Norris, S.; Falck-Ytter, Y.; Glasziou, P.; DeBeer, H.; et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* **2011**, *64*, 383–394. [CrossRef]
8. Zhu, H.; Liu, J.; Suo, L.; Zhou, C.; Sun, Y.; Jiang, H. A randomized controlled comparison of non-channeled king vision, McGrath MAC video laryngoscope and Macintosh direct laryngoscope for nasotracheal intubation in patients with predicted difficult intubations. *BMC Anesthesiol.* **2019**, *19*, 1–9. [CrossRef]
9. Yoo, J.Y.; Chae, Y.J.; Lee, Y.B.; Kim, S.; Lee, J.; Kim, D.H. A comparison of the Macintosh laryngoscope, McGrath video laryngoscope, and Pentax Airway Scope in paediatric nasotracheal intubation. *Sci. Rep.* **2018**, *8*, 17365. [CrossRef]
10. Seo, K.H.; Kim, K.M.; John, H.; Jun, J.H.; Han, M.; Kim, S. Comparison of C-MAC D-blade videolaryngoscope and McCoy laryngoscope efficacy for nasotracheal intubation in simulated cervical spinal injury: A prospective randomized comparative study. *BMC Anesthesiol.* **2020**, *20*, 1–9. [CrossRef]
11. Kadapamannil, D.; Rajan, S.; Barua, K.; Tosh, P.; Paul, J.; Kumar, L. Ease of intubation and hemodynamic responses to nasotracheal intubation using C-MAC videolaryngoscope with D blade: A comparison with use of traditional Macintosh laryngoscope. *J. Anaesthesiol. Clin. Pharmacol.* **2018**, *34*, 381–385. [CrossRef] [PubMed]
12. Xue, F.-S.; Li, X.-Y.; Liu, Q.-J.; Liu, H.-P.; Yang, Q.-Y.; Xu, Y.-C.; Liao, X.; Liu, Y. Circulatory responses to nasotracheal intubation: Comparison of GlideScope®videolaryngoscope and Macintosh direct laryngoscope. *Chin. Med. J.* **2008**, *121*, 1290–1296. [CrossRef] [PubMed]
13. Hazarika, H.; Saxena, A.; Meshram, P.; Bhargava, A.K. A randomized controlled trial comparing C Mac D Blade and Macintosh laryngoscope for nasotracheal intubation in patients undergoing surgeries for head and neck cancer. *Saudi J. Anaesth.* **2018**, *12*, 35–41. [CrossRef] [PubMed]
14. Jones, P.M.; Armstrong, K.P.; Armstrong, P.M.; Cherry, R.A.; Harle, C.C.; Hoogstra, J.; Turkstra, T.P. A Comparison of GlideScope®Videolaryngoscopy to Direct Laryngoscopy for Nasotracheal Intubation. *Anesth. Analg.* **2008**, *107*, 144–148. [CrossRef]
15. Kwak, H.-J.; Lee, S.-Y.; Lee, S.-Y.; Cho, S.-H.; Kim, H.-S.; Kim, J.-Y. McGrath Video Laryngoscopy Facilitates Routine Nasotracheal Intubation in Patients Undergoing Oral and Maxillofacial Surgery: A Comparison With Macintosh Laryngoscopy. *J. Oral Maxillofac. Surg.* **2016**, *74*, 256–261. [CrossRef]

16. Sato, A.; Sobue, K.; Kako, E.; Tachi, N.; Okumura, Y.; Kanazawa, M.; Hashimoto, M.; Harada, J.; Boku, A.S. The usefulness of the McGrath MAC laryngoscope in comparison with Airwayscope and Macintosh laryngoscope during routine nasotracheal intubation: A randomaized controlled trial. *BMC Anesthesiol.* **2017**, *17*, 160. [CrossRef]
17. Chae, Y.J.; Kim, D.H.; Park, E.J.; Oh, J.; Yi, I.K. A comparison of McGrath MAC, Pentax AWS, and Macintosh direct laryngoscopes for nasotracheal intubation: A randomized controlled trial. *Ther. Clin. Risk Manag.* **2019**, *15*, 1121–1128. [CrossRef]
18. Roh, G.U.; Kwak, H.J.; Lee, K.C.; Lee, S.Y.; Kim, J.Y. Randomized comparison of McGrath MAC videolaryngoscope, Pentax Airway Scope, and Macintosh direct laryngoscope for nasotracheal intubation in patients with manual in-line stabilization. *Can. J. Anaesth.* **2019**, *66*, 1213–1220. [CrossRef]
19. Ambulkar, R.; Ranganathan, P.; Savarkar, S.; Divatia, J.V. A randomized controlled trial comparing McGRATH series 5 video-laryngoscope with the Macintosh laryngoscope for nasotracheal intubation. *J. Anaesthesiol. Clin. Pharmacol.* **2020**, *36*, 477–482. [CrossRef]
20. Kleine-Brueggeney, M.; Greif, R.; Schoettker, P.; Savoldelli, G.L.; Nabecker, S.; Theiler, L.G. Evaluation of six videolaryngoscopes in 720 patients with a simulated difficult airway: A multicentre randomized controlled trial. *Br. J. Anaesth.* **2016**, *116*, 670–679. [CrossRef]
21. Savoldelli, G.L.; Schiffer, E.; Abegg, C.; Baeriswyl, V.; Clergue, F.; Waeber, J.L. Comparison of the Glidescope®, the McGrath®, the Airtraq® and the Macintosh laryngoscopes in simulated difficult airways*. *Anaesthesia* **2008**, *63*, 1358–1364. [CrossRef] [PubMed]
22. Combes, X.; Dhonneur, G. Difficult tracheal intubation. *Br. J. Anaesth.* **2010**, *104*, 260–261. [CrossRef] [PubMed]
23. King, B.J.; Padnos, I.; Mancuso, K.; Christensen, B.J. Comparing Video and Direct Laryngoscopy for Nasotracheal Intubation. *Anesth. Prog.* **2020**, *67*, 193–199. [CrossRef] [PubMed]
24. Yeom, J.H.; Oh, M.K.; Shin, W.J.; Ahn, D.W.; Jeon, W.J.; Cho, S.Y. Randomized comparison of the effectiveness of nasal intubation using a GlideScope video laryngoscope with Magill forceps versus vascular forceps in patients with a normal airway. *Can. J. Anaesth.* **2017**, *64*, 1176–1181. [CrossRef] [PubMed]
25. Hu, R.; Niu, J.-Y.; Wu, L.-N.; Sun, H.; Sun, P.; Huang, J.-Y.; Yu, J.-M. Comparison of a tube core and Magill forceps for nasotracheal intubation: A randomised controlled trial. *Trials* **2021**, *22*, 1–6. [CrossRef] [PubMed]
26. Yamamoto, T.; Flenner, M.; Schindler, E. Complications associated with nasotracheal intubation and proposal of simple countermeasure. *Anaesthesiol. Intensive Ther.* **2019**, *51*, 72–73. [CrossRef] [PubMed]

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The Effect of Low-Dose Dexmedetomidine on Pain and Inflammation in Patients Undergoing Laparoscopic Hysterectomy

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Abstract: Dexmedetomidine has sedative, sympatholytic, analgesic, and anti-inflammatory effects. We investigated the effects of intraoperative dexmedetomidine infusion without a loading dose in the prevention of pain and inflammation after laparoscopic hysterectomy. In this study, 100 patients undergoing laparoscopic hysterectomy under desflurane anesthesia were randomized to receive either 0.9% saline or dexmedetomidine (0.4 μg/kg/h) after induction to trocar removal. The primary endpoints were postoperative pain and inflammatory response presented by the level of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-10, and C-reactive protein (CRP). The secondary endpoints were hemodynamics during the anesthesia and surgery and postoperative nausea and vomiting. Postoperative pain was decreased in the dexmedetomidine group for every time point, and post-anesthesia care unit (PACU) rescue fentanyl doses were decreased in the dexmedetomidine group. The inflammatory response representing TNF-α, IL-6, IL-10, and CRP were similar across the two groups. Postoperative nausea and vomiting from PACU discharge to 24 h post-surgery were reduced in the dexmedetomidine group. During anesthesia and surgery, the patient's heart rate was maintained lower in the dexmedetomidine-receiving group. Dexmedetomidine of 0.4 μg/kg/h given as an intraoperative infusion significantly reduced postoperative pain but did not reduce the inflammatory responses in patients undergoing laparoscopic hysterectomy.

Keywords: dexmedetomidine; pain; inflammation; hysterectomy

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1. Introduction

Laparoscopic hysterectomy is the second most frequent operative procedure conducted in women following cesarean delivery. The postoperative pain after laparoscopy is less severe than laparotomy [1], but there might be pain during surgery, which may affect the nervous system and inflammatory response [2]. Moreover, women tend to be more sensitive to pain than men [3], and approximately 32% of patients experience chronic pain after a hysterectomy that does not disappear after a year [4]. Therefore, control of inflammation and pain may be of clinical significance in patients undergoing laparoscopic hysterectomy.

Dexmedetomidine, a highly selective α2-adrenergic receptor agonist in the central nervous system, has sedative, anti-anxiety, anti-shivering, analgesic, and anesthetic-sparing effects [5–7]. Dexmedetomidine is also known to reduce the inflammatory and stress

responses and was identified in a meta-analysis to reduce serum inflammatory markers significantly [8].

Most of the previous studies on the reduction of inflammatory response or postoperative pain were conducted by continuous infusion (0.2–0.7 μg/kg/h) after administration of a loading dose (0.5–1 μg/kg) which was according to the dosing regimen. Additionally, these studies were performed in many surgeries, including general surgery, orthopedic surgery, spinal surgery, cardiac surgery, laparoscopic surgery, etc. However, a loading dose may cause transient hypotension and bradycardia [9] to severe adverse effects such as asystole [10]. Recent studies demonstrated that continuous dexmedetomidine infusion of 0.4–0.5 μg/kg/h without a loading dose is also effective for intraoperative and postoperative pain and is hemodynamically stable in laparoscopic cholecystectomy, abdominal surgery, and multiple fracture surgery [9,11,12]. Until now, there was no study conducted on the effects of continuous infusion of dexmedetomidine without a loading dose on pain and inflammation during laparoscopic hysterectomy. We hypothesized that continuous dexmedetomidine infusion without a loading dose might be effective in reducing pain and inflammation. The goal of this study was to evaluate the efficacy of continuous infusion of low-dose dexmedetomidine without a loading dose to minimize hemodynamic instability while reducing pain and inflammation in laparoscopic hysterectomy.

2. Materials and Methods

This study was approved by the Institutional Review Board of CHA Bundang Medical Center, CHA University, Seongnam, South Korea (approval number: CHAMC 2018-11-027, approval date: 18 December 2018) and was conducted in accordance with the tenets of the Declaration of Helsinki. After we registered this trial at the Clinical Research Information Service (Effects of dexmedetomidine on inflammation and analgesia in patients undergoing laparoscopic hysterectomy. Available online: https://cris.nih.go.kr/cris/search/detailSearch.do?seq=13521&status=5&seq_group=13521&search_page=M (accessed on 23 February 2019)), we enrolled the first patient. Written informed consent, including study design and drugs, was obtained from every eligible subject in the aforementioned trial. This study was conducted between 15 May 2019 and 14 September 2021. Patients who were aged 19–65 years with an American Society of Anesthesiologists (ASA) physical status classification of I or II and were scheduled for an elective laparoscopic hysterectomy were included. The exclusion criteria were as follows: patients with body mass index (BMI) > 30 kg/m^2; the presence of allergy to study drugs; with heart, lung, kidney, cerebrovascular, or psychiatric diseases; with sinus bradycardia; who were unable to express pain; with chronic pelvic pain; with chronic use of opioids; who were pregnant or breastfeeding; with diabetes mellitus; with infection (fever within 1 week); with conversion to open surgery; co-operation; or with ASA physical status of III or more. The patients who were eligible to participate in the trial were randomly designated to either the control or dexmedetomidine group using sealed and opaque envelopes. Simple randomization with a 1:1 ratio was produced by a computer-generated table of random numbers.

2.1. Anesthesia and Surgery

The anesthesiologist, blinded to the randomization, conducted the anesthesia induction, maintenance, and recovery. The subjects were monitored routinely by conducting pulse oximetry, electrocardiography, noninvasive blood pressure, and bispectral index (BIS). Intravenous (IV) lidocaine 30 mg, propofol 2.0 mg/kg, fentanyl 1.0 μg/kg, and rocuronium 0.8 mg/kg were administered for endotracheal intubation. After anesthesia induction, the dexmedetomidine group started dexmedetomidine infusion of 0.4 μg/kg/h, and the control group received the same volume of 0.9% saline. The syringes containing dexmedetomidine or 0.9% saline were not distinguishable and had no drug label. When trocar was removed from the patient, continuous infusion of dexmedetomidine or normal saline was stopped.

Mechanical ventilation was used in 40% oxygen with air to maintain an end-tidal partial pressure of CO_2 between 35 and 40 mmHg. Desflurane 6–8 vol% on the vaporizer dial setting was given to maintain the effect of anesthesia to sustain a BIS of 40–65 [13]. If the patient's pulse rate or blood pressure increased > 20% of the baseline value in spite of increasing the dose of desflurane by 8 vol%, additional fentanyl of 50 μg would be administered. After anesthetic induction, IV dexamethasone 4 mg was administered as a prophylactic measure of postoperative nausea and vomiting (PONV). At the end of the surgery, fentanyl 1 μg/kg and ondansetron 4 mg were administered intravenously. IV-patient-controlled analgesia (PCA) (Anaplus; Ewha Meditech, Seoul, South Korea) containing sufentanil 2.5 μg/kg, ondansetron 12 mg, and normal saline in a total volume of 100 mL was started on every patient. Basal rate, bolus dose, and lockout interval were 2 mL/h, 0.5 mL, and 15 min, respectively.

2.2. Blood Sampling and Laboratory Data Collection

A blood sample was collected for tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-10, and C-reactive protein (CRP) after the anesthesia induction (baseline), at the end of the surgery, and on the first postoperative day (POD1). Blood samples for TNF-α, IL-6, and IL-10 were instantly centrifuged at 5000 rpm for 5 min at 4 °C, and the collected plasma was stored at −80 °C up to the examination. The plasma TNF-α, IL-6, and IL-10 levels were assessed using the specific immunoassay kit (R&D, Cat. No. HSTA00E; D6050; D1000B, Minneapolis, MN, USA), and all examinations were duplicated. Blood samples for these cytokines were collected repeatedly. CRP was analyzed at baseline and POD1.

2.3. Postoperative Management

The visual analog scale (VAS), ranging from 0 (no pain) to 10 (worst possible imaginable pain) cm, was used to assess postoperative pain. PONV was assessed as present or absent. Pain and PONV were assessed through three intervals: post-anesthesia care unit (PACU), from PACU discharge to 6 h after surgery, and from 6 h to 24 h after surgery. Pain and PONV were measured at three different time points: at the PACU, 6 h after surgery, and 24 h after surgery. The highest VAS score of pain assessed every 10 min at the PACU was used. The highest patient-reported VAS score of pain from PACU discharge to 6 h after surgery was noted at 6 h after surgery. The highest patient-reported VAS score of pain from 6 h to 24 h after surgery was noted at 24 h after surgery. Both the assessing anesthesiologist and patients were blinded to the randomization.

IV fentanyl was administered, 50 μg once or twice (100 μg), in the PACU for rescue analgesia. For rescue analgesia in the general ward, IV ketorolac 30 mg was administered, in addition to IV-PCA. For rescue antiemetic, IV metoclopramide 10 mg was administered.

2.4. Primary Endpoints and Secondary Endpoints

The primary endpoints were postoperative pain and inflammatory response presented by TNF-α, IL-6, IL-10, and CRP levels. The secondary endpoints were the incidence of PONV and hemodynamics during the anesthesia and surgery (T0, baseline; T1, before endotracheal intubation; T2, surgical incision; T3, 10 min after CO_2 insufflation; T4, end of surgery; T5, after extubation).

2.5. Statistical Analyses

According to previous medical records of our institute, the mean VAS score of patients 24 h after laparoscopic hysterectomy with fentanyl-based IV-PCA was 2.4 cm, and the standard deviation (SD) was 2.1 cm [14]. Assuming that a 50% reduction in pain score is clinically meaningful ($\alpha = 0.05$, $\beta = 0.2$), the number of calculated subjects is 48 per group, and 100 patients are required to account for a dropout rate of 5%. Statistical analyses were performed using SPSS version 26.0 for Windows (IBM Corp., Armonk, NY, USA). For quantitative variables, normality was assessed using the Kolmogorov–Smirnov test, Shapiro–Wilk test, skewness, and kurtosis. The independent t-test and Mann–Whitney

U test were performed for the normally and non-normally distributed data, respectively. For dichotomous variables between the two groups, the chi-square test or Fisher's exact test was employed. A linear mixed-effects model using the restricted maximum likelihood method was used on the postoperative pain, TNF-α, IL-6, IL-10, and vital signs during the surgery to assess the interaction among groups and times (Pgroup $\times$ time): random effect (for the subject) and fixed effect (for treatment groups and time points).

Data are presented as mean (SD), median (interquartile range), or the number of patients (%). p-values < 0.05 were considered statistically significant. Bonferroni's methods for p-values adjustment were used to test for the difference among groups with repeated measurements over time.

3. Results

3.1. Patient Demographics and Operative Details

A total of 100 subjects were randomized after their consent, and 88 subjects finished this study (Figure 1). Patient demographics, including age, BMI, and ASA classification, were not significantly different between the two groups (Table 1).

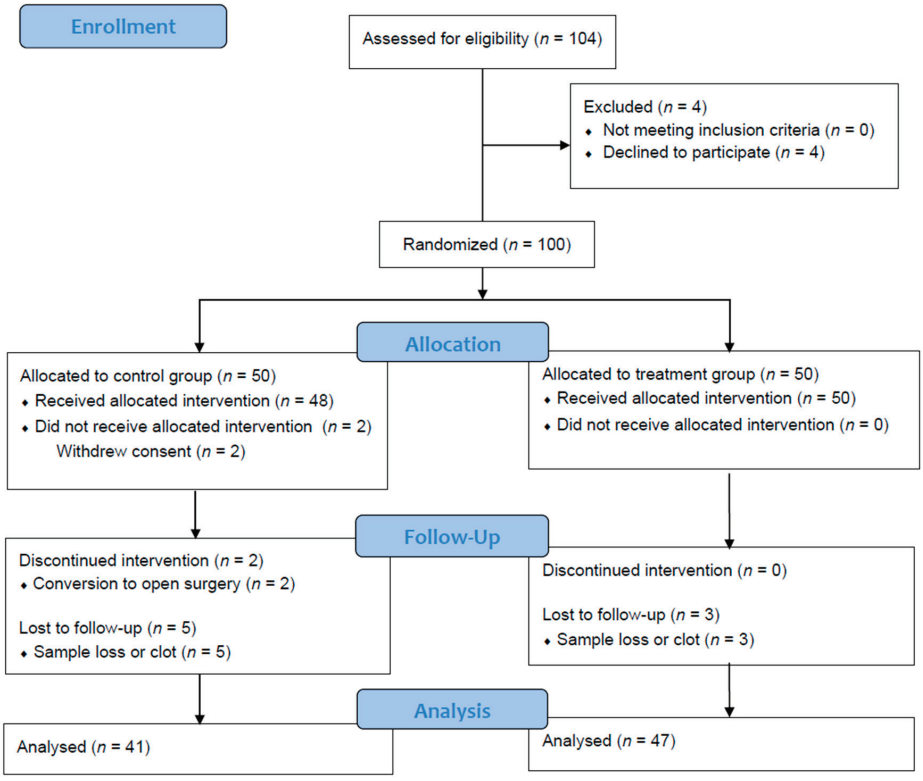

Figure 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

Table 1. Patient demographics and operative details.

	Control (n = 41)	Dexmedetomidine (n = 47)	p-Value
Age	46.6 (5.1)	45.3 (4.9)	0.23
Height	159.3 (4.7)	159.3 (4.4)	0.99
Weight	60.4 (8.9)	63.0 (10.3)	0.21
BMI, Kg/m^2	23.8 (3.4)	24.8 (3.9)	0.19
ASA physical status I/II	18/23	26/21	0.29
Cesarean delivery history	21 (51%)	17 (36%)	0.16
Abdominal surgery history	14 (34%)	10 (21%)	0.18
Intraoperative fluid, mL	1320.7 (527.9)	1253.2 (479.5)	0.53
Estimated blood loss, mL	300.0 [100.0–1300.0]	200.0 [50.0–1700.0]	0.60
Transfusion	4 (10%)	3 (6%)	0.70
Insertion of drain	17 (42%)	15 (32%)	0.35
Duration of operation (min)	108.5 (53.5)	107.3 (54.2)	0.92
Duration of anesthesia (min)	141.3 (55.4)	141.7 (55.8)	0.98
Duration of emergence (min)	5.8 (1.9)	6.4 (2.2)	0.16

Values are presented as mean (SD), median [interquartile range], or number of patients (%). BMI, body mass index; ASA, American Society of Anesthesiologists; PACU, post-anesthesia care unit.

The operative details, including duration of surgery and duration of emergence, were also not significantly different. Four patients had one unit of red blood cell (RBC) transfusion in the control group. Moreover, one patient had one unit of RBC, and two patients had two units of RBC transfusion in the dexmedetomidine group (p = 0.12). For the dexmedetomidine group, the mean administered dexmedetomidine dosage was 47.2 ± 29.0 μg, and no adverse effect was observed during the surgery and anesthesia.

3.2. Perioperative Profile (Postoperative Pain and Postoperative Nausea and Vomiting)

Postoperative pain was decreased in the dexmedetomidine group for every time point, and rescue fentanyl use in the PACU was decreased (Table 2 and Figure 2).

Table 2. Perioperative profile.

	Control (n = 41)	Dexmedetomidine (n = 47)	p-Value
Pain			
PACU	4 [3–5]	2 [1–4]	<0.001
PACU discharge to 6 h after surgery	3 [2–3]	2 [1–2]	<0.001
6 to 24 h after surgery	2 [1–2]	1 [1–2]	<0.01
Rescue analgesic			
PACU Fentanyl (ug)	29.3 (29.5)	16.0 (25.8)	0.03
PACU discharge to 6 h after surgery	3 (7%)	4 (9%)	1.00
6 to 24 h after surgery	5 (12%)	8 (17%)	0.52
PONV			
PACU	3 (7%)	2 (4%)	0.66
PACU discharge to 6 h after surgery	13 (32%)	6 (13%)	0.03
6 to 24 h after surgery	12 (29%)	5 (11%)	0.03
Antiemetic			
PACU	3 (7%)	2 (4%)	0.66
PACU discharge to 6 h after surgery	6 (15%)	4 (9%)	0.37
6 to 24 h after surgery	1 (2%)	3 (6%)	0.62
Side effect			
PACU			<0.01
Hypotension	0 (0%)	7 (15%)	0.01
Bradycardia	0 (0%)	4 (9%)	0.12
Shivering	2 (5%)	0 (0%)	0.21
Hypertension	1 (2%)	0 (0%)	0.47

Table 2. *Cont.*

	Control (n = 41)	Dexmedetomidine (n = 47)	p-Value
PACU discharge to 6 h after surgery			0.47
Dizziness	1 (2%)	0 (0%)	
6 to 24 h after surgery			0.47
Dizziness	1 (2%)	0 (0%)	
RSS score at PACU			
PACU arrival 2/3/4	10/29/2	20/24/3	0.16
30 min after PACU arrival 2/3	39/2	44/3	1.00
Duration of PACU stay (minutes)	54.1 (19.1)	54.3 (15.4)	0.66

Values are presented as median [IQR], mean (SD), or number of patients (%). PACU, post-anesthesia care unit; PONV, postoperative nausea, and vomiting; RSS, Ramsay sedation scale.

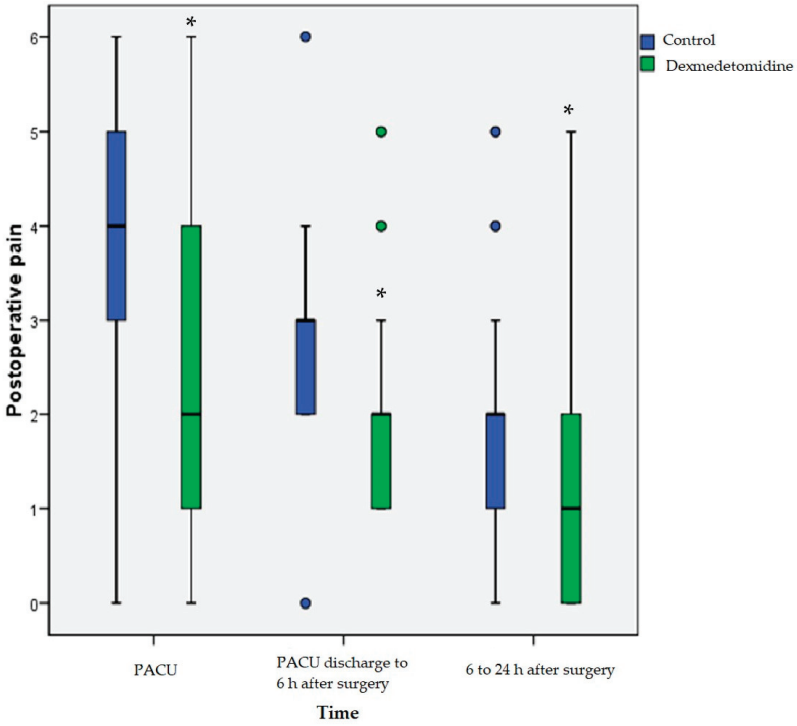

Figure 2. Postoperative pain. Postoperative pain was assessed by using visual analog scale from 0 to 10. The box plots represent the median, interquartile range, 10th and 90th percentile (whiskers), and outliers (points). PACU, post-anesthesia care unit. * $p < 0.05$ compared with two groups.

However, intergroup differences in change in pain from baseline were not significant over time (Pgroup × time = 0.09). Administered fentanyl doses at the PACU were also decreased in the dexmedetomidine group. The incidence rates of PONV from PACU discharge to 6 h after surgery and 6 h to 24 h after surgery were decreased in the dexmedetomidine group, but rescue antiemetic administration was similar between the two groups. PACU side effects, including hypotension and bradycardia, were significantly increased in the dexmedetomidine group. However, Ramsay Sedation Scale scores at the PACU and duration of PACU stay according to the modified Aldrete recovery score were similar between the two groups.

3.3. Inflammatory Response

Inflammatory response, including cytokines and CRP, was not significant between the two groups at every time point (Table 3).

Table 3. Cytokines and C-reactive protein.

	Control (n = 41)	Dexmedetomidine (n = 47)	*p*-Value
TNF-α (pg/mL)			
After induction	0.50 [0.43–0.72]	0.57 [0.44–0.79]	0.35
End of surgery	0.42 [0.30–0.52]	0.45 [0.35–0.55]	0.38
POD 1	0.44 [0.35–0.59]	0.46 [0.28–0.62]	0.97
IL-6 (pg/mL)			
After induction	0.45 [0.00–1.68]	0.33 [0.00–1.51]	0.92
End of surgery	4.43 [2.14–19.41]	7.98 [3.19–11.35]	0.75
POD 1	8.53 [4.07–16.43]	7.07 [4.15–16.67]	0.77
IL-10 (pg/mL)			
After induction	2.14 [0.58–4.23]	2.50 [0.00–4.85]	0.84
End of surgery	16.34 [7.45–34.21]	16.14 [5.79–32.65]	0.62
POD 1	2.98 [1.07–5.44]	2.37 [0.44–5.22]	0.65
CRP (mg/dL)			
After induction	0.05 [0.03–0.10]	0.05 [0.03–0.11]	0.76
POD 1	0.68 [0.42–1.33]	0.52 [0.28–1.06]	0.38

Values are presented as median [IQR]. TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-10, interleukin-10; CRP, C-reactive protein; POD, postoperative day.

Moreover, intergroup differences in change in TNF-α, IL-6, and IL-10 from baseline was not significant over time (Pgroup × time = 0.69, Pgroup × time = 0.80, and Pgroup × time = 0.16, respectively).

3.4. Vital Signs during Anesthesia and Surgery

During surgery, heart rate maintained lower in the dexmedetomidine group (Figure 3).

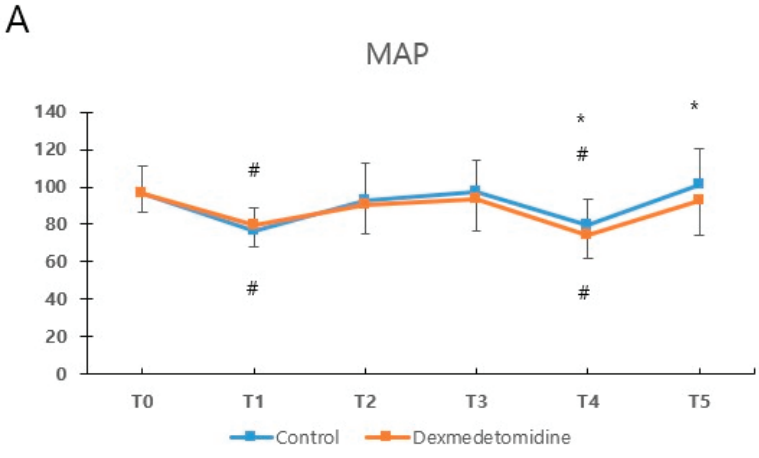

Figure 3. *Cont.*

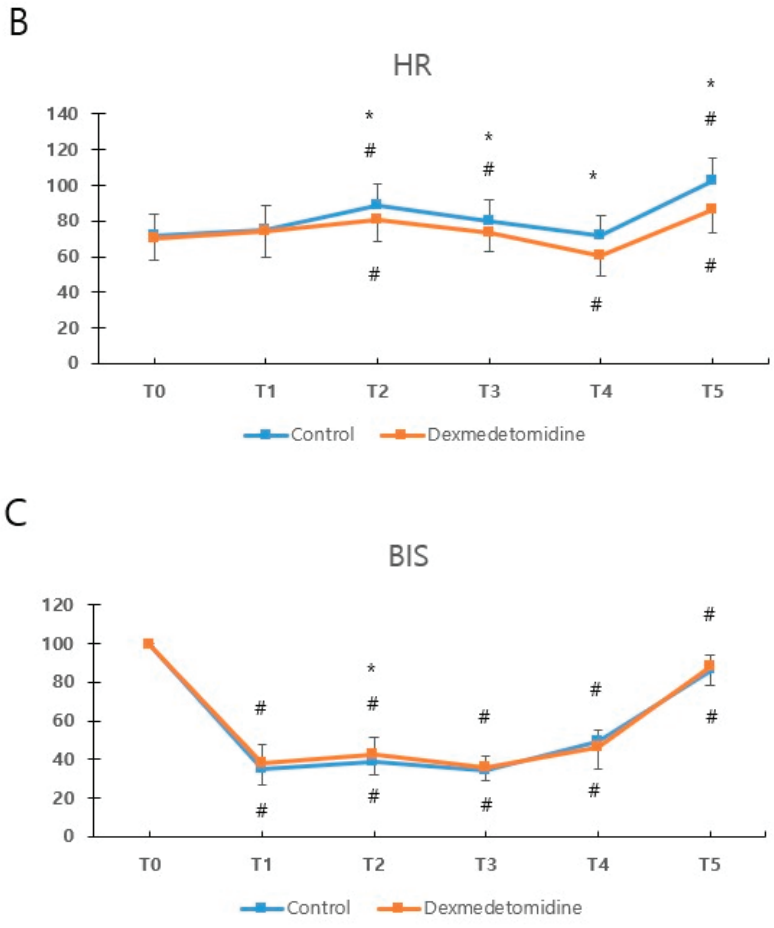

Figure 3. Hemodynamic changes during anesthesia and surgery. MAP (**A**), mean arterial pressure; HR (**B**), heart rate; BIS (**C**), bispectral index. Data are expressed as mean ± standard deviation. T0, baseline; T1, before endotracheal intubation; T2, surgical incision; T3, 10 min after CO_2 insufflation; T4, end of surgery; T5, after extubation. * $p < 0.05$ compared with two groups. # Bonferroni-adjusted $p < 0.05$ compared with T0.

Moreover, intergroup differences in change in heart rate from baseline were also significant over time (Pgroup × time < 0.001). At the end of surgery and after extubation, the mean arterial pressure (MAP) was lower in the dexmedetomidine group than in the control group. However, intergroup differences in change in MAP from baseline were not statistically significant over time (Pgroup × time = 0.06). BIS value was similar during the surgery, except for the timing of surgical incision, and intergroup differences in change in BIS from baseline were significant over time (Pgroup × time = 0.04).

4. Discussion

This study demonstrated that intraoperative infusion of dexmedetomidine 0.4 μg/kg/h could reduce pain up to 24 h postoperatively after surgery and reduce fentanyl requirement in the PACU but did not reduce the postoperative inflammatory responses presented by cytokines and CRP. This is the first randomized, double-blind study to investigate the anal-

gesic and anti-inflammatory effects of continuous infusion of low-dose dexmedetomidine without a loading dose during laparoscopic hysterectomy.

Dexmedetomidine appears to exert an analgesic effect by activating α2A and α2C receptors at the level of the spinal cord and other supraspinal sites [15]. In addition, dexmedetomidine induces sedation by decreasing the activity of noradrenergic neurons in the locus ceruleus in the brain stem, thereby increasing the downstream activity of inhibitory gamma-aminobutyric acid neurons in the ventrolateral preoptic nucleus [16,17].

Dexmedetomidine was reported to reduce postoperative pain and opioid consumption after general anesthesia in many surgeries [18]. Although the elimination half-life of dexmedetomidine is approximately 2 h [19], previous studies showed a longer analgesic effect [9,20]. This is consistent with our results, showing that the use of fentanyl rescue in the PACU and pain scores up to 24 h post-surgery were significantly lower in the dexmedetomidine group than in the control group.

Surgery may produce traumatic stress responses and immune dysfunctions [21]. Recently, the anti-inflammatory effect of dexmedetomidine has been further emphasized, and this anti-inflammatory effect is due to the reduction in the endotoxin-induced inflammatory response and the inhibition of an increase in TNF-α, IL-6, and neutrophil levels [8]. Immune cells secret many cytokines with immunomodulatory effects, among which IL-6 is a key cytokine in the acute phase response. Plasma levels of IL-6 are related to the severity of surgical injury [22], which modulates cellular immunity by strengthening the innate immune system and protecting tissues from damage [23]. Moreover, IL-6 promotes CRP synthesis in the liver, which is most often measured as an active phase protein of inflammation and is stimulated by TNF-α [24]. IL-10 is one of the main anti-inflammatory cytokines that inhibit IL-6 synthesis and antagonize inflammatory cytokines [25]. Studies on the anti-inflammatory effect of dexmedetomidine infusion without a loading dose were recently reported. In an earlier study, dexmedetomidine infusion of 0.5 μg/kg/h during major spinal surgery under general anesthesia with propofol and fentanyl did not reduce the elevated levels of CRP and IL-6 at POD1 compared to baseline [26]. This was consistent with our result. This study investigated the changes in inflammatory cytokines induced by intraoperative dexmedetomidine infusion at 0.4 μg/kg/h during laparoscopic hysterectomy and demonstrated that dexmedetomidine did not reduce the increase in IL-6 and CRP levels in POD1.

In contrast, dexmedetomidine infusion of 0.3 μg/kg/h was shown to reduce the increases in IL-6 and TNF-α levels during myocardial surgery under mini-cardiopulmonary bypass using propofol and sufentanil [27]. Moreover, dexmedetomidine infusion of 0.5 μg/kg/h during thoracoscopy with one-lung ventilation under sevoflurane anesthesia reduced the increase in IL-6 levels at POD1 [28]. The difference in the anti-inflammatory effect of dexmedetomidine may be due to the differences in the type of surgery-related inflammatory responses and differences in the total doses of dexmedetomidine administered during surgery. Laparoscopic procedures are less invasive, so the possibility of a large release of inflammatory mediators that is influenced by dexmedetomidine is quite remote. In this study, the IL-6 increase after laparoscopic hysterectomy in the control group was approximately 1/10 less than that after myocardial surgery or one-lung ventilation [27,28]. In addition, due to the short operation time of laparoscopic hysterectomy, the total dose of dexmedetomidine in this study was approximately half that of other previous studies [27,28]. In this study, dexmedetomidine of 0.4 μg/kg/h was infused after anesthesia induction to the end of pneumoperitoneum. When the concentration of dexmedetomidine was calculated later on using a simulation program (Asan Pump, version2.1.5; Bionet Co., Ltd., Seoul, South Korea) with Dyck kinetics [29], the expected concentration in this study was 0.31 ± 0.10 ng/mL at the end of pneumoperitoneum, which might not be sufficient to induce the significant anti-inflammatory effect on an already not significant inflammation.

According to the dosing regimen, dexmedetomidine administered continuously at a dose of 0.2–1 μg/kg/h after a loading dose of 0.5–1 μg/kg for 10 min, which is temporary, may cause hemodynamic changes, such as bradycardia and hypotension [9]. According to

a previous case report, in patients with an anterior fascicular block on electrocardiogram, asystole was observed following sudden bradycardia after 2 min with a loading dose and then was resuscitated and recovered without sequelae [10]. Regarding severe side effects, including high-degree atrioventricular block, severe hypotension, and bradycardia, we used dexmedetomidine infusion without a loading dose. We did not observe these severe side effects, but several patients experienced bradycardia and hypotension in the dexmedetomidine group at the PACU. Our patients with bradycardia and hypotension were not severe and recovered soon with atropine 0.5 mg or ephedrine 6–8 mg.

This study has some limitations. First, 48 patients per group were calculated when we planned this study, but 41 and 47 patients completed, respectively. The dropout rate was differential, and differential attrition is known to introduce bias, particularly when the sample size was not achieved. We should have made a dropout rate of 20% not to create bias [30]. Therefore, our results might be mere speculations of this inadequate sample size. Second, we used fentanyl during the surgery. Since opioids have an immunosuppressive effect [31], they might have affected the inflammatory responses in this study. However, the dose of fentanyl during the surgery was similar between the two groups, and its effect is likely to be minimal in this study. Third, dexamethasone is one of the most commonly used antiemetic agents [32], and we used dexamethasone to prevent PONV. Synthetic glucocorticoids, including dexamethasone, have anti-inflammatory effects on the immune system [33]. In a previous randomized trial of gynecologic laparoscopy, dexamethasone of 4 mg attenuated inflammation up to 24 h after surgery, which was visualized as an attenuated increase in CRP concentration [34]. Thus, in this study, the anti-inflammatory effect of dexamethasone might have attenuated the difference in inflammatory responses between the two groups. Fourth, we were concerned about the side effects of the dexmedetomidine loading dose, so we compared only the continuous infusion group without loading and the placebo group: this was also the purpose of our study. However, if the loading dose followed by infusion group was also included, it would have been helpful to clarify the anti-inflammatory effect and analgesic effect of dexmedetomidine.

5. Conclusions

Intraoperative infusion of dexmedetomidine 0.4 μg/kg/h could reduce pain up to 24 h postoperatively after surgery and reduce fentanyl requirement in the PACU but did not reduce the postoperative inflammatory responses presented by cytokines and CRP.

Author Contributions: Conceptualization, J.L. and J.Y.K.; methodology, H.W.H.; software, C.P.; validation, J.Y.K.; formal analysis, J.L.; investigation, H.W.H. and J.-Y.J.; resources, Y.M.K.; data curation, J.L.; writing—original draft preparation, J.L.; writing—review and editing, J.Y.K.; visualization, J.-Y.J.; supervision, J.Y.K.; project administration, J.L. and J.Y.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Institutional Review Board of CHA Bundang Medical Center, CHA University, Seongnam, Korea (approval number: CHAMC 2018-11-027, approval date:18 December 2018) and was conducted in accordance with the tenets of the Declaration of Helsinki. Before the enrollment of the first patient, we registered this study at the Clinical Research Information Service (https://cris.nih.go.kr, Registration No. KCT0003684, Registered Date: 23 February 2019).

Informed Consent Statement: Written informed consent was obtained from every eligible subject in the aforementioned trial.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ASA	American Society of Anesthesiologists
CRP	c-related peptide
IL	interleukin
IV	intravenous
PACU	post-anesthesia care unit
PCA	patient-controlled analgesia
PONV	postoperative nausea and vomiting
VAS	visual analog scale
TNF	tumor necrosis factor

References

1. Aarts, J.W.; Nieboer, T.E.; Johnson, N.; Tavender, E.; Garry, R.; Mol, B.W.; Kluivers, K.B. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst. Rev.* **2015**, *2015*, Cd003677. [CrossRef] [PubMed]
2. Long, J.B.; Bevil, K.; Giles, D.L. Preemptive Analgesia in Minimally Invasive Gynecologic Surgery. *J. Minim. Invasive Gynecol.* **2018**, *26*, 198–218. [CrossRef] [PubMed]
3. Bartley, E.J.; Fillingim, R.B. Sex differences in pain: A brief review of clinical and experimental findings. *Br. J. Anaesth.* **2013**, *111*, 52–58. [CrossRef] [PubMed]
4. Brandsborg, B.; Nikolajsen, L.; Hansen, C.T.; Kehlet, H.; Jensen, T.S. Risk Factors for Chronic Pain after HysterectomyA Nationwide Questionnaire and Database Study. *Anesthesiol. J. Am. Soc. Anesthesiol.* **2007**, *106*, 1003–1012.
5. Bhana, N.; Goa, K.L.; McClellan, K.J. Dexmedetomidine. *Drugs* **2000**, *59*, 263–268; discussion 269–270. [CrossRef]
6. Schmidt, A.P.; Valinetti, E.A.; Bandeira, D.; Bertacchi, M.F.; Simoes, C.M.; Auler, J.O., Jr. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Paediatr. Anaesth.* **2007**, *17*, 667–674. [CrossRef]
7. Elvan, E.G.; Oc, B.; Uzun, S.; Karabulut, E.; Coskun, F.; Aypar, U. Dexmedetomidine and postoperative shivering in patients undergoing elective abdominal hysterectomy. *Eur. J. Anaesthesiol.* **2008**, *25*, 357–364. [CrossRef]
8. Li, B.; Li, Y.; Tian, S.; Wang, H.; Wu, H.; Zhang, A.; Gao, C. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: A meta-analysis. *Sci. Rep.* **2015**, *5*, 12342. [CrossRef]
9. Fan, W.; Yang, H.; Sun, Y.; Zhang, J.; Li, G.; Zheng, Y.; Liu, Y. Comparison of the pro-postoperative analgesia of intraoperative dexmedetomidine with and without loading dose following general anesthesia: A prospective, randomized, controlled clinical trial. *Medicine* **2017**, *96*, e6106. [CrossRef]
10. Kim, B.J.; Kim, B.I.; Byun, S.H.; Kim, E.; Sung, S.Y.; Jung, J.Y. Cardiac arrest in a patient with anterior fascicular block after administration of dexmedetomidine with spinal anesthesia: A case report. *Medicine* **2016**, *95*, e5278. [CrossRef]
11. Bielka, K.; Kuchyn, I.; Babych, V.; Martycshenko, K.; Inozemtsev, O. Dexmedetomidine infusion as an analgesic adjuvant during laparoscopic small es, Cyrillicholecystectomy: A randomized controlled study. *BMC Anesthesiol.* **2018**, *18*, 44. [CrossRef] [PubMed]
12. Zhao, J.N.; Kong, M.; Qi, B.; Ge, D.J. Comparison of the morphine-sparing effect of intraoperative dexmedetomidine with and without loading dose following general anesthesia in multiple-fracture patients: A prospective, randomized, controlled clinical trial. *Medicine* **2016**, *95*, e4576. [CrossRef] [PubMed]
13. Johansen, J.W.; Sebel, P.S.; Fisher, D.M. Development and Clinical Application of Electroencephalographic Bispectrum Monitoring. *Anesthesiology* **2000**, *93*, 1336–1344. [CrossRef] [PubMed]
14. Lee, J.; Park, C.; Kim, J.; Ki, Y.; Cha, S.H.; Kim, J.Y. Effect of Low-pressure Pulmonary Recruitment Maneuver on Postlaparoscopic Shoulder Pain: Randomized Controlled Trial. *J. Minim. Invasive Gynecol.* **2020**, *27*, 173–177. [CrossRef]
15. Panzer, O.; Moitra, V.; Sladen, R.N. Pharmacology of sedative-analgesic agents: Dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. *Crit. Care Clin.* **2009**, *25*, 451–469. [CrossRef]
16. Brown, E.N.; Purdon, P.L.; Van Dort, C.J. General anesthesia and altered states of arousal: A systems neuroscience analysis. *Annu. Rev. Neurosci.* **2011**, *34*, 601–628. [CrossRef]
17. Nelson, L.E.; Lu, J.; Guo, T.; Saper, C.B.; Franks, N.P.; Maze, M. The α2-Adrenoceptor Agonist Dexmedetomidine Converges on an Endogenous Sleep-promoting Pathway to Exert Its Sedative Effects. *Anesthesiology* **2003**, *98*, 428–436. [CrossRef]
18. Wang, X.; Liu, N.; Chen, J.; Xu, Z.; Wang, F.; Ding, C. Effect of Intravenous Dexmedetomidine During General Anesthesia on Acute Postoperative Pain in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clin. J. Pain.* **2018**, *34*, 1180–1191. [CrossRef]

19. Ebert, T.J.; Hall, J.E.; Barney, J.A.; Uhrich, T.D.; Colinco, M.D. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* **2000**, *93*, 382–394. [CrossRef]
20. Ge, D.J.; Qi, B.; Tang, G.; Li, J.Y. Intraoperative Dexmedetomidine Promotes Postoperative Analgesia and Recovery in Patients after Abdominal Hysterectomy: A Double-Blind, Randomized Clinical Trial. *Sci. Rep.* **2016**, *6*, 21514. [CrossRef]
21. Green, J.S.; Tsui, B.C. Impact of anesthesia for cancer surgery: Continuing professional development. *Can. J. Anaesth.* **2013**, *60*, 1248–1269. [CrossRef] [PubMed]
22. Cruickshank, A.M.; Fraser, W.D.; Burns, H.J.; Van Damme, J.; Shenkin, A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin. Sci.* **1990**, *79*, 161–165. [CrossRef] [PubMed]
23. Zheng, L.; Zhao, J.; Zheng, L.; Jing, S.; Wang, X. Effect of Dexmedetomidine on Perioperative Stress Response and Immune Function in Patients With Tumors. *Technol. Cancer Res. Treat.* **2020**, *19*, 1533033820977542. [CrossRef] [PubMed]
24. Povoa, P. C-reactive protein: A valuable marker of sepsis. *Intensive Care Med.* **2002**, *28*, 235–243. [CrossRef]
25. Kato, M.; Honda, I.; Suzuki, H.; Murakami, M.; Matsukawa, S.; Hashimoto, Y. Interleukin-10 production during and after upper abdominal surgery. *J. Clin. Anesth.* **1998**, *10*, 184–188. [CrossRef]
26. Bekker, A.; Haile, M.; Kline, R.; Didehvar, S.; Babu, R.; Martiniuk, F.; Urban, M. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. *J. Neurosurg. Anesthesiol.* **2013**, *25*, 16–24. [CrossRef]
27. Bulow, N.M.; Colpo, E.; Pereira, R.P.; Correa, E.F.; Waczuk, E.P.; Duarte, M.F.; Rocha, J.B. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. *Braz. J. Med. Biol. Res.* **2016**, *49*, e4646. [CrossRef]
28. Wu, C.Y.; Lu, Y.F.; Wang, M.L.; Chen, J.S.; Hsu, Y.C.; Yang, F.S.; Cheng, Y.J. Effects of Dexmedetomidine Infusion on Inflammatory Responses and Injury of Lung Tidal Volume Changes during One-Lung Ventilation in Thoracoscopic Surgery: A Randomized Controlled Trial. *Mediat. Inflamm.* **2018**, *2018*, 2575910. [CrossRef]
29. Dyck, J.B.; Maze, M.; Haack, C.; Azarnoff, D.L.; Vuorilehto, L.; Shafer, S.L. Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* **1993**, *78*, 821–828. [CrossRef]
30. Furlan, A.D.; Pennick, V.; Bombardier, C.; van Tulder, M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* **2009**, *34*, 1929–1941. [CrossRef]
31. Lee, J.S.; Hu, H.M.; Edelman, A.L.; Brummett, C.M.; Englesbe, M.J.; Waljee, J.F.; Smerage, J.B.; Griggs, J.J.; Nathan, H.; Jeruss, J.S.; et al. New Persistent Opioid Use among Patients with Cancer after Curative-Intent Surgery. *J. Clin. Oncol.* **2017**, *35*, 4042–4049. [CrossRef] [PubMed]
32. Henzi, I.; Walder, B.; Tramèr, M.R. Dexamethasone for the prevention of postoperative nausea and vomiting: A quantitative systematic review. *Anesth. Analg.* **2000**, *90*, 186–194. [CrossRef]
33. Rhen, T.; Cidlowski, J.A. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. *N. Engl. J. Med.* **2005**, *353*, 1711–1723. [CrossRef] [PubMed]
34. Corcoran, T.; Paech, M.; Law, D.; Muchatuta, N.A.; French, M.; Ho, K.M. Intraoperative dexamethasone alters immune cell populations in patients undergoing elective laparoscopic gynaecological surgery. *Br. J. Anaesth.* **2017**, *119*, 221–230. [CrossRef] [PubMed]

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Magnesium Sulfate and Cerebral Oxygen Saturation in Mild Traumatic Brain Injury: A Randomized, Double-Blind, Controlled Trial

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Abstract: Perioperative cerebral hypoperfusion/ischemia is considered to play a pivotal role in the development of secondary traumatic brain injury (TBI). This prospective randomized, double-blind, controlled study investigated whether magnesium sulfate ($MgSO_4$) infusion was associated with neuroprotection in maintaining regional cerebral oxygen saturation (rSO_2) values in patients with mild TBI undergoing general anesthesia. Immediately after intubation, we randomly assigned patients with TBI to receive either intravenous $MgSO_4$ (30 mg/kg for 10 min, followed by a continuous infusion of 15 mg/kg/h) or a placebo (saline) during surgery. We also implemented an intervention protocol for a sudden desaturation exceeding 20% of the initial baseline rSO_2. The intraoperative rSO_2 values were similar with respect to the median (left. 67% vs. 66%, respectively; $p = 0.654$), lowest, and highest rSO_2 in both groups. The incidence (left 31.2% vs. 24.3%; $p = 0.521$) and duration (left 2.6% vs. 3.5%; $p = 0.638$) of cerebral desaturations (the relative decline in $rSO_2 < 80\%$ of the baseline value) were also similar for both groups. Although the patients suffered serious traumatic injuries, all critical desaturation events were restored (100%) following stringent adherence to the intervention protocol. Intraoperative remifentanil consumption, postoperative pain intensity, and fentanyl consumption at 6 h were lower in the $MgSO_4$ group ($p = 0.024$, 0.017, and 0.041, respectively) compared to the control group, whereas the satisfaction score was higher in the $MgSO_4$ group ($p = 0.007$). The rSO_2 did not respond to intraoperative $MgSO_4$ in mild TBI. Nevertheless, $MgSO_4$ helped the postoperative pain intensity, reduce the amount of intraoperative and postoperative analgesics administered, and heighten the satisfaction score.

Keywords: magnesium; multiple trauma; spectroscopy; near-infrared; cerebral oxygen saturation; neuroprotection; traumatic brain injury; analgesia; opioid consumption

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1. Introduction

Traumatic brain injury (TBI) is characterized by a variety of pathophysiological changes that occur immediately after trauma [1,2]. Moreover, secondary insult can cause irreversible changes in the brain, resulting in persistent injury-related difficulties and disabilities, even in mild TBI [3]. Surgery and anesthesia may subject the injured brain to secondary injuries as a result of inadequate cerebral oxygenation, changes in cerebral blood flow (hypoperfusion and hyperperfusion), impaired cerebrovascular autoregulation, cerebral metabolic dysfunction, and increased intracranial pressure; thus, the perioperative period is particularly important in the course of TBI management [1,4]. Given the complexity and dynamics of these changes, rapid diagnosis and vigilant neuromonitoring form the core principles of TBI management [5,6].

Perioperative magnesium sulfate ($MgSO_4$), an N-methyl-D-aspartate receptor antagonist, is known to decrease pain and/or anesthetic/analgesic use, though its exact mechanism of action is unknown [7–9]. Magnesium is known to participate in vasodilation, hemostasis, and blood–brain barrier preservation and may also function as a potential neuroprotectant in acute stroke and brain hemorrhage [10,11]. Although one Cochrane systematic review found no evidence to support the use of magnesium salts in patients with acute TBI [12], subsequent evidence has emerged that magnesium plays a central role in the pathophysiology of TBI. Magnesium can protect neurons from ischemic damage and support neuronal survival following TBI through diverse mechanisms, such as through a cofactor of cellular energy metabolism and protein synthesis, as a potent calcium channel blocker [13], and via involvement in the mitigation of the cellular changes owing to global ischemia during trauma, suppression of cortical spreading depression, and relaxation of vascular smooth muscle, thereby possibly increasing cerebral blood flow [14]. One animal head injury model demonstrated that hypomagnesemia is associated with poor neurologic outcomes and increased mortality [15], whereas restoring magnesium levels reduces brain edema and enhances neurological and cognitive outcomes [16]. A recent clinical study found that magnesium was associated with a lower increase in hematoma volume and improved patient outcomes after intracerebral hemorrhage [17].

Near-infrared spectroscopy (NIRS) is a continuous, non-invasive method that facilitates the measurement of the regional cerebral oxygen saturation (rSO_2). NIRS has been shown to reflect the cerebral mixed venous oxygen saturation. It is a useful modality for monitoring the balance of cerebral oxygen supply and demand during surgery with a high risk of cerebrovascular complications [2,18]. As patients subjected to multiple traumas present with mild to severe TBIs, NIRS can be used to assess the cerebral oxygenation status, guide its optimization, and predict the prognosis of brain function in these patients.

We hypothesized that the intraoperative administration of $MgSO_4$ may be related to the prevention of deleterious secondary events in patients with TBI, as evidenced by rSO_2 value changes. We also implemented an intervention protocol to hinder or restore cerebral desaturation. Therefore, we conducted this prospective, randomized double-blinded study to measure the hitherto uninvestigated brain oxygenation/desaturation state using NIRS in TBI patients under general anesthesia, while simultaneously evaluating the neuroprotective effects of $MgSO_4$. As secondary outcomes, we expected $MgSO_4$ to alleviate the pain felt after multiple trauma surgery and reduce perioperative analgesic consumption.

2. Materials and Methods

2.1. Study

This study was approved by the institutional review board of Ajou University Hospital (IRB No. AJIRB-MED-CT4-19-377), Suwon, Korea, on 1 November 2019, and registered at cris.nih.go.kr (Date of registration 4 June 2020, Registration No. KCT0005091). All patients provided written informed consent before surgery.

2.2. Patients

Eighty patients who were admitted to a tertiary academic medical and level-1 trauma center were enrolled in this prospective randomized study. The inclusion criteria were as follows: patients who experienced TBI within the last month, undergoing traumatic orthopedic surgery under general anesthesia, receiving or not receiving supplemental oxygen due to various lung injuries in the ward or intensive care unit, aged between 20 and 70 years, with a BMI between 18 and 35 kg/m^2, and with an American Society of Anesthesiologists physical status of I, II, or III. The exclusion criteria for the study were patients with end-stage renal failure, atrioventricular block, or neurological disorder; already intubated patients for whom extubation was not possible after surgery; those diagnosed with a psychiatric disorder or drug or alcohol addiction; patients with previous history of stroke or brain surgery; those who refused to participate in the study; and

patients with cognitive impairments or any other physical or mental illness that rendered them unable to provide a pain score.

2.3. Anesthesia and Monitoring

No premedication was administered before the administration of general anesthesia. Standard monitoring was established using electrocardiography, non-invasive blood pressure measurement, peripheral oxygen saturation, and a bispectral index sensor (BIS, A-2000 BIS™ monitor; Aspect® Medical Systems Inc., Norwood, MA, USA) before the induction of anesthesia. Bilateral NIRS sensors (INVOS 5100; Covidien, Dublin, Ireland) were placed above the eyebrow on either side of the forehead, i.e., left (rSO_2 L) and right (rSO_2 R), to monitor the rSO_2. Baseline rSO_2 was measured for more than 1 min in the supine position without any medication before anesthesia, and the measurement was continued until the patient was transferred to the intensive care unit. Some patients received supplemental oxygen through various methods, depending on their condition, and the baseline rSO_2 values were measured while maintaining the oxygen supplementation during transfer from the intensive care unit to the operating room. The intraoperative fraction of inspired oxygen (FiO_2) was maintained at 0.5, and the minimal and maximal values of rSO_2 and the maximal degree of desaturation were also recorded.

Anesthesia was induced by a continuous infusion of remifentanil via a target-controlled infusion pump (Orchestra®, Fresenius vial, Brezins, France) (2–4 μg/mL) and propofol 1.5–2.5 mg/kg. Rocuronium 0.6 mg/kg was administered to facilitate tracheal intubation after ensuring loss of consciousness. After intubation, the patients were administered either $MgSO_4$ or saline according to a randomization list given to the blinded anesthesiologist: the Mg group received $MgSO_4$ 30 mg/kg intravenously for 10 min, followed by a continuous infusion of 15 mg/kg/h during surgery, whereas the control group received the same volume of isotonic saline. This bolus dose, which was 60% of that of previous studies [8,9], was intended to prevent potential hemodynamic instability induced by rapid administration of a high dose of magnesium to patients with acute and severe traumatic injuries. Thereafter, anesthesia was maintained with sevoflurane, whose concentration was adjusted depending on the BIS value. The target concentration of remifentanil was adjusted to maintain arterial pressure and heart rate within 20% of the preoperative values. Controlled ventilation was adjusted to an end-tidal CO_2 level of 4.0–4.7 kPa.

We endeavored to prevent the incidence of hypotension (mean blood pressure > 65 mmHg), anemia (hemoglobin > 7 g/dL), hypoxemia (arterial partial pressure of oxygen >100 mmHg), and hypothermia (core temperature > 35.5 °C) during surgery. After the return of the fourth twitch of the train-of-four response, glycopyrrolate 0.01 mg/kg and neostigmine 0.03 mg/kg were administered. The patient was extubated in the operating room when the train-of-four ratio recovered to $\geq$0.90 and was transferred to the postanesthetic care unit or the trauma intensive care unit.

2.4. Intervention Protocol

For all patients using rSO_2, we had a strict intervention protocol for the occurrence of desaturation. We ensured that there was no external compression of the INVOS-NIRS electrodes during recording. After establishing the baseline value for each side, rSO_2 changes during the duration of anesthesia were recorded. There were no changes in the degree of head tilt or rotation during the procedure. A sudden fall in rSO_2 value exceeding 20% of the initial baseline value was designated as critical. In the event of a critical decrease in rSO_2, the neck position was first checked to eliminate the possibility of external compression. The second step involved increasing the blood pressure, inspired concentration of FiO_2, and end-tidal CO_2 to approximately 40 mmHg and optimization of the preload using a mini-fluid bolus challenge of 100 mL [18,19]. Finally, if all interventions failed to restore the rSO_2 value above 80% of the baseline value, a transfusion of red blood cells was considered at hemoglobin levels of 8–9 g/dL.

2.5. Assessment of Outcomes

The primary outcome was cerebral oximetry measurements at baseline and throughout surgery. The frequency and duration of cerebral desaturation was also reviewed. Postoperative pain was evaluated by a blinded investigator, who questioned patients about their pain using a numeric rating scale, which ranged from 0 (free of pain) to 10 (worst pain imaginable), at 6, 24, and 48 h after surgery. The cumulative consumption of analgesics via patient-controlled analgesia and rescue analgesics was recorded at each time point. The incidence of postoperative nausea and vomiting, use of rescue antiemetics, and the patients' overall satisfaction score (subjective assessment of the patient, numeric rating scale = 10, was indicative of "very satisfied") were recorded by a blinded investigator. The preparation and administration of parenteral drugs and the collection and measurement of data were performed by doctors and nurses who were blinded to the study group.

2.6. Sample Size Calculation

The sample size was determined based on the results of a previous study [8]. Baseline rSO_2 was 52.8 ± 11.5 (%) in cardiac surgery for the control group, and an increase of 15% in rSO_2 was considered clinically significant. The calculated sample size was 70 with an alpha error of 0.05 and power of 80%. The required sample size was established to be 80 patients, accounting for a 15% attrition rate.

2.7. Statistical Analysis

The results are presented as absolute values, means (SD), frequencies (percentages), or medians (IQR) after assessing the normality of the distribution using the Kolmogorov–Smirnov test. Continuous data were compared using the Student's *t*-test, Mann–Whitney U test, ANOVA, or the Kruskal–Wallis test with post hoc analysis, wherever appropriate. The incidence data were compared using the X^2 test or Fisher's exact test, according to the expected counts. The changes between the time points within each group were compared using repeated-measures ANOVA. All statistical analyses were performed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA), and the significance level was set to 0.05 for all tests.

3. Results

Eighty patients were initially assessed for eligibility for inclusion in this study. Eleven patients were excluded from the final analysis for the following reasons: one patient from the Mg group declined to participate; another from the Mg group experienced a massive bleeding event early during surgery; data recording errors occurred in two patients from the Mg group; one patient from the control group had concomitant panperitonitis requiring another urgent surgery; and the operative time exceeded 5 h in four and two patients from the Mg and control groups, respectively (Figure 1). The remaining 69 patients were included in the analysis.

The demographic and surgical factors of the 69 patients are provided in Table 1. Road traffic accidents were the cause of trauma in a large portion of the study population. The average interval between injury and current surgery was approximately 5 days in both groups. The preoperative magnesium levels at admission were similar for both groups.

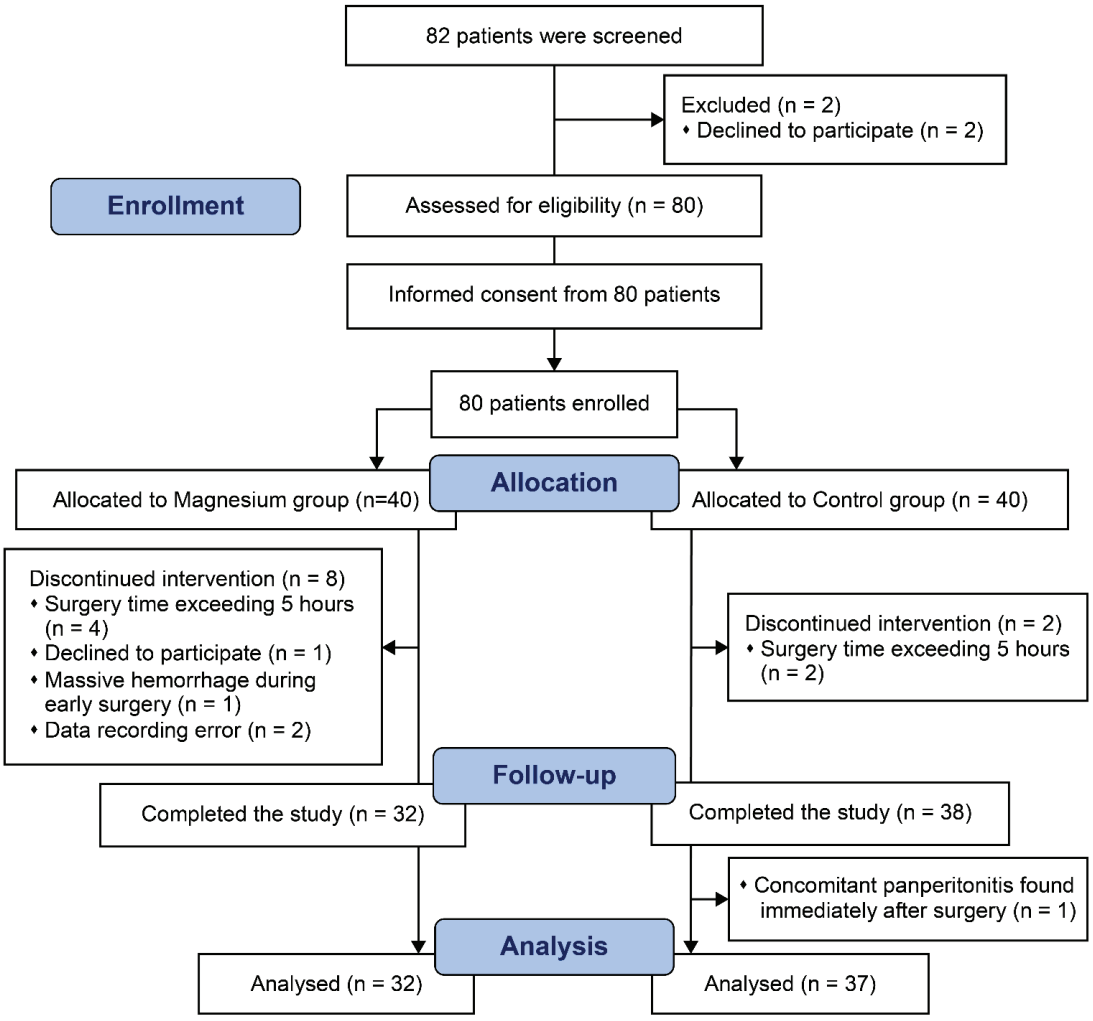

Figure 1. CONSORT diagram.

The most common TBI symptoms included loss of consciousness, headache, and somnolence. The severity of TBI was mild in all cases (Table 2). Common findings on brain computed tomography were subarachnoid hemorrhage, subdural hemorrhage, and scalp swelling. In more than half of the patients, no evidence of trauma-related intracranial hemorrhage or skull fracture was found. The Glasgow Coma Scale score at the time of arrival to the trauma bay, exit from the trauma bay, and immediately before surgery (Mg group, 14.97 vs. control group, 14.92) were similar for both groups. On the contrary, the injury itself was severe in both groups according to Injury Severity Score (ISS, 21.2 vs. 22.0).

Table 1. Baseline characteristics of patients and perioperative data assigned to magnesium or the control group.

	Magnesium Group (n = 32)	Control Group (n = 37)	p Value
Sex (Male/Female)	25/7	32/5	0.361
Age (year)	49.5 ± 15.2	50.1 ± 14.9	0.879
Height (cm)	168.5 ± 7.2	167.9 ± 8.1	0.749
Weight (kg)	71.9 ± 11.6	69.9 ± 11.4	0.479
ASA (I/II/III)	3/18/11	3/28/6	0.211
Mechanism of Injury, n (%)			0.642
Fall	11 (34.4%)	11 (29.7%)	
Transportation accident	20 (62.5%)	26 (70.3%)	
Explosion	1 (3.1%)	0 (0%)	
Days after injury (days) (range)	4.5 ± 3.7 (6 h–13 day)	5.1 ± 4.7 (6 h–21 day)	0.569
Surgery, Orthopedic			0.315
Upper extremity	11 (34.4%)	9 (24.3%)	
Lower extremity	12 (37.5%)	15 (40.5%)	
Hip	4 (12.5%)	4 (10.8%)	
Other parts	4 (12.5%)	6 (16.2%)	
Combined op	1 (3.1%)	3 (8.1%)	
Magnesium at admission (normal range: 1.6–2.6) (mg/dL)	1.96 ± 0.41	2.03 ± 0.20	0.361
Duration of surgery (min)	81.1 ± 43.0	99.6 ± 63.3	0.167
Duration of anesthesia (min)	126.4 ± 49.0	143.1 ± 66.7	0.247
Aldrete score *	10 (n = 20)	10 (n = 25)	
PACU stay time (min) *	34.6 ± 7.7 (n = 20)	37.8 ± 9.9 (n = 25)	0.239

ASA, American Society of Anesthesiologists; PACU, post-anesthesia care unit. Values are number (proportion) or mean ± SD. * only those who have been transferred to PACU after surgery.

Regarding the primary outcome measures, the cerebral oximetry measurements, including the baseline (left 67.0 ± 7.8% vs. 66.1 ± 8.0%; p = 0.654), lowest and highest intraoperative rSO_2 values, were similar for both groups (Figure 2, online Supplementary Material Table S1). The absolute rSO_2 values when FiO_2 was elevated, which occurred at the time of magnesium bolus administration and at extubation, were found to be significantly greater than the baseline rSO_2 values (Figure 2a). However, there was no difference between the baseline values and those obtained at other time points. The incidence of rSO_2 < 20% (critical events) and that between 20% and 10% were similar in both groups (Figure 2b, left p = 0.521 and p = 0.265, respectively). The duration of these cerebral desaturation percentages did not differ between the groups (Figure 2c, left p = 0.638 and p = 0.675, respectively). In the subgroup analysis performed according to whether or not oxygen was administered, the rSO_2 values were not different within each group. The critical desaturation events were reversible in all cases due to stringent adherence to the intervention protocol. Red blood cells were similarly transfused between the groups and independently of the rSO_2 intervention protocol.

The amount of remifentanil infused during surgery was significantly lower in the Mg group (221.1 ± 148.4 mcg vs. 314.6 ± 181.9, p = 0.024) than in the control group. The magnesium level at the end of the surgery in the Mg group was higher, and its value approximated the upper limit of the normal range (2.68 ± 0.32 mg/dL vs. 1.95 ± 0.22 mg/dL, p = 0.000). The amount of phenylephrine, total duration of hospitalization, and physical activity at discharge were similar between the groups (online Supplementary Material Table S2).

The pain intensity was lower and satisfaction scores were higher in the Mg group during the first 6 h postoperatively than in the control group (p = 0.017 and 0.007, respectively) (Table 3). Cumulative fentanyl-equivalent consumption (including fentanyl patient-controlled analgesia, fentanyl rescue and tramadol) (191.6 ± 143.6 vs. 280.9 ± 201.6, p = 0.041) was lower in the Mg group 6 h postoperatively.

Table 2. Traumatic brain injury aspects preoperatively.

	Magnesium Group (n = 32)	Control Group (n = 37)	p Value
TBI, Symptom, n (%)			
Loss of consciousness at the time of injury	24 (75.0%)	33 (89.2%)	0.121
Headache	6 (18.8%)	8 (21.6%)	0.767
Dizziness	3 (9.4%)	6 (16.2%)	0.489
Nausea/vomiting	5 (15.6%)	5 (13.5%)	0.804
Memory impairment	5 (15.6%)	6 (16.2%)	0.947
Sleeping tendency	10 (31.3%)	13 (35.1%)	0.733
TBI, Severity, n (%) immediately before surgery			
Mild (GCS 15/14)	31/1	34/3	0.618
Moderate	0	0	
Severe	0	0	
Brain CT, n (%) *			
Subarachnoid hemorrhage	8 (25.0%)	5 (13.5%)	0.224
Subdural hemorrhage	6 (18.8%)	4 (10.8%)	0.350
Epidural hemorrhage	4 (12.5%)	2 (5.4%)	0.349
Intracerebral hemorrhage	0 (0%)	1 (2.7%)	0.279
Cerebral Contusion	2 (6.3%)	4 (10.8%)	0.503
Skull fracture	7 (21.9%)	3 (8.1%)	0.105
Scalp/soft tissue swelling	8 (25.0%)	14 (37.8%)	0.254
Midline shift > 5 mm, n (%)	0	0	
The others	4 (12.5%)	3 (8.1%)	0.547
No intracranial hemorrhage or bony skull fracture	16 (50.5%)	17 (51.5%)	0.737
TBI site (Left/Right/Both/non-specific/none)	(3/9/4/0/16)	(4/4/4/8/17)	
Preoperative antiepileptic prescription	10 (31.3%)	6 (16.2%)	0.140
GCS at the time of entering trauma-bay	14.16 ± 2.02	14.62 ± 0.83	0.210
15/14/13–11/less than 11, n	24/6/1/1	21/11/4/1	
GCS at the time of leaving trauma-bay	14.62 ± 0.73	14.74 ± 0.56	0.451
15/14/13–11/less than 11, n	26/3/0/3	23/8/4/2	
Invasive ICP monitoring, n	0	0	
Evacuation of brain mass lesion, n	0	0	
ISS score			
Median (range, IQR)	22 (5–43, 17–23)	19 (9–43, 17–22)	
Mean ± SD	21.2 ± 6.7	22.0 ± 9.3	0.691

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CT, computed tomography; ICP, intracranial pressure; ISS, injury severity score; IQR, interquartile range. Values are number (proportion) or mean ± SD. * Allow duplicate counts because of concurrent brain injuries identified by CT scan.

There was no difference between the frequency and dose of analgesics (fentanyl rescue, acetaminophen, tramadol, and nefopam) administered after surgery between the groups; however, the frequency of nonsteroidal anti-inflammatory drug use was lower in the Mg group at 6 h postoperatively. There was no difference in the incidence of postoperative nausea and vomiting and the use of rescue antiemetics between the groups (28% vs. 32%, p = 0.698). The initial and intraoperative hemodynamic variables did not differ between the groups (online Supplementary Material Table S3). No magnesium-related untoward side effects, such as bradycardia, electrocardiographic changes, respiratory depression, delayed reversal of the neuromuscular blockade, or delayed discharge from the post-anesthesia care unit, were reported.

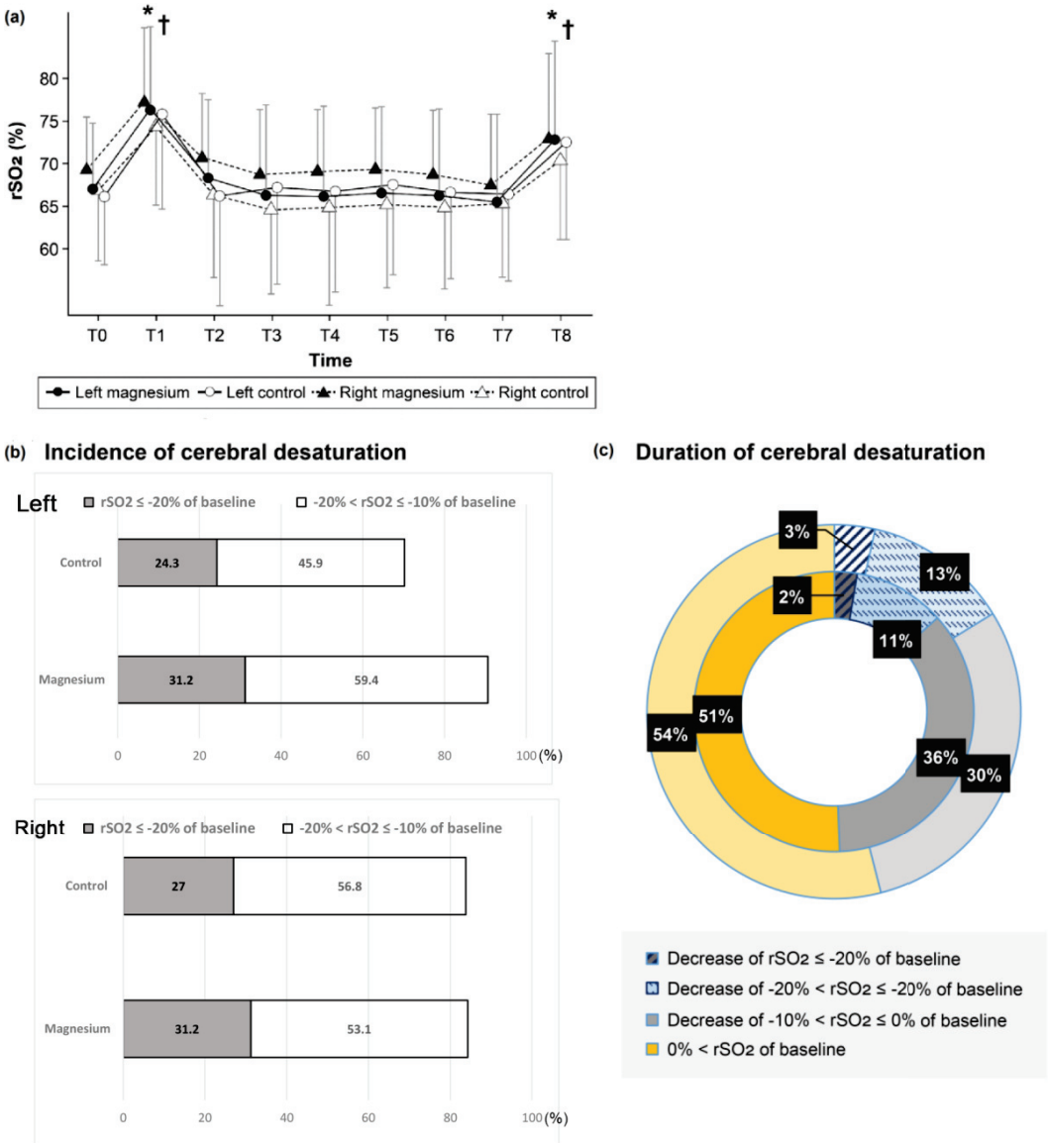

Figure 2. Representative values of regional cerebral oxygen saturation (rSO_2) in the operating room. (**a**) Time trend of rSO_2. T0: baseline at admission to operating room (OR), T1: Mg bolus administration, T2: Mg continuous infusion, T3–T6: 10, 20, 30, 40 min after Mg infusion, T7: end of surgery, T8: leaving the OR. ● Left ▲ Right ● Magnesium ○ control. (**b**) Incidence of percentage decreases in rSO_2 (%), below or equal to minus 20% and below or equal to 10% to less than 20% relative to each baseline value. (**c**) Duration of percentage decreases in rSO_2 (%). The inner circle is the Magnesium group. The outer circle is the Control group. * $p < 0.05$ from baseline value in Magnesium (Mg) group, † $p < 0.05$ from baseline value in control group.

Table 3. Postoperative analgesic consumption and pain scores during the first 48 h after surgery.

	Magnesium Group (n = 32)	Control Group (n = 37)	p Value
PCA fentanyl consumption	n = 17 (53.1%)	n = 24 (64.9%)	0.322
postoperative 6 h (mcg)	201.9 ± 134.1 *	302.8 ± 140.4	0.026
postoperative 24 h (mcg)	574.7 ± 380.7	598.6 ± 264.9	0.814
postoperative 48 h (mcg)	762.8 ± 464.4	853.8 ± 357.4	0.482
Fentanyl bolus iv until 6 h	n = 12 (37.5%)	n = 11 (29.7%)	0.495
postoperatively (mcg)	75.0 ± 26.1	95.8 ± 54.2	0.243
Nefopam consumption	n = 23 (71.9%)	n = 31 (83.8%)	0.232
postoperative 6 h (mg)	21.6 ± 2.3	21.9 ± 2.5	0.700
postoperative 24 h (mg)	70.6 ± 8.5	71.9 ± 5.4	0.519
postoperative 48 h (mg)	86.2 ± 23.6	93.4 ± 8.1	0.137
NSAIDs use, number (%)			
postoperative 6 h	5 (15.6%) *	14 (37.8%)	0.039
postoperative 24 h	6 (18.8%)	8 (21.6%)	0.767
postoperative 48 h	8 (25.0%)	6 (16.2%)	0.366
Tramadol consumption	n = 29 (90.6%)	n = 36 (97.3%)	0.330
postoperative 6 h (mg)	56.3 ± 50.4	49.3 ± 47.3	0.558
postoperative 24 h (mg)	120.3 ± 71.9	104.1 ± 76.7	0.370
postoperative 48 h (mg)	116.4 ± 65.6	127.0 ± 74.9	0.536
Pain scores (NRS)			
postoperative 6 h	6.8 ± 2.8 *	8.2 ± 2.0	0.017
postoperative 24 h	5.1 ± 2.5	5.4 ± 2.3	0.660
postoperative 48 h	3.3 ± 2.2	3.2 ± 2.6	0.839
Satisfaction scores (NRS)			
postoperative 6 h	66.1 ± 28.9 *	47.1 ± 27.6	0.007
postoperative 24 h	71.8 ± 21.1	65.7 ± 20.6	0.226
postoperative 48 h	78.3 ± 21.3	73.4 ± 24.6	0.389

PCA, patient-controlled analgesia; NSAIDs, nonsteroidal anti-inflammatory drugs; NRS, numeric rating scale. Values are mean ± SD. * $p < 0.05$ = between groups.

4. Discussion

This prospective randomized, double-blind controlled study investigated the relationship between the intraoperative administration of $MgSO_4$ and the changes in the rSO_2 values in patients with TBI. It revealed no association in both the *absolute* rSO_2 values and the incidence and duration of the *relative* decrease in the rSO_2 values < 80% of baseline. After strict compliance to our intervention protocol, critical desaturation events in all cases were restored. Remifentanil consumption was significantly lower in the Mg group than in the control group. The pain intensity and fentanyl consumption were lower during the first 6 h postoperatively, and the satisfaction score was higher in the Mg group.

Preventive measures addressing brain protection in TBI deserve a high priority to alleviate additional harm. Subsequent injuries can be incurred, especially when patients with TBI are required to undergo major surgery under general anesthesia as a result of hypotension, hypoxemia, hypo- or hypercarbia, fever, and hypo- or hyperglycemia [1,4]. This secondary brain injury contributes to the increase in healthcare costs, prolonged hospitalization, poor functional outcomes, increased postoperative complications, and even mortality [3,20].

Although the exact pathophysiology of secondary TBI is unclear, decreased cerebral perfusion and oxygenation are closely related mechanisms [1]. Cerebral oxygenation is well known as a potentially modifiable risk factor for TBI, and if insufficient cerebral oxygenation can be accurately and timely detected, it can be improved through adaptation/correction of the relevant variables [5,19,21]. Therefore, NIRS can be a practical option for perioperative rSO_2 monitoring, as it provides an opportunity for the early detection of cerebral oxygen supply/demand imbalance. Recent studies detailed the potential therapeutic roles of $MgSO_4$ in vasodilation, hemostasis, blood–brain barrier preservation, and direct neuroprotection [12,22,23]. Hypomagnesemia in TBI is associated with poorer outcomes [15,24]. $MgSO_4$ can reliably confer cerebroprotective effects in animal models of

TBI [11,15,25], though clinical studies have not shown consistent beneficial effects. Therefore, the administration of magnesium to patients with TBI could theoretically help mitigate secondary injury.

However, contrary to our expectations, no significant association was observed between the intraoperative changes in rSO_2 and magnesium infusion in the current study. The absolute degree of decline was similar in the two groups. Comparison of the relative percentage decrease, which has greater clinical utility, also revealed that the incidence and duration of rSO_2 reduction below 80% of the baseline was not affected by magnesium administration.

The potential causes for the current observation are as follows. First, our participants had mild TBI; consequently, we found that the rSO_2 levels did not fluctuate rapidly in mild TBI as long as adequate brain tissue oxygenation and vascular hemostasis could be maintained. We may expect different results if similar studies are conducted in patients with moderate or severe TBI. Our initial rSO_2 values were higher than those in patients undergoing cardiac surgery with cardiopulmonary bypass, who have been studied extensively in this regard. We observed desaturations greater than 10% from baseline in 50% of patients, and greater than 20% from baseline in 30% of patients. In one study on cardiac surgery, corresponding decrements occurred in 60% and 40% of patients, respectively [21]. The absolute baseline, maximal, and minimal values were also 8–10% higher in patients with mild TBI than in patients undergoing cardiac surgery (online Supplementary Material Table S1) [26]. Contrary to the severity of the patients' injury (ISS 21.2 vs. 22.0, an ISS of 16–24 is considered severe, 25 and higher very severe), few patients showed markedly low levels of baseline rSO_2. Additionally, the predictive or diagnostic role of NIRS in monitoring the progression or mitigation of TBI may not be relevant in the absence of significant hemodynamic disturbances, i.e., in non-pulsatile perfusion.

Second, NIRS monitoring itself could have influenced the favorable outcomes in this study. NIRS monitoring alone has been shown to be associated with the amelioration of secondary brain injury [2,27]. We prospectively implemented an intervention protocol to reverse cerebral desaturation in both groups [19,28], which prevented a potential deleterious situation very early. Monitoring and applying the mandatory corrective intervention protocol in our institution were effective in restoring cerebral oxygenation in all patients, both of which could play powerful neuroprotective roles in this study. Third, the cerebral oxygen saturation measured by NIRS does not reflect the cerebral oxygen utilization or that cerebral hypoxia is not the principal driver of the TBI course. The influence of the oxygenation of the extracerebral tissue cannot be excluded due to the technical limitations of the non-invasive monitoring device [18]. Moreover, it is not possible to monitor multiple brain regions using NIRS.

Fourth, the dose or duration of magnesium infusion could have been insufficient to alter the course of TBI [9,14]. An adequate magnesium level at admission is an indicator of neuroprotection [10,17], and our initial magnesium levels were not low at the time of admission and immediately after surgery, even in the control group. While the dose of magnesium required to reduce pain and anesthetic usage has been studied extensively (30–50 mg/kg bolus), the respective doses required to improve microcirculation (through vasodilation of the cerebral vascular beds) and reduce cerebral edema (by maintaining and preserving blood–brain barrier permeability) need further investigation [29]. Fifth, the incidence of hypotensive events was similar between the groups, which were appropriately handled according to our management protocol. Abrupt changes in cerebral perfusion, especially reperfusion following a hypoperfusion event, are considered to be factors associated with additional brain injury [30]. There was no association between rSO_2 levels falling below 80% of the baseline and hypotensive events in the current study. This indicates that the transient changes in cerebral perfusion cannot be accurately reflected by rSO_2 monitoring and highlights the importance of strict blood pressure management during surgery in patients with TBI.

The intensity of pain was substantially stronger in patients with multiple traumas in the present study, than in those who underwent a single orthopedic surgery [31]. Particularly, the patients identified very severe pain (8.2 in the numeric rating scale) at 6 h postoperatively in the control group, despite receiving patient-controlled analgesia and injections of opioid and non-opioid rescue analgesics. Moderate pain continued in both groups until 24 h postoperatively. Consistent with our results, conventional opioid-based pain protocols in surgical patients often remain suboptimal for pain control [32]. Furthermore, patients undergoing major trauma surgery already experience pre-existing concurrent pain, including in other parts of the body, making it more difficult to manage the acute pain added with the current surgery [33]. Recently, multimodal pain management integrates the use of several analgesic medications targeting a different pain-related receptor to maximize pain relief and minimize adverse effects [34]. The mechanisms underlying the antinociceptive effects of $MgSO_4$ include the inhibition of calcium influx, antagonism of N-methyl-D-aspartate (NMDA) receptors, and inhibition of enhanced ligand-induced NMDA signaling in hypomagnesemia. This calcium channel blocker effect augments opioid-induced analgesia, decreases total opioid consumption, and even attenuates central sensitization or delays the development of opioid tolerance [7,35]. Thus, we demonstrated the representative advantages of intraoperative $MgSO_4$, which ameliorates pain and is capable of reducing analgesic requirements, which remain consistent with many other previous studies [8,31]. Patient satisfaction increased with the gradual decrease in pain.

The present study is subject to the following limitations. First, baseline rSO_2 was measured when the patient entered the operating room, regardless of supplemental oxygen to some patients. Patients who experienced multiple traumas may receive oxygen depending on their condition. The oxygenation state and initial rSO_2 levels at the time of entering the operating room are known to be associated with the prognosis regardless of oxygen supplementation [36]. The rSO_2 does not seem to deteriorate substantially if adequate oxygen supply and proper management are performed, even in patients with hemodynamic instability or respiratory distress. Second, we did not extend the rSO_2 measurement to the immediate postoperative period or intensive care unit stay, which might also be a potential confounder of the observed results and subsequent prognosis. Third, we did not assess cerebral injury using different parameters such as neurocognitive function and brain injury serum biomarker release (e.g., S100B), which could have represented positive differences between the groups. Invasive monitoring, such as intracranial pressure monitoring, was not used for the comparison of the effect of $MgSO_4$. Fourth, outpatient follow-up was performed selectively only in a few patients because of the low severity of TBI. Therefore, comparisons of postoperative functional outcomes, such as the Glasgow Outcome Score and modified Rankin scale, were not possible between the groups.

This is the first study to investigate the relationship between $MgSO_4$ infusion and rSO_2 in TBI, exploring the neuroprotective effect of $MgSO_4$ on TBI with respect to its safety and potential efficacy. Together, we expanded the applicability of NIRS and determined the incidence and extent of cerebral desaturation in patients with TBI who were susceptible to cerebral hypoxia. However, it was difficult to envision the brain environment or predict outcomes via NIRS when there was substantial regional heterogeneity. Instead, we clearly obtained the benefits of NIRS-based corrective interventions by sequentially restoring cerebral desaturation and reaffirmed the analgesia-potentiating and opioid-sparing effects of $MgSO_4$.

5. Conclusions

In summary, continuous perioperative rSO_2 monitoring with NIRS did not demonstrate the diagnostic or clinical benefit of $MgSO_4$ in patients with mild TBI undergoing major orthopedic surgery. We suggest evaluating the role of rSO_2 monitoring in patients with various TBIs at risk of neurologic complications and assessing the benefits of NIRS-based corrective interventions. Additionally, further studies are needed to extend our findings of $MgSO_4$ to cases of more severe TBI, to determine the effects of various doses

and durations of $MgSO_4$ aimed at optimizing cerebral oxygenation and intracranial physiology, and to prevent or mitigate secondary injury. Even if negative results are obtained, as in the present study, future research will be able to identify the benefits of reducing analgesic consumption and pain relief through $MgSO_4$ administration.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11123388/s1. Table S1. Baseline and intraoperative regional cerebral oxygen saturation (rSO2) data. Table S2. Intraoperative anesthetic and postoperative clinical variables. Table S3. Perioperative hemodynamics and laboratory variables immediate after surgery.

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Informed Consent Statement: All patients provided written informed consent before surgery.

Data Availability Statement: Data are available from the authors (HMS) upon reasonable request. The clinical data are fully anonymized, and the experiments were performed by a qualified anesthesiologist with good clinical practice in accordance with the relevant guidelines and regulations.

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References

1. Werner, C.; Engelhard, K. Pathophysiology of traumatic brain injury. *Br. J. Anaesth.* **2007**, *99*, 4–9. [CrossRef] [PubMed]
2. Mathieu, F.; Khellaf, A.; Ku, J.C.; Donnelly, J.; Thelin, E.P.; Zeiler, F.A. Continuous near-infrared spectroscopy monitoring in adult traumatic brain injury: A systematic review. *J. Neurosurg. Anesthesiol.* **2020**, *32*, 288–299. [CrossRef] [PubMed]
3. Nelson, L.D.; Temkin, N.R.; Dikmen, S.; Barber, J.; Giacino, J.T.; Yuh, E.; Levin, H.S.; McCrea, M.A.; Stein, M.B.; Mukherjee, P.; et al. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: A transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. *JAMA Neurol.* **2019**, *76*, 1049–1059. [CrossRef] [PubMed]
4. Curry, P.; Viernes, D.; Sharma, D. Perioperative management of traumatic brain injury. *Int. J. Crit. Illn. Inj. Sci.* **2011**, *1*, 27–35.
5. Lumba-Brown, A.; Yeates, K.O.; Sarmiento, K.; Breiding, M.J.; Haegerich, T.M.; Gioia, G.A.; Turner, M.; Benzel, E.C.; Suskauer, S.J.; Giza, C.C.; et al. Centers for Disease Control and Prevention guideline on the diagnosis and management of mild traumatic brain injury among children. *JAMA Pediatr.* **2018**, *172*, e182853. [CrossRef]
6. Silverberg, N.D.; Duhaime, A.C.; Iaccarino, M.A. Mild traumatic brain injury in 2019–2020. *JAMA* **2020**, *323*, 177–178. [CrossRef]
7. Albrecht, E.; Kirkham, K.R.; Liu, S.S.; Brull, R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: A meta-analysis. *Anaesthesia* **2013**, *68*, 79–90. [CrossRef]
8. Do, S.H. Magnesium: A versatile drug for anesthesiologists. *Korean J. Anesthesiol.* **2013**, *65*, 4–8. [CrossRef]
9. Sohn, H.M.; Jheon, S.H.; Nam, S.; Do, S.H. Magnesium sulphate improves pulmonary function after video-assisted thoracoscopic surgery: A randomised double-blind placebo-controlled study. *Eur. J. Anaesthesiol.* **2017**, *34*, 508–514. [CrossRef]
10. Chang, J.J.; Mack, W.J.; Saver, J.L.; Sanossian, N. Magnesium: Potential roles in neurovascular disease. *Front. Neurol.* **2014**, *5*, 52. [CrossRef]
11. Kemp, P.A.; Gardiner, S.M.; March, J.E.; Rubin, P.C.; Bennett, T. Assessment of the effects of endothelin-1 and magnesium sulphate on regional blood flows in conscious rats, by the coloured microsphere reference technique. *Br. J. Pharmacol.* **1999**, *126*, 621–626. [CrossRef]
12. Arango, M.F.; Bainbridge, D. Magnesium for acute traumatic brain injury. *Cochrane Database Syst. Rev.* **2008**, *4*, CD005400. [CrossRef]
13. Iseri, L.T.; French, J.H. Magnesium: nature's physiologic calcium blocker. *Am. Heart J.* **1984**, *108*, 188–193. [CrossRef]
14. Temkin, N.R.; Anderson, G.D.; Winn, H.R.; Ellenbogen, R.G.; Britz, G.W.; Schuster, J.; Lucas, T.; Newell, D.W.; Mansfield, P.N.; Machamer, J.E.; et al. Magnesium sulfate for neuroprotection after traumatic brain injury: A randomised controlled trial. *Lancet Neurol.* **2007**, *6*, 29–38. [CrossRef]

15. Vink, R.; McIntosh, T.K.; Demediuk, P.; Weiner, M.W.; Faden, A.I. Decline in intracellular free Mg^{2+} is associated with irreversible tissue injury after brain trauma. *J. Biol. Chem.* **1988**, *263*, 757–761. [CrossRef]
16. Lozada-Martinez, I.D.; Padilla-Durán, T.J.; González-Monterroza, J.J.; Aguilar-Espinosa, D.A.; Molina-Perea, K.N.; Camargo-Martinez, W.; Llamas-Medrano, L.; Hurtado-Pinillos, M.; Guerrero-Mejía, A.; Janjua, T.; et al. Basic considerations on magnesium in the management of neurocritical patients. *J. Neurocrit. Care* **2021**, *14*, 78–87. [CrossRef]
17. Behrouz, R.; Hafeez, S.; Mutgi, S.A.; Zakaria, A.; Miller, C.M. Hypomagnesemia in intracerebral hemorrhage. *World Neurosurg.* **2015**, *84*, 1929–1932. [CrossRef]
18. Weigl, W.; Milej, D.; Janusek, D.; Wojtkiewicz, S.; Sawosz, P.; Kacprzak, M.; Gerega, A.; Maniewski, R.; Liebert, A. Application of optical methods in the monitoring of traumatic brain injury: A review. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 1825–1843.
19. Deschamps, A.; Hall, R.; Grocott, H.; Mazer, C.D.; Choi, P.T.; Turgeon, A.F.; de Medicis, E.; Bussières, J.S.; Hudson, C.; Syed, S.; et al. Cerebral oximetry monitoring to maintain normal cerebral oxygen saturation during high-risk cardiac surgery: A randomized controlled feasibility trial. *Anesthesiology* **2016**, *124*, 826–836. [CrossRef]
20. Stocchetti, N.; Zanier, E.R. Chronic impact of traumatic brain injury on outcome and quality of life: A narrative review. *Crit. Care* **2016**, *20*, 148. [CrossRef]
21. Hogue, C.W.; Levine, A.; Hudson, A.; Lewis, C. Clinical applications of near-infrared spectroscopy monitoring in cardiovascular surgery. *Anesthesiology* **2021**, *134*, 784–791. [CrossRef] [PubMed]
22. Goyal, N.; Tsivgoulis, G.; Malhotra, K.; Houck, A.L.; Khorchid, Y.M.; Pandhi, A.; Inoa, V.; Alsherbini, K.; Alexandrov, A.V.; Arthur, A.S.; et al. Serum magnesium levels and outcomes in patients with acute spontaneous intracerebral hemorrhage. *J. Am. Heart Assoc.* **2018**, *7*, e008698. [CrossRef] [PubMed]
23. Sen, A.P.; Gulati, A. Use of magnesium in traumatic brain injury. *Neurotherapeutics* **2010**, *7*, 91–99. [CrossRef] [PubMed]
24. Polderman, K.H.; Bloemers, F.W.; Peerdeman, S.M.; Girbes, A.R. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit. Care Med.* **2000**, *28*, 2022–2025. [CrossRef]
25. Heath, D.L.; Vink, R. Improved motor outcome in response to magnesium therapy received up to 24 h after traumatic diffuse axonal brain injury in rats. *J. Neurosurg.* **1999**, *90*, 504–509. [CrossRef]
26. Jo, Y.Y.; Shim, J.K.; Soh, S.; Suh, S.; Kwak, Y.L. Association between cerebral oxygen saturation with outcome in cardiac surgery: Brain as an index organ. *J. Clin. Med.* **2020**, *9*, 840. [CrossRef]
27. Davie, S.; Mutch, W.A.C.; Monterola, M.; Fidler, K.; Funk, D.J. The incidence and magnitude of cerebral desaturation in traumatic brain injury: An observational cohort study. *J. Neurosurg. Anesthesiol.* **2021**, *33*, 258–262. [CrossRef]
28. Subramanian, B.; Nyman, C.; Fritock, M.; Klinger, R.Y.; Sniecinski, R.; Roman, P.; Huffmyer, J.; Parish, M.; Yenokyan, G.; Hogue, C.W. A multicenter pilot study assessing regional cerebral oxygen desaturation frequency during cardiopulmonary bypass and responsiveness to an intervention algorithm. *Anesth. Analg.* **2016**, *122*, 1786–1793. [CrossRef]
29. Anastasian, Z.H. Anaesthetic management of the patient with acute ischaemic stroke. *Br. J. Anaesth.* **2014**, *113* (Suppl. 2), ii9–ii16. [CrossRef]
30. Gardner, C.J.; Lee, K. Hyperperfusion syndromes: Insight into the pathophysiology and treatment of hypertensive encephalopathy. *CNS Spectr.* **2007**, *12*, 35–42. [CrossRef]
31. Sohn, H.M.; Kim, B.Y.; Bae, Y.K.; Seo, W.S.; Jeon, Y.T. Magnesium sulfate enables patient immobilization during moderate block and ameliorates the pain and analgesic requirements in spine surgery, which can not be achieved with opioid-only protocol: A randomized double-blind placebo-controlled study. *J. Clin. Med.* **2021**, *10*, 4289. [CrossRef]
32. Gan, T.J. Poorly controlled postoperative pain: Prevalence, consequences, and prevention. *J. Pain Res.* **2017**, *10*, 2287–2298. [CrossRef]
33. Loftus, R.W.; Yeager, M.P.; Clark, J.A.; Brown, J.R.; Abdu, W.A.; Sengupta, D.K.; Beach, M.L. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* **2010**, *113*, 639–646. [CrossRef]
34. Bohl, D.D.; Louie, P.K.; Shah, N.; Mayo, B.C.; Ahn, J.; Kim, T.D.; Massel, D.H.; Modi, K.D.; Long, W.W.; Buvanendran, A.; et al. Multimodal versus patient-controlled analgesia after an anterior cervical decompression and fusion. *Spine* **2016**, *41*, 994–998. [CrossRef]
35. Rodriguez-Rubio, L.; Nava, E.; Del Pozo, J.S.G.; Jordan, J. Influence of the perioperative administration of magnesium sulfate on the total dose of anesthetics during general anesthesia. a systematic review and meta-analysis. *J. Clin. Anesth.* **2017**, *39*, 129–138. [CrossRef]
36. Vilke, A.; Bilskiene, D.; Saferis, V.; Gedminas, M.; Bieliauskaitė, D.; Tamašauskas, A.; Macas, A. Predictive value of early near-infrared spectroscopy monitoring of patients with traumatic brain injury. *Medicina* **2014**, *50*, 263–268. [CrossRef]

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Expert Multinational Consensus Statement for Total Intravenous Anaesthesia (TIVA) Using the Delphi Method†

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Abstract: Introduction: The use of total intravenous anaesthesia (TIVA) has been well established as an anaesthetic technique over the last few decades. Significant variation in practice exists however, and volatile agents are still commonly used. This study aims to determine the motivations and barriers for using TIVA over the use of volatile agents by analysing the opinion of several international anaesthetists with specific expertise or interests. **Methods and participants:** The Delphi method was used to gain the opinions of expert panellists with a range of anaesthetic subspecialty expertise. Twenty-nine panellists were invited to complete three survey rounds containing statements regarding the use of TIVA. Anonymised data were captured through the software REDCap and analysed for consensus and prioritisation across statements. Starting with 12 statements, strong consensus was defined as ≥75% agreement. Stability was assessed between rounds. **Results:** Strong consensus was achieved for four statements regarding considerations for the use of TIVA. These statements addressed whether TIVA is useful in paediatric anaesthesia, the importance of TIVA in reducing the incidence of postoperative nausea and vomiting, its positive impact on the environment and effect on patient physiology, such as airway and haemodynamic control. **Conclusions:** Using the

Delphi method, this international consensus showed that cost, lack of familiarity or training and the risk of delayed emergence are not considered obstacles to TIVA use. It appears, instead, that the primary motivations for its adoption are the impact of TIVA on patient experience, especially in paediatrics, and the benefit to the overall procedure outcome. The effect of TIVA on postoperative nausea and vomiting and patient physiology, as well as improving its availability in paediatrics were considered as priorities. We also identified areas where the debate remains open, generating new research questions on geographical variation and the potential impact of local availability of monitoring equipment.

Keywords: TIVA; total intravenous anaesthesia; volatile anaesthesia; anaesthetic techniques; peri-operative anaesthesia

1. Introduction

The intravenous anaesthetic propofol has been widely used to induce general anaesthesia since its introduction in the 1980s. However, what has divided clinical opinion across the board is the use of intravenous agents for both induction and maintenance of anaesthesia, in a technique called propofol-based total intravenous anaesthesia (TIVA) [1]. The literature suggests several potential benefits for the use of TIVA over volatile agents. It is thought to be more environmentally friendly as it reduces the production of waste anaesthetic gases which is attributed to volatile anaesthesia [2,3]. TIVA may also be associated with a positive effect on patient physiology, such as more stable haemodynamic conditions due to high dose opiate analgesia, less reliance on airway to achieve hypnosis, as well as a reduction in the incidence of post-operative nausea and vomiting [1,4,5]. Several studies also suggest that TIVA may improve the overall survival in cancer patients [6–8]. However, arguments against the use of TIVA may include a higher incidence of awareness and delayed emergence from anaesthesia, especially in paediatric cases [9,10]. Nevertheless, popularity of TIVA seems to be increasing [11–13]. Additionally, TIVA being a newer technique than volatile anaesthesia, it may not be as widely popular, possibly leading to geographic variations in familiarity or training. Lastly, until recently, intravenous agents were generally thought to be more expensive than older, widely used volatile anaesthetics [14]. It could be argued, however, that by inherently considering volatile anaesthesia a cheaper technique, volatile agents would be administered more liberally, increasing the cost overall. As a result of these varying opinions on the adoption of TIVA in the anaesthetic arsenal, it is no surprise that significant variations in practice exist regarding anaesthesia administration.

As outlined above, there is a wealth of information available regarding the potential advantages and disadvantages of the use of TIVA over volatile agents. Most of these data, however, do not differentiate any variations in practice from a subspecialty, geographical or academic perspective. We formulated the hypothesis that by collecting expert opinions from a variety of anaesthetic subspecialties across the world, we may be able to better understand the motivations for the use of TIVA and whether global challenges or barriers exist, which may result in lower popularity in its use.

2. Methods

2.1. Model

The Delphi method is a well-known process used for obtaining group consensus in healthcare, as it encourages decision making and new ideas to be formed by whole group feedback [15,16]. The method involves several rounds of anonymous questionnaires, where after each round structured feedback and aggregated responses from previous rounds are presented to panellists (Figure 1).

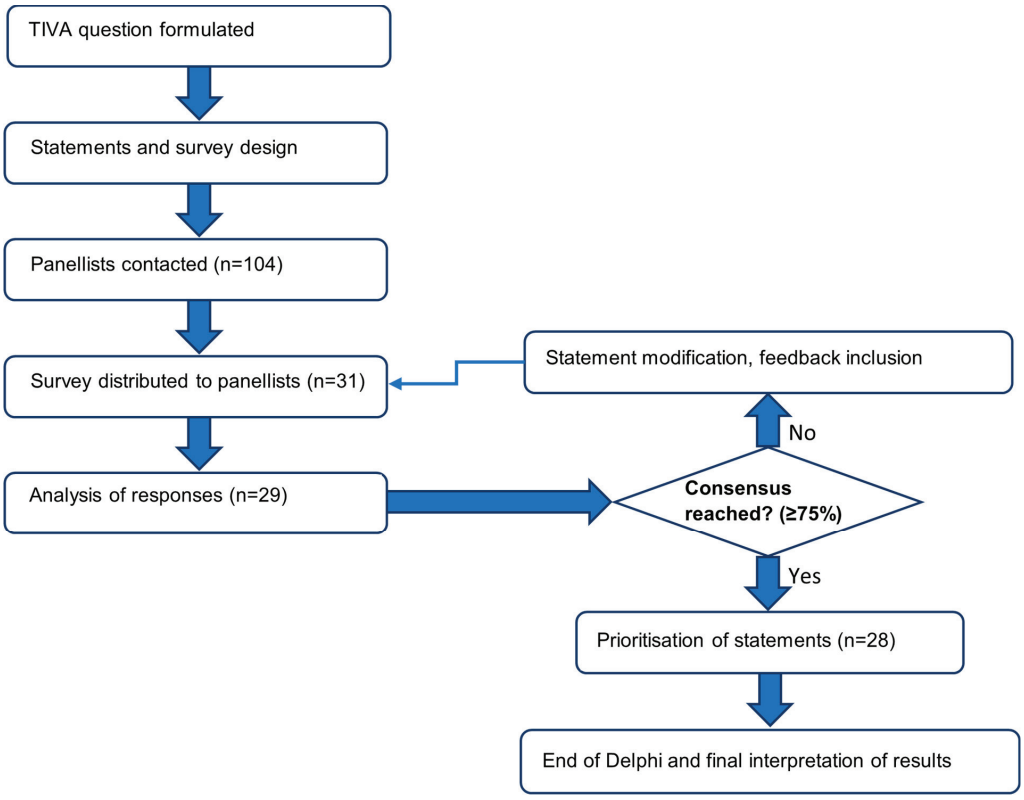

Figure 1. Flowchart depicting the process of the Delphi method.

2.2. Panellist Recruitment

In order to obtain perspectives on anaesthetic techniques from a broad range of professional and geographical settings, an international panel of anaesthetists was recruited with a range of subspecialty interests. All communication was carried out via email. We created an email template outlining the project and explaining the requirements of prospective panellists, and contacted a large number of specialists across the world, only including individuals to the panellist list once they replied citing interest in their involvement. Whilst assured that responses would be anonymous, participants were invited to be listed as collaborators on a future publication, as an additional incentive for participation. Once prospective panellists agreed to participate in the study, their email addresses were added to the final participant list for survey distribution. In terms of the selection of individuals to invite, we selected panellists by either identifying a key opinion leader in an anaesthetic field (e.g., neuro-anaesthesia, obstetric anaesthesia, pain management) or by reaching out to committees of international anaesthetic societies, including the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTAIC), European Society of Anaesthesiology and Intensive Care (ESAIC), UK Society for Intravenous Anaesthesia (SIVA) and European Society for Regional Anaesthesia and Pain Therapy (ESRA), requesting for an interested member to volunteer as panellist. Clinicians were contacted from across all continents; however, the majority of specialists who responded and agreed to participate in the project were European (79%), creating potential bias in terms of the geographical popularity of TIVA use.

Anonymous demographic data were gathered from the panel during Round 1 to determine location of practice and experience. This showed that twenty-one (72.4%)

panellists practice in tertiary care centres, whereas eight (27.6%) are based in secondary care. Furthermore, the average amount of anaesthetic practice was twenty years, with two panellists possessing less than ten years of experience, thirteen possessing between ten and twenty years of experience and fourteen possessing between twenty and fifty years of experience. We hoped that this extensive collective knowledge would reveal interesting opinions from the panel.

2.3. Statements

A list of twelve statements was formulated regarding the use, advantages and disadvantages of general use of TIVA as an anaesthetic technique. In order to formulate these statements, the team conducted a review of the available scientific literature describing the use of TIVA in a range of anaesthetic settings, whilst also attempting to collect evidence of its possible benefits and disadvantages to its use. The search identified factors such as practicality, environmental impact, physiological benefits, the availability of training and knowledge of the technique and the usefulness of TIVA in subspecialties such as paediatric anaesthesia and onco-anaesthesia (Appendix B). Once identified through the literature search, these aspects of TIVA use were used as a basis on which to build the statements for Round 1 of the survey.

For the consecutive survey rounds, statements were modified according to comments offered by the panellists, facilitated through the addition of an open text box at the end of each round. This was arranged to provide panellists with an opportunity to add suggestions or opinions which could be agreed on to form consensus in the wider group.

2.4. Survey Design and Data Collection

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Aberdeen [17,18]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources [19].

REDCap was also used for building the surveys themselves. Three surveys were created: Round 1 proposed the initial 12 statements, each linked to a 5-level Likert scale of agreement, ranging from "Not at all" to "Very much". A free text box was included at the end of the first survey, for panellists to add comments or suggestions on their experience with using TIVA.

Round 2 contained the same statements as the first round, with the possibility to be edited based on comments and additional statements made by panellists during round one. Furthermore, during round two, each participant would be presented with their answer to each statement during the previous round, as well as the aggregated responses and percentage of agreement of other panellists to the statements.

Round 3, the final survey, saw the removal of statements which had not reached a strong positive or negative consensus over the course of the two previous rounds: participants would be asked to rank the remaining statements, which had indeed reached strong consensus, in terms of prioritisation or importance.

2.5. Data Analysis

Through the exportation of the results from REDCap, we analysed the overall consensus for each statement by gathering the number of times participants had "agreed" or "strongly agreed" to a statement, or inversely whether a majority "somewhat disagreed" or "strongly disagreed". The threshold for a strong consensus was established as $\geq$75%, and the stability of each answer was determined as a change in agreement proportions of <10% between each round.

Prioritisation of statements in the final round was calculated as the proportion of participants who had agreed on each statement to be a priority.

2.6. Ethical Review

All participants in this study were contacted directly via email and were only included in the participant list once a clear affirmative response was received to the invitation to participate.

As per the Medical Research Council and the NHS Health Research Authority, a submission was made to determine whether this study required NHS Research Ethics Committee (REC) review. A formal confirmation was obtained attesting that NHS REC review would not be required for this project.

3. Results

3.1. Round 1

Twenty-nine out of thirty-one participants who originally agreed to take part in the project completed the first survey round. Two panellists were unable to participate due to local holidays. A breakdown of the panellists' countries of provenience is shown in Figure 2, and a full list of panellists' anaesthetic fields of interest is shown in Appendix B. Panellists stated their level of agreement with all twelve statements, which resulted in three statements reaching strong consensus (Appendix B). Eighteen participants added additional statements in the free text box regarding further challenges to the use of TIVA. These comments primarily raised issues around the availability of TIVA equipment such as pumps and monitoring, the practicality of the use of TIVA in terms of equipment and type and length of surgery, as well as patient factors such as needle phobia (although rare) and a history or family history of malignant hyperthermia.

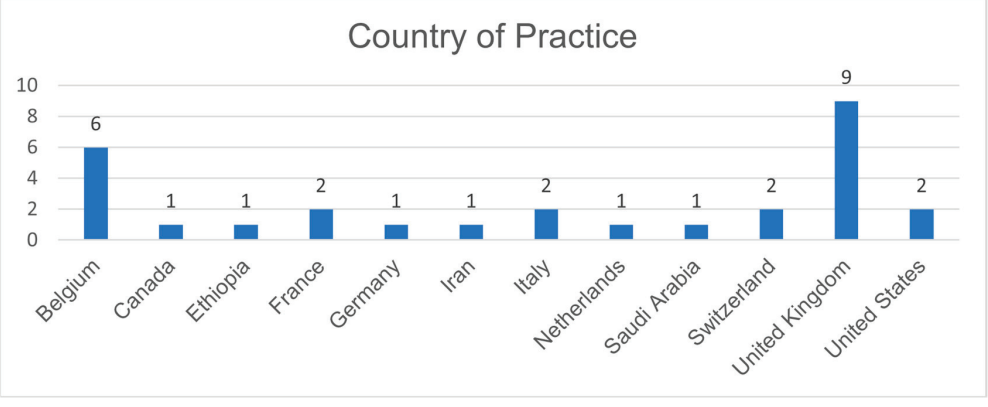

Figure 2. This chart shows the range of countries from which panellists were recruited.

3.2. Round 2

All twenty-nine panellists who completed Round 1 also completed Round 2. The second survey round saw the modification of four statements to incorporate the suggestions that participants had provided during Round 1 (Appendix B). The altered statements were proposed to the panellists with the inclusion of their answers from the previous round and the aggregated responses of the other panellists. At the end of the second survey, the three statements which had reached consensus after Round 1 remained stable (less than 10% change in answers between the two rounds), and a fourth reached consensus following the modification of the statement (Appendix B). An additional statement was identified with the potential to reach consensus with further modifications suggested by some of the panellists via email.

3.3. Round 3

Twenty-eight out of twenty-nine panellists completed the third and final round. This survey contained four statements with strong, stable consensus which participants were asked to rank in terms of priority or importance (Figure 3). It also included one modified statement for a final assessment of whether consensus could be reached (Appendix B). The modified statement received a total of 74.1% agreement therefore not reaching strong consensus, so its consequent prioritisation question was disregarded in the results. As shown in Figure 3, panellists considered post-operative nausea and vomiting and the availability of TIVA for paediatric anaesthesia as priorities. Next came the effects of TIVA on intraoperative physiology, and the consideration of the environmental impact of TIVA was prioritised last.

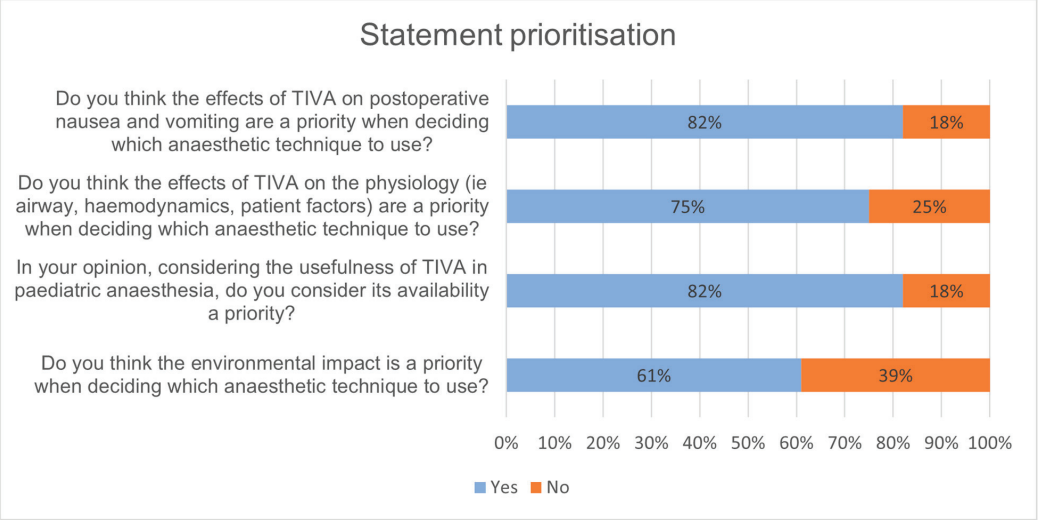

Figure 3. This graph shows the panellists' prioritisation of the statements with a strong consensus.

4. Discussion

The results from this Delphi survey show that despite scientific evidence and considerations regarding cost, familiarity and training, departmental preferences and even the benefits for the environment, the decision to use TIVA is largely attributed to what is best for the patient, both in terms of personal experience and physiological benefit.

It is interesting to note that participants did not collectively agree on the majority of statements put to them, and only three found a strong consensus from Round 1. This suggests that, at least sometimes, there may be a gap between the efficacy of an anaesthetic technique and its appropriateness, and that this appropriateness may depend on various reasons.

Most participants agreed that the reduced environmental impact of TIVA was important to them (Appendix A). There was also an immediate strong consensus on the fact that TIVA is a useful technique in paediatric anaesthesia, and that one of its main benefits lies in the reduced occurrence of nausea and vomiting postoperatively. This suggested early on that patient experience plays a role in the decision to use TIVA. However, only half the panellists considered the potential benefit of TIVA on cancer biology to be a significant factor in deciding its use, which may be a result of subspecialty variation or a lack of practical value.

Through feedback received in Round 1, it became clear that panellists considered practicality an important challenge for the use of TIVA: panellists were asked about practicalities (or impracticalities) as a whole in order to garner opinions on a range of practical consider-

ations. As a result, some panellists voiced concerns over the amount of additional work involved when using TIVA if the procedure time is short, and the relative inconvenience of having to change syringes. It was also suggested that the use of TIVA may be impacted by lack of ready availability of drugs, equipment and technology such as target controlled infusion (TCI) pumps and depth of anaesthesia monitoring equipment such as processed encephalograms (pEEG), as well as patient factors such as strong needle phobia or difficult access (e.g., small children). These factors were therefore specified in the later statement in order to assess the overall opinion on whether these factors impact TIVA use. Remarkably, when these considerations were included in the statement to reflect panellists' opinions, a strong consensus was still not reached, with the proportion of panellist agreement increasing from 34.4% to only 64.3% between rounds (Appendix B). It is worth noting at this point that when considering the practical aspect of TIVA use, despite comments suggesting that monitoring equipment availability may be a barrier to TIVA use, the anonymity of the survey renders it impossible to comment on the distribution among panellists of pEEG and TCI pump use when employing TIVA as a technique. We are, therefore, unable to establish whether a possible variation in the use of monitoring equipment among panellists may have caused interference when attempting to reach a consensus regarding TIVA practicality, or indeed whether it may be the cause of that statement not reaching consensus.

Similarly, when panellists were asked whether they believe there is strong evidence to suggest TIVA reduces the incidence of emergence agitation, initially, only 62.1% to 68.9% of panellists agreed. When feedback was added to the statement specifying that this reduction in emergence agitation may be more widely observed in paediatric anaesthesia, consensus only reached 74.1%, therefore, also not reaching a strong consensus. This suggests that the challenges and considerations proposed by panellists are observed by a few individuals, but do not necessarily reflect the experience of the majority; these differences could again be due to the variation in subspecialty expertise, geographical differences, or even as a result of working in a regional rather than a national hospital. Although the results of this survey suggest hypotheses rather identified factors, they highlight the added value of such a Delphi project, generating new research questions on variations in anaesthetic technique use. Future studies, informed by the current work, may aim to clarify the importance of local or regional aspects to be addressed when, or before, implementing TIVA.

In contrast to the abovementioned statements, which failed to reach consensus despite comments suggested by the panellists, the inclusion of feedback that patient factors, as well as the effect of TIVA on patient physiology such as haemodynamic stability and the uncoupling of airway and hypnosis, determine whether panellists use this technique, did increase the consensus between rounds from 55.1% to 75.8% (Appendix B). This is an important finding, as similarly to the consensus regarding paediatric anaesthesia and the reduction of post-operative nausea and vomiting, it is evident that patient factors constitute a substantial consideration in the decision to use TIVA regardless of subspecialty or location. While this may not be surprising as individual patient factors can be a driving factor for variation in many clinical areas, we consider it an important finding as it demonstrates objective evidence that this may specifically be the case for TIVA use as well.

There was a consistent lack of collective agreement on statements suggesting that TIVA may not be used due to financial burden, lack of training, familiarity or departmental preferences to use volatile agents. This may suggest that, regardless of subspecialty or geographical location, the main considerations for the use of TIVA are patient dependent rather than departmental or organisational. However, this may also reflect the fact that, for instance, financial inequities or local constraints lead to different limitations in practice and therefore a lack of consensus. Future surveys could identify which specific patient factors may carry more weight when deciding to use TIVA, and investigate local variations in these patient factors considering different patient demographics depending on location and anaesthetic subspecialty. Further work could also be directed at possible reasons for lack of consensus and geographical variability when considering local factors, such as financial, training and departmental aspects.

When it came to prioritising statements, it was clear that the reduction of nausea and vomiting and availability of TIVA in paediatric anaesthesia are considered to be the main priorities when deciding on its use. This was closely followed by the opinion that TIVA's effect on the patients' physiology should be prioritised, further demonstrating the patient focused approach to TIVA use. Interestingly, TIVA's positive environmental impact, which in Round 1 gained a very strong agreement, was considered as a priority by the fewest participants. This suggests once more that even when moral causes such as protecting the environment are concerned, patient experience and factors play a more significant role in deciding whether to use TIVA.

4.1. Strengths

We used the Delphi approach to gather opinions on motivations or challenges for the use of TIVA as an anaesthetic technique, and analyse responses and feedback from experts in different anaesthetic subspecialties and geographical areas. This method was useful for this study as, due to our wish to involve an international panel, remote survey completion seemed the most practical method to collect data.

The study itself provided useful insight into the motivations that drive clinicians from various anaesthetic subspecialties to use TIVA as a technique, providing clear results on what individual panellists believe is important. Specifically, it allowed us to identify that despite location, range of anaesthetic experience and subspecialty, patient factors and overall patient experience (especially in paediatric cases) are among the main considerations when choosing which technique to use for induction of anaesthesia. We also believe the results of this survey have posed interesting questions for future research into the variability of anaesthetic practice.

4.2. Limitations

Due to the study design, it is, however, impossible to determine if opinions are correlated to geographical location, anaesthetic subspecialty or even the type of hospital panellists work in. This is particularly highlighted as the majority of the panellists who took part in the project are based in Europe, creating the potential for geographical bias and misrepresenting the value and use of TIVA in other continents. Further work could focus on these variations, by increasing the number of panellists from different subspecialties to highlight any specialty-specific preferences, as well as widening the geographical representation in the panel to extrapolate whether differences in opinion can be attributed to the country a panellist practices in or the subspecialty they have particular expertise in. Furthermore, this project addressed the reasons for the use of TIVA as an anaesthetic technique. Although the survey considers this in comparison with volatile agents, it does not specifically put to the panellists the benefits or otherwise of the use of the latter. In future research, a parallel survey could determine motivations for the use of volatile anaesthesia over TIVA, to establish whether there is a reciprocal relationship between the downsides of using TIVA and the reasons for using volatile agents.

5. Conclusions

This manuscript aimed to address the variation in practice when administering anaesthetic techniques. By asking participants to state their agreement and ranking priorities relating to the use of TIVA in their respective subspecialties, it became apparent that despite scientific evidence and considerations regarding cost, familiarity and training, departmental preferences or even the benefits for the environment, the decision to use TIVA is largely attributed to what is best for the patient, both in terms of personal experience and physiological benefit. Whilst the results of this survey may not directly impact clinical practice, we believe they provide useful insight into the motivations of TIVA use and may provide a foundation for future research on anaesthetic technique employment from an individual preference basis, departmental and equipment availability perspective and wider geographical variation. They also provide helpful opinions regarding the use of

TIVA in paediatric anaesthesia, which may be looked into further to establish whether departmental changes or training curricula may be adjusted in the future to reflect this.

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Appendix A

Table A1. Panellists' Fields of Interest.

Panellists' Fields of Interest	No.
Airway Management	1
Ambulatory Anaesthesia	1
Burn Care	1
Cardiothoracic Anaesthesia	1
Cardiovascular Anaesthesia	4
Critical/Intensive Care	4
Education and Teaching	2
Emergency Anaesthesia	1
General Anaesthesia	5
Locoregional Anaesthesia	1
Malignant Hyperthermia	2
Myopathies	1
Neuro-Anaesthesia	3
Neuromuscular Blockers and Monitoring	1
Non-Operating Room Anaesthesia	3
Not specified	2
Obstetric Anaesthesia	3
Onco-Anaesthesia	1
Opioid-Free Anaesthesia	1
Orthopaedics	2
Paediatric Anaesthesia	2
Pain Management	5
Quality and Safety	1
Regional Anaesthesia	5
Total Intravenous Anaesthesia	1
Transfusions	1
Vascular Anaesthesia	1

This table shows the full range of panellists' fields of interest. Some subspecialties were mentioned more than once.

Appendix B

Table A2. Delphi Method Statements.

Statement 1.	Round 1: Whether the use of total intravenous anaesthesia may have benefits over volatile anaesthesia for reducing greenhouse gases and waste anaesthetic gases is important for me.	**82.8%**
	Round 2: Statement unmodified.	**89.6%**
Statement 2	Round 1: There is a strong body of evidence supporting the use of total intravenous anaesthesia for reducing the incidence of emergence agitation compared with volatile anaesthesia.	62.1%
	Round 2: Statement unmodified.	68.9%
	Round 3: *In paediatric anaesthesia*, there is a strong body of evidence supporting the use of total intravenous anaesthesia for reducing the incidence of emergence agitation compared with volatile anaesthesia.	74.1%
Statement 3	Round 1: The potential effect of total intravenous anaesthesia on cancer biology is an important aspect for me.	51.7%
	Round 2: Statement unmodified.	53.6%
Statement 4	Round 1: In paediatric anaesthesia, total intravenous anaesthesia is an impractical technique compared with volatile anaesthesia.	34.4%
	Round 2: In paediatric *and adult* anaesthesia, *practicality aspects (e.g., changing syringes, local resources and availability of drugs, pumps and anaesthesia monitoring, duration and type of procedure) influence the use of TIVA* compared with volatile anaesthesia.	64.3%
Statement 5	Round 1: In paediatric anaesthesia, total intravenous anaesthesia is a useful technique.	**79.3%**
	Round 2: Statement unmodified.	**82.7%**
Statement 6	Round 1: The risk of awareness during total intravenous anaesthesia compared with volatile anaesthesia is an obstacle for its use.	20.6%
	Round 2: Statement unmodified.	21.5%
Statement 7	Round 1: The financial cost of the anaesthetic technique in the context of total intravenous anaesthesia and volatile anaesthesia is important for me.	44.8%
	Round 2: Statement unmodified.	50%
Statement 8	Round 1: Departmental preferences and guidelines influence my technique choice, in the context of total intravenous anaesthesia versus volatile anaesthesia.	44.8%
	Round 2: Departmental preferences, *resistance to change, or* guidelines influence my *(or colleagues')* technique choice, in the context of total intravenous anaesthesia versus volatile anaesthesia.	53.6%
Statement 9	Round 1: Lack of familiarity and/or training with the use of total intravenous anaesthesia (compared with volatile anaesthesia) is a key reason why myself, or colleagues I know, do not use it.	41.4%
	Round 2: Statement unmodified.	46.4%

Table A2. *Cont.*

Statement 10	Round 1: The effects of total intravenous anaesthesia on the physiology (airway, haemodynamics) influence my technique choice when compared with volatile anaesthesia.	55.1%
	Round 2: *My technique choice is influenced by the effects of TIVA on the physiology such as airway, haemodynamics, or other patient related factors (not including malignant hyperthermia, which is universally considered an absolute contraindication for the use of volatile agents).*	**75.8%**
Statement 11	Round 1: The effect of total intravenous anaesthesia on postoperative nausea and vomiting risk influences my choice.	**79.3%**
	Round 2: Statement unmodified.	**86.2%**
Statement 12	Round 1: Total intravenous anaesthesia is becoming more widely used in my clinical practice or the clinical practice of my department.	62.1%
	Round 2: The use of total intravenous anaesthesia is in expansion in my clinical practice or the clinical practice of my department, *where not already widely used*.	60.7%

This table displays the 12 statements including modifications (in italics) and the percentage of agreement reached after each round (bold indicates consensus).

References

1. Nimmo, A.F.; Absalom, A.; Bagshaw, O.; Biswas, A.; Cook, T.M.; Costello, A.; Grimes, S.; Mulvey, D.; Shinde, S.; Whitehouse, T.; et al. Guidelines for the safe practice of total intravenous anaesthesia (TIVA): Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia. *Anaesthesia* **2018**, *74*, 211–224. Available online: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/doi/10.1111/anae.14428 (accessed on 14 December 2021). [CrossRef] [PubMed]
2. Sherman, J.; Le, C.; Lamers, V.; Eckelman, M. Life cycle greenhouse gas emissions of anesthetic drugs. *Anesth. Analg.* **2012**, *114*, 1086–1090. Available online: https://journals.lww.com/anesthesia-analgesia/Fulltext/2012/05000/Life_Cycle_Greenhouse_Gas_Emissions_of_Anesthetic.25.aspx (accessed on 2 November 2021). [CrossRef] [PubMed]
3. Koch, S.; Pecher, S. Neue Herausforderungen für die Anästhesie durch den Klimawandel [New challenges for anesthesia due to the climate change]. *Anaesthesist* **2020**, *69*, 453–462. Available online: https://link.springer.com/article/10.1007/s00101-020-00770-1 (accessed on 2 November 2021). [CrossRef] [PubMed]
4. Jo, J.Y.; Jung, K.W.; Kim, H.J.; Park, S.U.; Park, H.; Ku, S.; Choi, S.S. Effect of Total Intravenous Anesthesia vs Volatile Induction with Maintenance Anesthesia on Emergence Agitation after Nasal Surgery: A Randomized Clinical Trial. *AMA Otolaryngol.-Head Neck Surg.* **2019**, *145*, 117–123. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6440219/ (accessed on 2 November 2021). [CrossRef] [PubMed]
5. Talih, G.; Yüksek, A.; Şahin, E. Evaluation of emergence agitation after general anaesthesia in rhinoplasty patients: Inhalation anaesthesia versus total intravenous anaesthesia. *Am. J. Otolaryngol.* **2020**, *41*, 102387. Available online: https://www.sciencedirect.com/science/article/pii/S0196070919311378 (accessed on 2 November 2021). [CrossRef] [PubMed]
6. Wigmore, T.J.; Mohammed, K.; Jhanji, S. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgery: A retrospective analysis. *Anesthesiology* **2016**, *124*, 69–79. Available online: https://pubs.asahq.org/anesthesiology/article/124/1/69/14249/Long-term-Survival-for-Patients-Undergoing (accessed on 2 November 2021). [CrossRef] [PubMed]
7. Yap, A.; Lopez-Olivo, M.A.; Dubowitz, J.; Hiller, J.; Riedel, B.; Global Onco-Anesthesia Research Collaboration Group. Anesthetic technique and cancer outcomes: A meta-analysis of total intravenous versus volatile anesthesia. *Can. J. Anaesth.* **2019**, *66*, 546–561. Available online: https://pubmed.ncbi.nlm.nih.gov/30834506/ (accessed on 2 November 2021). [CrossRef] [PubMed]
8. Chang, C.Y.; Wu, M.Y.; Chien, Y.J.; Su, I.M.; Wang, S.C.; Kao, M.C. Anesthesia and Long-term Oncological Outcomes: A Systematic Review and Meta-analysis. *Anesth Analg.* **2021**, *132*, 623–634. Available online: https://oce.ovid.com/article/00000539-202103000-00006/HTML (accessed on 14 December 2021). [CrossRef] [PubMed]
9. Grundmann, U.; Uth, M.; Eichner, A.; Wilhelm, W.; Larsen, R. Total intravenous anaesthesia with propofol and remifentanil in paediatric patients: A comparison with a desflurane-nitrous oxide inhalation anaesthesia. *Acta Anaesthesiol. Scand.* **1998**, *42*, 845–850. Available online: https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1399-6576.1998.tb05332.x?saml_referrer (accessed on 2 November 2021). [CrossRef] [PubMed]
10. Anderson, B.J.; Bagshaw, O. Practicalities of Total Intravenous Anesthesia and Target-controlled Infusion in Children. *Anesthesiology* **2019**, *131*, 164–185. Available online: https://pubs.asahq.org/anesthesiology/article/131/1/164/18098/Practicalities-of-Total-Intravenous-Anesthesia-and (accessed on 2 November 2021). [CrossRef] [PubMed]

11. Hill, M.; Peat, W.; Courtman, S. A national survey of propofol infusion use by paediatric anaesthetists in Great Britain and Ireland. *Pediatr. Anesth.* **2008**, *18*, 488–493. Available online: https://onlinelibrary.wiley.com/doi/10.1111/j.1460-9592.2008.02459.x (accessed on 14 December 2021). [CrossRef] [PubMed]
12. Lauder, G.R.; Thomas, M.; von Ungern-Sternberg, B.S.; Engelhardt, T. Volatiles or TIVA: Which is the standard of care for pediatric airway procedures? A pro-con discussion. *Pediatr. Anesth.* **2020**, *30*, 209–220. Available online: https://onlinelibrary.wiley.com/doi/10.1111/pan.13809 (accessed on 16 December 2021). [CrossRef] [PubMed]
13. Lauder, G.R. Total intravenous anesthesia will supercede inhalational anesthesia in pediatric anesthetic practice. *Pediatric Anesth.* **2015**, *25*, 52–64. Available online: https://onlinelibrary.wiley.com/doi/10.1111/pan.12553 (accessed on 2 November 2021). [CrossRef] [PubMed]
14. Smith, I. Total Intravenous Anaesthesia. *CNS Drugs* **2003**, *17*, 609–619. Available online: https://link.springer.com/article/10.2165/00023210-200317090-00001 (accessed on 2 November 2021). [CrossRef] [PubMed]
15. Jünger, S.; Payne, S.A.; Brine, J.; Radbruch, L.; Brearley, S.G. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat. Med.* **2017**, *31*, 684–706. Available online: https://journals.sagepub.com/doi/10.1177/0269216317690685?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed (accessed on 23 November 2021). [CrossRef] [PubMed]
16. Forget, P.; Patullo, C.; Hill, D.; Ambekar, A.; Baldacchino, A.; Cata, J.; Chetty, S.; Cox, F.J.; de Boer, H.D.; Dinwoodie, K.; et al. System-level policies on appropriate opioid use, a multi-stakeholder consensus. *BMC Health Serv. Res.* **2022**, *22*, 329. [CrossRef] [PubMed]
17. Harris, P.A.; Taylor, R.; Thielke, R.; Payne, J.; Gonzalez, N.; Conde, J.G. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* **2009**, *42*, 377–381. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2700030/ (accessed on 14 December 2021). [CrossRef] [PubMed]
18. Harris, P.A.; Taylor, R.; Minor, B.L.; Elliott, V.; Fernandez, M.; O'Neal, L.; McLeod, L.; Delacqua, G.; Delacqua, F.; Kirby, J.; et al. REDCap Consortium, The REDCap consortium: Building an international community of software partners. *J. Biomed. Inform.* **2019**, *95*, 103208. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254481/ (accessed on 16 December 2021). [CrossRef] [PubMed]
19. REDCap. Citations. 2021. Available online: https://projectredcap.org/resources/citations/ (accessed on 16 December 2021).

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Accuracy of Catheter Positioning during Left Subclavian Venous Access: A Randomized Comparison between Radiological and Topographical Landmarks

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Abstract: Left subclavian venous access increases the risk of vascular damage and thrombosis based on the catheter course and location of the catheter tip. We investigated the accuracy of tip positioning with conventional landmarks using transesophageal echocardiography. The carina as a radiological landmark and the right third intercostal space as a topographical landmark were selected for tip positioning within the target zone, defined as 2 cm above and 1 cm below the right atrial junction. A total of 120 participants were randomized into two groups. The catheter insertion depth was determined as 1.5 cm more than the distance between the venous insertion point and the carina via the right first intercostal space in the radiological group, and between the venous insertion point and the right third intercostal space via the right first intercostal space in the topographical group. The determined insertion depth and actual distance to the right atrial junction of the radiological and topographical groups were 19.5 cm and 20.5 cm, and 19.8 cm and 20.4 cm, respectively. Acceptable positioning was more frequent in the topographical group (96.4% vs. 85.7%; $p = 0.047$). The catheter tip is more accurately positioned in the distal superior vena cava using topographical landmarks than radiological landmarks.

Keywords: central venous catheters; echocardiography; left subclavian vein; superior vena cava; ultrasound

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1. Introduction

The safety and function of central venous catheter positioning based on site selection remains debatable [1,2]. It is recommended that the catheter tip should be placed in the superior vena cava (SVC) above the pericardial sac to prevent serious complications such as cardiac tamponade [3].

During left subclavian venous access, the catheter tip may be positioned in the middle portion of the innominate vein to ensure a parallel course and prevent SVC abutment. However, in this proximal position, it is prone to thrombosis due to the relatively small venous diameter, malfunction of the catheter owing to extravasation of the proximal access site, and infection in the case of repositioning [4,5]. In the middle position, including the upper and middle SVC, the catheter may result in vascular irritation due to abutment with the SVC at a steep angle [6,7]. In contrast, when positioned in the distal SVC, close to the right atrial junction, it reduces the risk of vascular damage and thrombotic complications due to the parallel pathway of the catheter tip and the large conduit of the vein [8]. Therefore, the catheter tip in this specific distal position is better suited for left subclavian venous access [9].

The conventional simple formula based on the patient's height is not accurate for catheter tip positioning during ultrasound-guided cannulation. For right-sided venous access, the catheter tip at 1.5 cm near the carina on chest radiography would be positioned in the distal SVC close to the right atrial junction [8]. However, there is no definite landmark for catheter tip positioning during left subclavian venous access. Therefore, we planned catheter tip positioning at the distal SVC close to the right atrial junction using anatomical landmarks. The SVC is identified based on the overlying structures on coronal and axial computed tomography images. It primarily originates behind the right first intercostal space and terminates in the right atrium in the third or fourth intercostal space [10,11]. The sternal angle formed by the manubriosternal joint is easily palpable over the skin. The second costal cartilages articulate on either side of the sternal angle [12].

This study investigated the accuracy of catheter tip positioning using landmark-based methods during left subclavian venous cannulation. In this study, we determined the carina as a radiological landmark and the right third intercostal space as a topographical landmark for left subclavian venous access. The accuracy of catheter tip positioning between the two landmark-based methods was compared using transesophageal echocardiography.

2. Materials and Methods

2.1. Study Design, Ethics Statement and Study Population

This prospective randomized controlled study investigated the accuracy of catheter tip positioning by landmark-based methods during left subclavian venous cannulation. Ethical approval for this study was provided by the Institutional Review Board of Kangdong Sacred Heart Hospital in Seoul, Republic of Korea (President: Soo Young Kim, protocol number: KANGDONG 2019-03-002-001) on 26 April 2019. All the experiments were carried out in accordance with the relevant guidelines and regulations of the Declaration of Helsinki involving human subjects. All the patients signed an informed consent form prior to study enrolment. After obtaining written informed consent from each patient, we recruited 120 patients (20–80 years of age) with the American Society of Anesthesiologists physical status class 1 to 3, who were eligible for left subclavian venous cannulation before abdominal and cardiovascular surgeries between April 2019 and November 2021. The exclusion criteria were a previous history of thoracic surgery, mediastinal mass, esophageal varices, and refusal to participate. This study was registered with the Clinical Research Information Service of Korea (https://cris.nih.go.kr (accessed on 20 July 2021); identifier: KCT0006388; principal investigator: Il Seok Kim).

2.2. Randomization and Allocation

Participants were randomly allocated in a 1:1 ratio to either the radiological landmark group (R group) or the topographical landmark group (T group) using computer-generated randomization (www.graphpad.com/quickcalcs (accessed on 16 May 2022)). The allocation of participants was concealed in a sequentially numbered opaque envelope, and the assignment envelope was opened before cannulation.

The carina was selected as the radiological landmark using a preoperative standard erect P-A chest radiograph in suspended full inspiration in the R group. To estimate the distance between the right first intercostal space and the carina, the vertical length between the lower border of the right first costal cartilage, close to the sternum, and a horizontal line connecting the carina were measured using the picture archiving and communication system (PACS, Infinite Healthcare Co., Seoul, Korea) and an internal electronic caliper (Figure 1a). The catheter insertion depth was calculated by adding the distance between the venous insertion point and the right first intercostal space measured over the skin, the distance between the right first intercostal space and the carina on chest radiography, and an additional 1.5 cm for safety against insertion of the catheter tip in the right atrium [8].

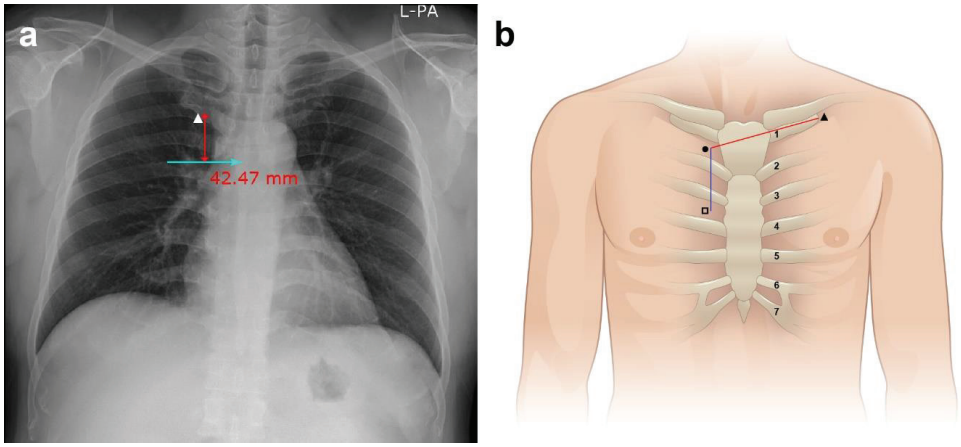

Figure 1. Radiological and topographical landmarks. (**a**) Chest radiograph for measuring the distance between the first intercostal space and the carina. The distance from the right first intercostal space to the carina is measured as the vertical length between the lower border of the right first costal cartilage (solid triangle) close to the sternum and a horizontal line connecting it to the carina using an electronic caliper in the radiological group. (**b**) Schematic illustration for estimating the distance from the venous insertion point through the right first intercostal space to the right third intercostal space in the topographical group. The distance is determined by adding the distance between the venous insertion point (solid triangle) and the midpoint of the right first intercostal space (solid circle) just lateral to the sternal angle, and the distance between the midpoints of the first and third intercostal spaces (open square) just lateral to the sternum as measured on the skin surface.

The right third intercostal space was selected as the topographical landmark over the chest skin surface in the T group. By measuring the distance between the midpoints of the first and third intercostal spaces over the skin, the catheter insertion depth was calculated by adding the distance between the venous insertion point and the right first intercostal space and the distance between the first and third intercostal spaces (Figure 1b).

2.3. Procedure and Data Collection

Following general anesthesia induction, an echocardiographic probe (X7-2t transesophageal transducer; Phillips, Andover, MA, USA) was inserted into the esophagus. During cannulation, the patient was maintained in the Trendelenburg position with arms abducted. After sterile preparation and draping, the puncture site in the infraclavicular area was pre-scanned using two-dimensional ultrasonography (Affiniti 70; Phillips, Andover, MA, USA) and a high-frequency linear transducer. After palpation of the sternal angle and identifying the right first intercostal space over the skin, the distance between the venous insertion point and the midpoint of the right first intercostal space just lateral to the sternal angle, and the distance between the first and third intercostal spaces just lateral to the sternum, were measured using a sterile graduated ruler. Central venous cannulation was performed by an ultrasound-guided in-plane approach in the longitudinal view. A 20 cm long, two-lumen catheter (Arrow G^{+}ard Blue Central Venous Catheter; Arrow International Inc., Reading, PA, USA) was inserted using the Seldinger technique and secured at the determined depth according to the protocol for each group. On the bicaval view of echocardiography (Figure 2), accurate positioning of the catheter tip was assessed relative to the right atrial junction, which was assumed to be at the level of the upper border of the crista terminalis [13]. We also assessed the incidence of the angle of the tip > 40° in relation to the SVC, abutment of the tip with the SVC, and flow streams hitting the vascular wall using injections of agitated saline at the radiologically or topographically predetermined insertion depth.

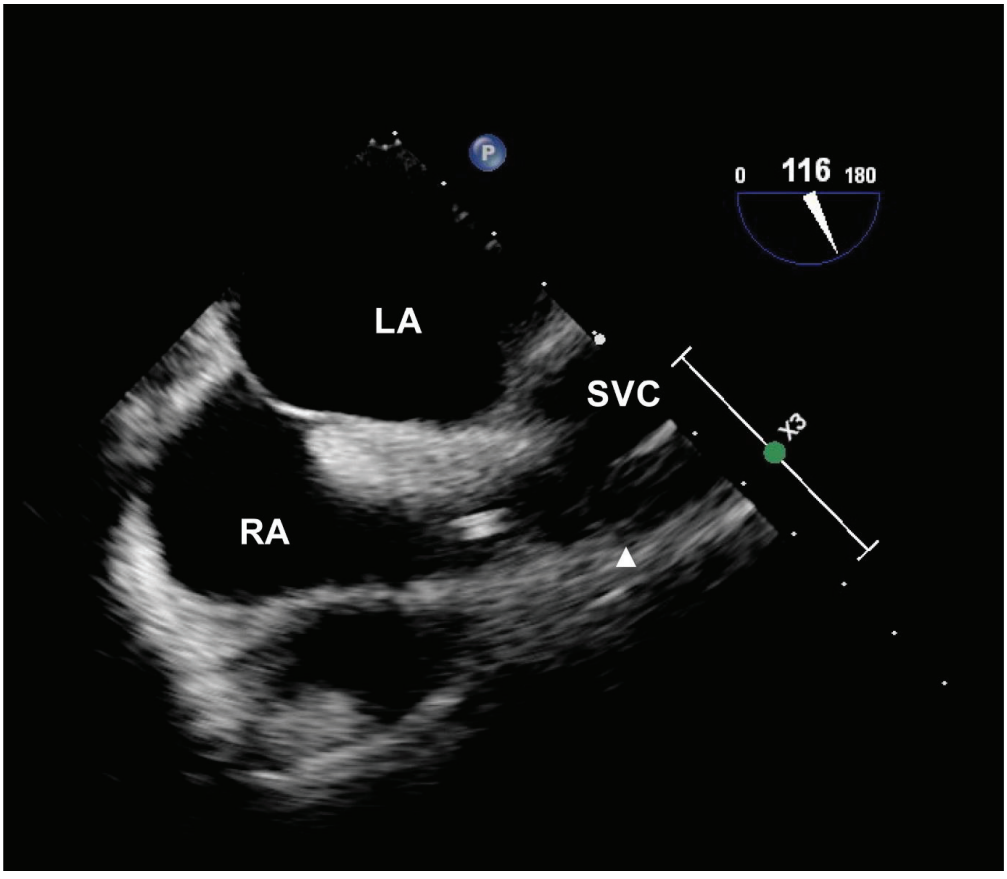

Figure 2. Echocardiographic image of catheter tip positioning. The catheter tip is identified as two parallel echogenic lines from the bicaval view. The solid triangle indicates the level of the upper border of the crista terminalis, defined as the echocardiographic junction of the SVC and the RA. Abbreviations: LA, left atrium; RA, right atrium; SVC, superior vena cava.

The actual distance between the venous insertion point and the right atrial junction was assessed using advancement or withdrawal of the catheter from the bicaval view. Following the repositioning of the catheter tip at the right atrial junction or the maximum depth of the 20 cm catheter, the catheter was fixed with a skin suture.

Postoperatively, the catheter position was rechecked using a recumbent chest radiograph upon inspiration at the bedside. Any complication related to cannulation was recorded until the removal of the catheter.

The primary outcome was the incidence of acceptable positioning of the catheter tip within the target zone, which was designated as 2 cm above and 1 cm below the right atrial junction, since this area has a large conduit of vessels and the catheter tip floats freely without impinging on the vascular wall. The secondary outcomes were the difference between the determined insertion depth and the actual distance to the right atrial junction, the incidence of the angle of the tip > 40° in relation to the SVC, tip abutment with the SVC, flow streams hitting the vascular wall, and any cannulation-related complications.

2.4. Statistical Analysis

2.4.1. Sample Size Calculation

Based on the landmarks and calculated values for right-sided cannulation from a previous study, the sample size was calculated from the data based on our preliminary observation, in which the patients were divided into two groups with the carina and the right third intercostal space as landmarks for positioning the catheter tip within the target zone [8]. Consequently, 30 patients were included in each group, and the incidence of acceptable positioning was 83.3% (25/30) and 96.6% (29/30) in the carina and third intercostal space groups, respectively. Based on the incidence rate, an alternative hypothesis and test type were chosen as one-sided (H1: P1 < P2) and the pooled Z test, respectively. We calculated that 56 patients were required in each group to detect a difference of this magnitude with an α error of 0.05 and a desired power of 0.80, using PASS 12 (NCSS, LLC, Kaysville, UT, USA). After accounting for a dropout rate of 6%, we recruited 120 patients for this study.

2.4.2. Data Analysis

Statistical analysis was performed using the SPSS version 23.0 (IBM Inc., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normal distribution of variables. Continuous variables are reported as medians (interquartile range (IQR)) and compared using the Mann–Whitney U test or the independent Student's *t*-test, as considered appropriate. Categorical variables are presented as numbers (proportion) and compared using Fisher's exact test or Pearson's chi-square test, as considered appropriate. A probability value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Participant Enrollment

Of the 120 patients screened for the study, six patients were excluded owing to the unavailability of echocardiography at cannulation (n = 2), conversion to other access sites (n = 3), and preoperative detection of an abnormal thoracovascular condition of persistent left SVC (n = 1). Accordingly, 114 participants were randomly allocated to one of the two intervention groups, with 57 participants in each group (Figure 3). All the participants underwent successful cannulation and catheter positioning, except two patients in whom the catheter tip could not be identified from the bicaval view. Misplacement of the catheter into the left internal jugular vein occurred in one patient in the R group, and an aberrant positioning of the catheter due to persistent left SVC occurred in one patient in the T group. These patients were not included in the statistical analysis. Finally, 56 patients per group were analyzed.

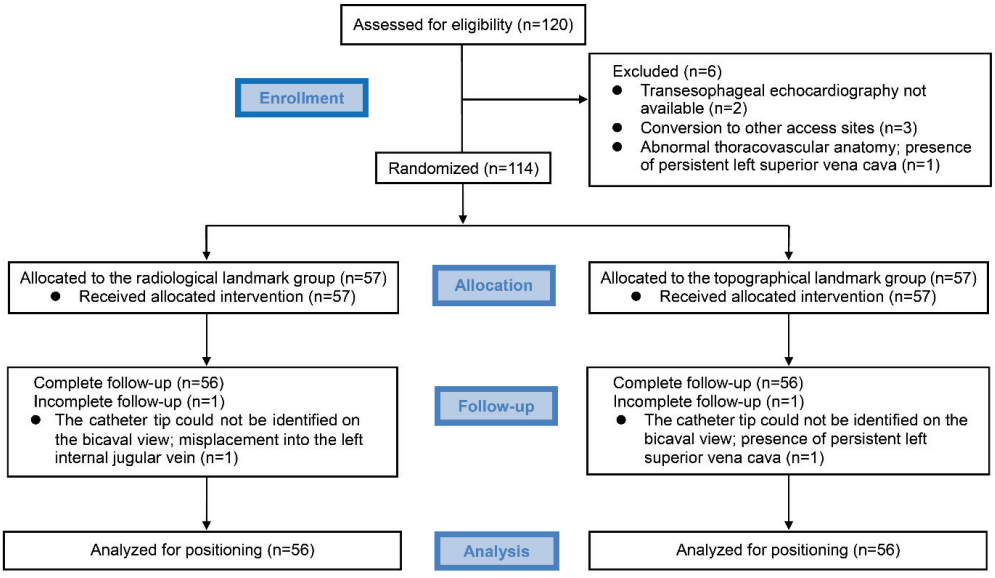

Figure 3. Consolidated Standards of Reporting Trials (CONSORT) flow diagram for participants included in the study.

3.2. Characteristics of the Participants and Measurements

The baseline characteristics of the study participants are presented in Table 1. Sex, age, height, weight, and body mass index were comparable between the groups.

Table 1. Baseline characteristics of study participants.

Variable	Radiological Group (n = 56)	Topographical Group (n = 56)	p
Male sex	36 (64.3)	39 (69.6)	0.547
Age (years)	65.0 [58.0–71.8]	67.0 [59.3–75.0]	0.230
Height (cm)	163.0 [153.3–166.0]	164.0 [158.0–169.0]	0.079
Weight (kg)	64.0 [55.0–71.8]	63.0 [56.0–69.8]	0.818
BMI (kg/m^2)	24.3 [21.9–26.5]	23.6 [21.7–26.2]	0.317

Values are reported as the median [interquartile range], number, or number (% of patients). Abbreviations: BMI, body mass index.

The measurements of catheter positioning are summarized in Table 2. Between the R and T groups, the determined insertion depth (19.5 [18.6–20.4] cm vs. 19.8 [18.8–20.2] cm, respectively; p = 0.645), the actual distance to the right atrial junction (20.5 [19.6–21.0] cm vs. 20.4 [19.5–21.0] cm, respectively; p = 0.802), and the difference between the measurements (0.7 [0.1–1.4] cm vs. 0.5 [0–0.8] cm, respectively; p = 0.171) were comparable. The proportion of acceptable positioning of the catheter tip within the target zone was higher in the T group than in the R group (96.4% vs. 85.7%, respectively, p = 0.047) (Figure 4). The proportion of tip positioning above the target zone was higher in the R group than in the T group (14.3% vs. 3.6%, respectively, p = 0.047). Tip position below the target zone was not observed in either group. The proportion of angle of the tip > 40° to the SVC, tip abutment with the SVC, and flow streams hitting the vascular wall were comparable between the groups. Until the removal of the catheter, no catheter-related complications were observed in either group.

Table 2. Measurement and assessment in catheter positioning.

Variable	Radiological Group (n = 56)	Topographical Group (n = 56)	p
Catheter insertion depth (cm)	19.5 [18.6–20.4]	19.8 [18.8–20.2]	0.645
Actual distance to junction (cm)	20.5 [19.6–21.0]	20.4 [19.5–21.0]	0.802
Difference between measurements (cm)	0.7 [0.1–1.4]	0.5 [0–0.8]	0.171
Acceptable positioning	48 (85.7)	54 (96.4)	0.047 *
Position above target zone	8 (14.3)	2 (3.6)	0.047 *
Position below target zone	0	0	
Angle of tip (>40°) to the SVC	0	0	
Abutment with the SVC	1 (1.8)	0	0.315
Flow streams hitting vascular wall	1 (1.8)	1 (1.8)	1.000

Values are reported as the median [interquartile range], number, or number (% of patients). * Statistically significant differences between groups. Abbreviations: SVC, superior vena cava.

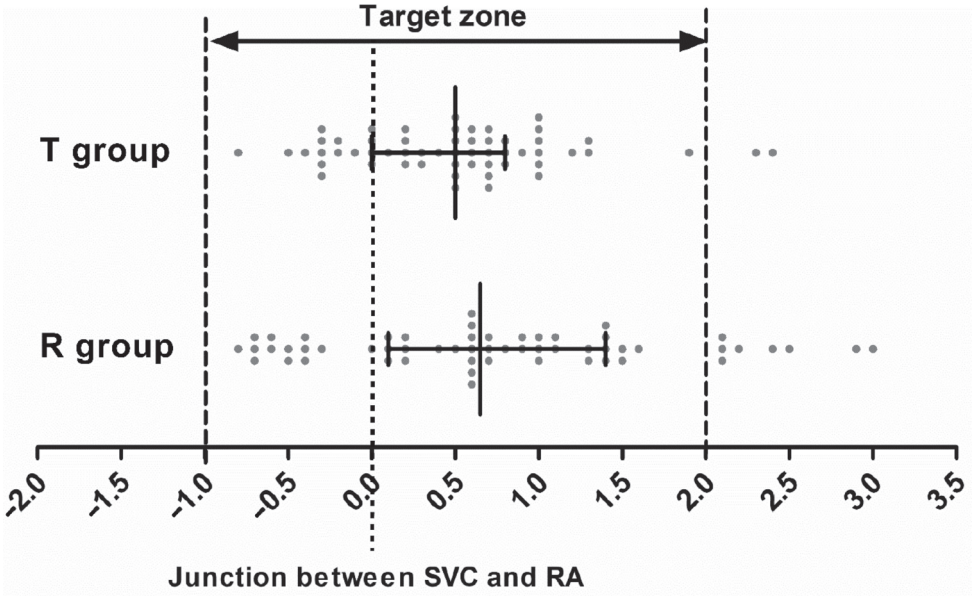

Figure 4. Scatter graph of catheter tip position within the target zone in both groups. Each circle represents an individual catheter tip position. Zero point refers to the junction between the SVC and the RA. Positive values indicate catheter tip position above the junction, and negative values indicate catheter tip position below the junction. Dashed lines indicate the upper and lower borders of the target zone. The solid vertical line indicates the median and the error bars indicate the interquartile range. Abbreviations: RA, right atrium; SVC, superior vena cava.

4. Discussion

The principal finding of our investigation was that during left subclavian venous access, we could place the catheter tip more accurately in the distal SVC close to the right atrial junction using the topographical method.

The placement of the central venous catheter is always associated with risks, and the optimal positioning of the catheter tip is an ongoing issue, especially in left-sided venous access. Vascular injuries are possible in any position in the SVC and cardiac chamber. Most devastating complications, such as cardiac tamponade, hemothorax, and hydrothorax, were reported in case reports and were attributed to mechanical and chemical irritation to the vascular wall, which were related to parenteral delivery of hyperosmolar solutions and an acute angle from left-sided access. The most important points to be considered for preventing these events are the alignment of the catheter tip to the vessel wall, free

movement of the tip, and non-impingement to the vessel wall. The distal SVC close to the right atrial junction has the advantage of ensuring a parallel pathway for the catheter tip and a large conduit during cardiac pulsation.

Several methods and landmarks are used for catheter positioning in right-sided vascular access. However, there is no definite landmark in left-sided access for catheter tip positioning in the distal SVC close to the right atrial junction.

In our study, although both the methods demonstrated comparable outcomes, the radiological method had a higher incidence of the catheter tip being located 2 cm above the right atrial junction. The catheter tip was more accurately positioned in the distal SVC close to the right atrial junction when using topographical landmarks compared to radiological landmarks.

The carina on chest radiography has been used as the landmark for catheter positioning, and when the catheter tip is positioned above the carina, it is generally accepted that the catheter tip could be located above the pericardial reflection during right-sided central venous access [14,15]. However, in left-sided access, if the catheter tip is located above the carina, it results in an acute angle with the vascular wall and increases the risk of vascular damage [7]. In catheter positioning using electrocardiogram guidance with P-wave normalization and the manubriosternal junction as a surface landmark assumed at the level of the carina, positioning the catheter tip above the carina results in a high incidence of the catheter tip being positioned at an acute angle with the vascular wall in left-sided access [16,17]. Therefore, the catheter tip would be positioned below the carina for left-sided vascular access; however, the distance for preventing intracardiac placement has not been specified [7]. The distance from the carina to the right atrial junction varies from 2.0 to 4.0 cm [18,19]. A previous study reported that the mean (standard deviation) distance from the carina to the right atrial junction was 2.6 (1.1) cm; therefore, we selected 1.5 cm as the minimum distance while positioning the catheter tip below the carina to prevent its placement in the right atrium in the R group [8]. Although the determined insertion depth, the actual distance to the right atrial junction, and the difference between the measurements were comparable between the groups, more catheter tips were positioned above the target zone (14%, 8/56), and a significant proportion of catheters were positioned below the atrial junction (21%, 12/56) in the R group. These results may be due to imprecise measurement of the right first intercostal space combined with a parallax effect on imaging of the right first rib from the central radiographic beam and the patient's position and height, individual variability in the distance between the right first intercostal space and the carina, and underestimation of the distance from the carina to the right atrial junction as only 1.5 cm.

Based on identifiable cutaneous landmarks overlying internal structures and their respective courses, several topographical landmarks have been proposed for catheter positioning [15,20]. Using the clavicular notch on the sternoclavicular joint and the sternal angle formed by the manubriosternal joint, the catheter tip can be reliably placed in the SVC above the pericardial reflection for right-sided venous access [17]. For placing the catheter tip near the radiographic junction of the SVC and the right atrium, the right third intercostal space is a reliable surface landmark in pediatric patients [21]. One study reported that by using the lower border of the clavicular notch as the reference point for a guidewire through the brachiocephalic vein and SVC, the lower border of the right third costosternal junction was more reliable at positioning the catheter tip within 1 cm of the echocardiographic junction of the SVC and the right atrium [22]. The SVC is a confluence of the right brachiocephalic vein and left brachiocephalic vein and commonly originates at the level of the right first intercostal space on computed tomography; therefore, the right first intercostal space is a more accurate reference point than the clavicular notch based on the course of the catheter inserted in the left-sided venous access [10,11]. Therefore, for positioning the catheter tip close to the echocardiographic junction of the right atrium, we selected the right first and third intercostal spaces as landmarks to appraise the origin, course, and termination of the SVC. The results demonstrated a high proportion of catheter

tips positioned within the target zone. We determined the target zone as 2 cm above and 1 cm below the right atrial junction, because this area is wide and parallel to the vascular conduit of the SVC; additionally, the catheter tip is likely to float freely without impinging on the atrial wall during cardiac contractions in echocardiographic imaging.

In the T group, the catheter tip was positioned 2 cm above the target zone in two participants. Of these, one outlier was a 31-year-old man with a height of 179 cm, and the other was a 73-year-old man with a height of 177 cm. The SVC length reportedly ranges widely from 4.4 to 10 cm on magnetic resonance imaging [18]. Additionally, in a computed tomography-based study, the termination of the SVC was more variable between the sexes and age groups in relation to the overlying surface structures than the origin of the SVC; the termination of the SVC into the right atrium was identified from the right third intercostal space to the fifth costal cartilage, and was higher in women and younger adults [23]. Therefore, the considerable variability in the SVC length and right atrial junction with the corresponding surface landmarks could have resulted in these outliers.

In the bicaval view of echocardiography, the catheter tip location could not be confirmed in two patients, who were subsequently excluded from the statistical analysis owing to incomplete follow-up. These events occurred owing to the misplacement into the internal jugular vein and the presence of a persistent left SVC. Although misplacement is less common in left-sided subclavian venous access owing to an obtuse angle of the innominate vein with the SVC, it did occur in one participant in the R group [24]. It may be associated with a tortuous path and a more distal approach from the axillary vein. Persistent left SVC is an abnormal thoracic venous condition that occurs in 0.3% of the general population [25]. This vein empties into the right atrium through the coronary sinus in up to 90% of people and is generally asymptomatic; however, it occasionally drains into the left atrium, which increases the risk of systemic embolism [26]. In our case, aberrant positioning of the catheter was discovered accidentally after cannulation. During cannulation, bubble streams in the right atrium were identified following injection of agitated saline, but the catheter tip was not detected from the bicaval view. Fortunately, this case remained uneventful after cannulation; however, awareness of the clinical implications and thoughtful examination of coronary sinus dilation using echocardiography can help avoid potential complications. These patients underwent transesophageal ultrasound for the measurement of catheter tip positioning; however, no clear benefit was observed. A confirmatory chest radiograph is still needed regardless of the calculation method used for catheter tip positioning.

There were certain limitations to our study. First, we performed cannulation solely of the left subclavian vein. Left internal jugular venous access carries a risk of vascular irritation since it exhibits two curvatures up to the right atrial junction, and achieving acceptable positioning with commercial catheters of 20 cm is challenging; therefore, we did not include the left internal jugular vein in this study. Second, we did not consider the possibility of catheter tip migration based on patients' posture and arm movements. The participants in this study required central venous cannulation as a part of perioperative care and not permanent implantation for long-term usage. Third, we did not consider the difference in patient position and breathing pattern, wherein for the calculation using a preoperative standard P-A chest radiograph, the patient was in an upright position in full inspiration, while for the measurement using transesophageal ultrasound, the patient was in a supine position and mechanically ventilated.

In conclusion, we demonstrated that the catheter tip could be more accurately positioned in the distal SVC close to the right atrial junction using the topographical method. Therefore, we recommend using the right first and third intercostal spaces as landmarks during cannulation of the left subclavian vein for positioning of the catheter tip close to the right atrial junction. If identifying the surface landmarks is challenging, radiological landmarks, such as the carina, can be alternatively used for positioning the catheter.

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Institutional Review Board Statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Kangdong Sacred Heart Hospital (IRB no. KANGDONG 2019-03-002-001, 26 April 2019).

Informed Consent Statement: A written informed consent was obtained from all participants involved in the study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon a reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Fletcher, S.J.; Bodenham, A.R. Safe placement of central venous catheters: Where should the tip of the catheter lie? *Br. J. Anaesth.* **2000**, *85*, 188–191. [CrossRef]
2. Vesely, T.M. Central venous catheter tip position: A continuing controversy. *J. Vasc. Interv. Radiol.* **2003**, *14*, 527–534. [CrossRef] [PubMed]
3. Shamir, M.Y.; Bruce, L.J. Central venous catheter-induced cardiac tamponade: A preventable complication. *Anesth. Analg.* **2011**, *112*, 1280–1282. [CrossRef] [PubMed]
4. Cadman, A.; Lawrance, J.A.; Fitzsimmons, L.; Spencer-Shaw, A.; Swindell, R. To clot or not to clot? That is the question in central venous catheters. *Clin. Radiol.* **2004**, *59*, 349–355. [CrossRef]
5. Ballard, D.H.; Samra, N.S.; Gifford, K.M.; Roller, R.; Wolfe, B.M.; Owings, J.T. Distance of the internal central venous catheter tip from the right atrium is positively correlated with central venous thrombosis. *Emerg. Radiol.* **2016**, *23*, 269–273. [CrossRef]
6. Gravenstein, N.; Blackshear, R.H. In vitro evaluation of relative perforating potential of central venous catheters: Comparison of materials, selected models, number of lumens, and angles of incidence to simulated membrane. *J. Clin. Monit.* **1991**, *7*, 1–6. [CrossRef]
7. Stonelake, P.A.; Bodenham, A.R. The carina as a radiological landmark for central venous catheter tip position. *Br. J. Anaesth.* **2006**, *96*, 335–340. [CrossRef]
8. Ahn, J.H.; Kim, I.S.; Yang, J.H.; Lee, I.G.; Seo, D.H.; Kim, S.P. Transoesophageal echocardiographic evaluation of central venous catheter positioning using Peres' formula or a radiological landmark-based approach: A prospective randomized single-centre study. *Br. J. Anaesth.* **2017**, *118*, 215–222. [CrossRef]
9. Pittiruti, M.; Lamperti, M. Late cardiac tamponade in adults secondary to tip position in the right atrium: An urban legend? A systematic review of the literature. *J. Cardiothorac. Vasc. Anesth.* **2015**, *29*, 491–495. [CrossRef]
10. Shen, X.H.; Su, B.Y.; Liu, J.J.; Zhang, G.M.; Xue, H.D.; Jin, Z.Y.; Mirjalili, S.A.; Ma, C. A reappraisal of adult thoracic and abdominal surface anatomy via CT scan in Chinese population. *Clin. Anat.* **2016**, *29*, 165–174. [CrossRef]
11. Pak, N.; Patel, S.G.; Hashemi Taheri, A.P.; Hashemi, F.; Eftekhari Vaghefi, R.; Naybandi Atashi, S.; Mirjalili, S.A. A reappraisal of adult thoracic and abdominal surface anatomy in Iranians in vivo using computed tomography. *Clin. Anat.* **2016**, *29*, 191–196. [CrossRef] [PubMed]
12. Carrier, G.; Fréchette, E.; Ugalde, P.; Deslauriers, J. Correlative anatomy for the sternum and ribs, costovertebral angle, chest wall muscles and intercostal spaces, thoracic outlet. *Thorac. Surg. Clin.* **2007**, *17*, 521–528. [CrossRef]
13. Andropoulos, D.B.; Stayer, S.A.; Bent, S.T.; Campos, C.J.; Bezold, L.I.; Alvarez, M.; Fraser, C.D. A controlled study of transesophageal echocardiography to guide central venous catheter placement in congenital heart surgery patients. *Anesth. Analg.* **1999**, *89*, 65–70. [CrossRef] [PubMed]
14. Schuster, M.; Nave, H.; Piepenbrock, S.; Pabst, R.; Panning, B. The carina as a landmark in central venous catheter placement. *Br. J. Anaesth.* **2000**, *85*, 192–194. [CrossRef] [PubMed]
15. Ryu, H.G.; Bahk, J.H.; Kim, J.T.; Lee, J.H. Bedside prediction of the central venous catheter insertion depth. *Br. J. Anaesth.* **2007**, *98*, 225–227. [CrossRef]
16. Schummer, W.; Herrmann, S.; Schummer, C.; Funke, F.; Steenbeck, J.; Fuchs, J.; Uhlig, T.; Reinhart, K. Intra-atrial ECG is not a reliable method for positioning left internal jugular vein catheters. *Br. J. Anaesth.* **2003**, *91*, 481–486. [CrossRef]

17. Kim, M.C.; Kim, K.S.; Choi, Y.K.; Kim, D.S.; Kwon, M.I.; Sung, J.K.; Moon, J.Y.; Kang, J.M. An estimation of right- and left-sided central venous catheter insertion depth using measurement of surface landmarks along the course of central veins. *Anesth. Analg.* **2011**, *112*, 1371–1374. [CrossRef]
18. Aslamy, Z.; Dewald, C.L.; Heffner, J.E. MRI of central venous anatomy: Implications for central venous catheter insertion. *Chest* **1998**, *114*, 820–826. [CrossRef]
19. Mahlon, M.A.; Yoon, H.C. CT angiography of the superior vena cava: Normative values and implications for central venous catheter position. *J. Vasc. Interv. Radiol.* **2007**, *18*, 1106–1110. [CrossRef]
20. Ezri, T.; Weisenberg, M.; Sessler, D.I.; Berkenstadt, H.; Elias, S.; Szmuk, P.; Serour, F.; Evron, S. Correct depth of insertion of right internal jugular central venous catheters based on external landmarks: Avoiding the right atrium. *J. Cardiothorac. Vasc. Anesth.* **2007**, *21*, 497–501. [CrossRef]
21. Kim, K.O.; Jo, J.O.; Kim, H.S.; Kim, C.S. Positioning internal jugular venous catheters using the right third intercostal space in children. *Acta Anaesthesiol. Scand.* **2003**, *47*, 1284–1286. [CrossRef] [PubMed]
22. Hsu, J.H.; Wang, S.S.; Lu, D.V.; Cheng, K.I.; Wang, C.K.; Wu, J.R. Optimal skin surface landmark for the SVC-RA junction in cancer patients requiring the implantation of permanent central venous catheters. *Anaesthesia* **2007**, *62*, 818–823. [CrossRef] [PubMed]
23. Mirjalili, S.A.; Hale, S.J.; Buckenham, T.; Wilson, B.; Stringer, M.D. A reappraisal of adult thoracic surface anatomy. *Clin. Anat.* **2012**, *25*, 827–834. [CrossRef] [PubMed]
24. Tarbiat, M.; Manafi, B.; Davoudi, M.; Totonchi, Z. Comparison of the complications between left side and right side subclavian vein catheter placement in patients undergoing coronary artery bypass graft surgery. *J. Cardiovasc. Thorac. Res.* **2014**, *6*, 147–151. [CrossRef]
25. Rossi, U.G.; Rigamonti, P.; Torcia, P.; Mauri, G.; Brunini, F.; Rossi, M.; Gallieni, M.; Cariati, M. Congenital anomalies of superior vena cava and their implications in central venous catheterization. *J. Vasc. Access.* **2015**, *16*, 265–268. [CrossRef]
26. Lee, M.S.; Pande, R.L.; Rao, B.; Landzberg, M.J.; Kwong, R.Y. Cerebral abscess due to persistent left superior vena cava draining into the left atrium. *Circulation* **2011**, *124*, 2362–2364. [CrossRef]

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Risk Factors for Prolonged Mechanical Ventilation and Delayed Extubation Following Bimaxillary Orthognathic Surgery: A Single-Center Retrospective Cohort Study

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Abstract: Background: Bimaxillary orthognathic surgery bears the risk of severe postoperative airway complications. There are no clear recommendations for immediate postoperative follow-up and monitoring. Objective: to identify potential risk factors for prolonged mechanical ventilation and delayed extubation in patients undergoing bimaxillary orthognathic surgery. Methods: The data of all consecutive patients undergoing bimaxillary surgery between May 2012 and October 2019 were analyzed in a single-center retrospective cohort study. The clinical data were evaluated regarding baseline characteristics and potential factors linked with delayed extubation. Results: A total of 195 patients were included; 54.9% were female, and the median age was 23 years (IQR 5). The median body mass index was 23.1 (IQR 8). Nine patients (4.6%) were of American Society of Anesthesiologists Physical Status Classification System III or higher. The median duration of mechanical ventilation in the intensive care unit was 280 min (IQR, 526 min). Multivariable analysis revealed that premedication with benzodiazepines (odds ratio (OR) 2.60, 95% confidence interval (0.99; 6.81)), the male sex (OR 2.43, 95% confidence interval (1.10; 5.36)), and the duration of surgery (OR 1.54, 95% confidence interval (1.07; 2.23)) were associated with prolonged mechanical ventilation. By contrast, total intravenous anesthesia was associated with shorter ventilation time (OR 0.19, 95% confidence interval (0.09; 0.43)). Conclusion: premedication with benzodiazepines, the male sex, and the duration of surgery might be considered to be independent risk factors for delayed extubation in patients undergoing bimaxillary surgery.

Keywords: bimaxillary surgery; airway complications; risk factors; extubation

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1. Introduction

Bimaxillary orthognathic surgery is performed to correct significant dental malocclusion, and to restore esthetic facial contour and proportion [1]. It reduces temporomandibular joint symptoms and plays a pivotal role in the treatment of obstructive apnea [2,3].

Considering the literature, bimaxillary surgery is a safe and reliable procedure, and the rate of intra- and postoperative complications is rather low [4,5]. However, Kantar et al. have recently reported that, compared to single-jaw surgery, double-jaw osteotomies are associated with an increased risk of early complications and surgery in the outpatient setting, and patients of American Society of Anesthesiology (ASA) physical status class 3 or higher have been identified as independent factors for postoperative adverse effects [6]. Taking this into account, there are no clear guidelines or recommendations for immediate postoperative follow-up and monitoring in patients undergoing bimaxillary surgery. With

the goal of avoiding early severe postoperative complications owing to nasal airway obstruction, edema, or intraoral bleeding, delayed controlled extubation in the ICU may be an approach after bimaxillary surgery. However, prolonged nasotracheal intubation bears the risk of adverse effects such as epistaxis, turbinectomy, retropharyngeal dissection, tympanites, and nasal alar pressure ulcers [7], and prolonged mechanical ventilation was linked with transient dysphonia, dysphagia, sore throat, and pneumonia [8,9].

While many studies have addressed the issue of predictors for postoperative wound complications [10–12], risk factors for delayed extubation in patients undergoing bimaxillary surgery are poorly defined to date. Therefore, the purpose of this study was to evaluate the duration of mechanical ventilation and to identify potential risk factors for delayed extubation.

2. Materials and Methods

2.1. Study Design, Setting, and Participants

This retrospective cohort study was conducted at the Department of Anesthesiology and Intensive Care, and the Department of Oral and Maxillofacial Surgery and Regional Plastic Surgery, University Medical Center, Freiburg, Germany. The study protocol was approved by the Ethics Committee of Freiburg University Medical Center (approval number 200/20). This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13]. A STROBE checklist has been provided in the Supplementary Materials. The study was initiated in 2020, and the retrospective data collection was conducted in 2020. Due to the initiation of an electronic patient data and management system in 2012 that allows for gaining the relevant data, we enclosed only files from 2012 or later. The study cohort consisted of all patients who had undergone bimaxillary orthognathic surgery followed by admission to the ICU between May 2012 and October 2019. The observational retrospective study design removed the need for a priori sample size calculation.

2.2. Anesthesia, Postoperative Care, and ICU Therapy

Patients fasted for 6 h for solid food and 2 h for clear liquid prior to the planned induction of anesthesia. If desired, patients received 3.75 or 7.5 mg midazolam orally before being transferred to the operating theater. Anesthesia was induced with the i.v. application of remifentanil, propofol, and cisatracurium, and maintained with propofol or volatile anesthetic sevoflurane or desflurane. Noninvasive arterial blood pressure, electrocardiography, and pulse oximetry were monitored continuously. Gastric feeding tube placement was performed in all patients. In order to control and reduce postoperative swelling after orthognathic surgery [14], patients who had no contraindications received a single preoperative high-dose injection of dexamethasone.

All patients were transferred to the intensive care unit (ICU) in a sedated state with a continuous i.v. application of propofol (doses in the range of 80–120 µg/kg/min) under controlled mechanical ventilation and intubated endotracheally for planned extubation. Local cooling of the midface and the neck with ice packs or an automated cooling mask (Hilotherapy®, Hilotherm GmbH, Argenbühl-Eisenharz, Germany) was consequently applied. Sedation was stopped with stable vital parameters, decayed muscle relaxant, and analgesic therapy with nonsteroidal drugs, and nurse-controlled opioid application was established. Desired sedation depth was between –1 and 0 using the Richmond agitation and sedation scale [15]. When patients were alert and calm, the standard operating procedure for the extubation of patients undergoing bimaxillary orthognathic surgery was applied. The main premises are the evaluation of a patient's ability to cough, swallow, and cooperate, and a successful leakage test with a deflated cuff of the endotracheal tube (Figure 1).

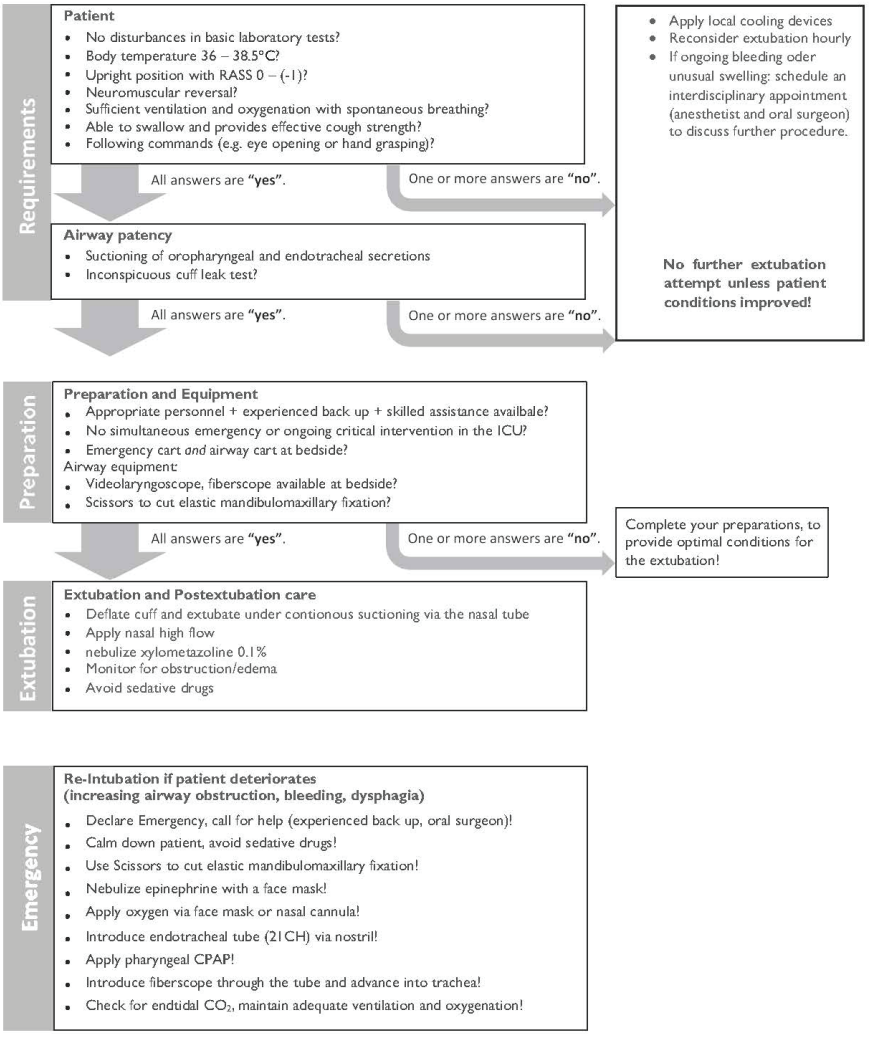

Figure 1. Standard operating procedure for the extubation of patients undergoing bimaxillary orthognathic surgery. Modified from standard operating procedure extubation of a difficult airway published in [16] by Schmutz et al.

2.3. Surgical Protocol

Each patient preoperatively received orthodontic treatment. The bimaxillary surgeries were performed under general anesthesia with nasal intubation. The virtual planning of the surgery was performed using Dolphin software (Patterson Dental, Chatsworth, CA, USA), and the surgical splints were printed out with a Stratasys Eden 260v 3D printer (Stratasys, Eden Prairie, MN, USA).

After applying local anesthesia with adrenaline 1:200,000 in the maxilla and the mandible, the surgery started in the maxilla with a leFort-I osteotomy. After repositioning, the maxilla was fixed with 4 L plates 1.5 mm and 16 Cortical Screws 2.0/6 mm (DePuy Synthes, Raynham, MA, USA); in the case of a gap, BioOss Kollagen (GeistlichPharma, Wolhusen, Switzerland) was added to the osteotomy line. In the mandible, bilateral sagittal split osteotomy (BSSO) was performed following the Obwegeser/Dal Pont technique; after adjustment, the newly positioned mandible was fixed with two SplitFix 2/40 mm plates

and 4 cortical screws 2.0/6 mm (DePuy Synthes, Raynham, MA, USA). In cases with large mandibular advancements, an additional osteosynthesis plate was used in the mandible to increase overall stability in comparison to SplitFixPlate alone. In the case of a maxillary and mandibular advancement because of sleep apnea or when performing counterclockwise rotation, the surgery was performed following a mandible first protocol.

2.4. Data Collection

To determine factors associated with the extubation period, the case records were reviewed for general demographic data, and specific medical, operative, and anesthesia predictor variables. Inclusion criteria for this study were patients with a developmental dentofacial deformity involving the two jaws. Demographic variables were age at the time of operation and gender. The medical variables were pre-existing comorbidities, ASA classification, Mallampati score, and body mass index (BMI). Operative and anesthesia variables were surgery duration and types of drugs used. As the primary outcome, variable time to extubation on ICU was defined.

2.5. Data Analyses

The data were collected in a MS Excel™ (Microsoft, Redmond, WA, USA) datasheet. Further statistical processing was performed using the Statistical Package for the Social Sciences (SPSS for Windows, V.27; SPSS Inc., Chicago, IL, USA).

Descriptive statistics were used to show the distribution of variables (median and range for continuous variables, and frequency for discrete variables). The quartiles of postoperative mechanical ventilation intervals were calculated. After that, two groups were formed: The "short-term postoperative mechanical ventilation interval" group, comprising the lower three quartiles, and the "long-term postoperative mechanical ventilation interval" group, comprising all patients with ventilation times longer than the 75th percentile. Normal distribution was tested using the Kolmogorov–Smirnov test. For the comparison of metric parameters between the two groups, such as duration of surgery, volume intake, and blood loss, a t-test for independent samples was used; for the comparison of nominal parameters such as sex and comorbidities, a chi-squared test was applied. A p-value of 0.05 was chosen to be the level of significance. To find the variables independently associated with longer postoperative ventilation, parameters with significant differences were included in binary logistic regression analysis. If the p value was less than 0.05, it was considered to be significant. For variable selection, the forward stepwise approach was applied.

3. Results

3.1. Preoperative Variables

The patients' characteristics are shown in Table 1. A total of 195 consecutive patients who had undergone bimaxillary surgery between May 2012 and October 2019 were included in this retrospective study. The patients' median age was 23 years (IQR 8; range from 18 to 61 years), and 107 patients (54.9%) were female. The median BMI was 23.1 (IQR 5.0). Nine patients (4.6%) were of ASA class 3 or higher. Fifteen patients (7.7%) had a Mallampati score of III or higher. Potentially relevant comorbidities included hypertension (3.1%), allergic asthma (12.3%), chronic obstructive pulmonary disease (COPD (1.0%)), hypothyroidism (4.6%), depression (5.1%), or a history of smoking (13.8%).

3.2. Anesthesia and Operative Variables

Of the patients, 125 (64.1%) had received premedication in the form of oral midazolam before they were transferred to the operating theater (Table 2). Airway management during surgery was successfully accomplished with nasotracheal intubation in all cases. In total, 179 patients (91.8%) received a single injection of dexamethasone. The maintenance of general anesthesia using propofol-based total intravenous anesthesia (TIVA) was performed in 135 patients (69.2%). The median open-wound operating time was 238 min (IQR, 95 min).

The median time of mechanical ventilation in the operating theater from the start of anesthesia till ICU arrival was 330 min (IQR, 106 min).

Table 1. Patient characteristics.

Entire Cohort	*n* = 195
Age in years, median (IQR)	23.0 (8)
BMI, median (IQR)	23.1 (5)
Gender	
Male, *n* (%) Female, *n* (%)	88 (45.1) 107 (54.9)
ASA classification, *n* (%)	
- I and II - III–V	186 (95.4) 9 (4.6)
Mallampati grading, *n* (%)	
- 1 and 2 - 3 or higher - Mallampati missing	151 (77.4) 15 (7.7) 29 (14.9)
Preexisting comorbidities, *n* (%)	
- Hypertension - Allergic asthma - COPD - Hypothyroidism - Depression - Smoker	6 (3.1) 24 (12.3) 2 (1.0) 9 (4.6) 10 (5.1) 27 (13.8)

Categorical variables are given as absolute number and percentage. Continuous variables are given as median (IQR (interquartile range)). *ASA*, American Society of Anesthesiologists; BMI, body mass index (kg/m^2); *COPD*, chronic obstructive pulmonary disease.

3.3. Time of Mechanical Ventilation in the ICU

As shown in Figure 2, the median time of mechanical ventilation in ICU was 280 min (IQR, 526 min).

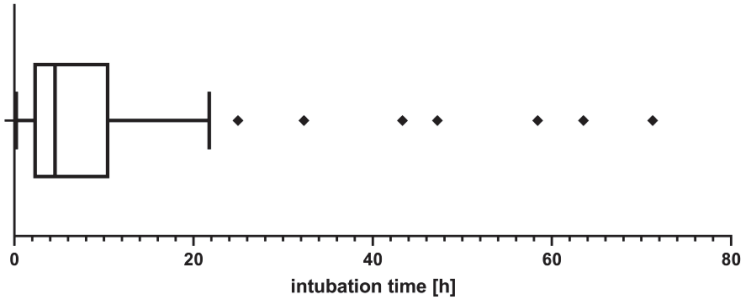

Figure 2. Box plot showing intubation time in ICU.

Consequently, the need for endotracheal intubation for more than 665 min (75th percentile) was defined as prolonged mechanical ventilation. Of the patients, 48 (32.7%) underwent delayed extubation.

Table 2. Perioperative variables.

Entire Cohort	*n* = 195
Received premedication	125 (64.1%)
Intraoperative comedication, *n* (%)	
- Parecoxib	30 (15.4)
- Metamizole	15 (7.7)
- Tranexamic acid	19 (9.7)
Preoperative dexamethasone, *n* (%)	
- None	16 (8.2)
- 4 mg	10 (5.1)
- 8 mg	4 (2.1)
- 16 mg	20 (10.3)
- 20 mg	83 (42.6)
- 40 mg	49 (25.1)
- 44 mg	6 (3.1)
- 80 mg	6 (3.1)
- 84 mg	1 (0.5)
Intraoperative blood loss (mL), median (IQR)	300 (280)
Intraoperative fluid intake (mL), median (IQR)	1700 (1550)
Anesthesia maintenance, *n* (%)	
- Balanced anesthesia	60 (30.8)
- Total intravenous anesthesia	135 (69.2)
Time intervals (min), median (IQR)	
- Contact anesthesia until the start of surgical preparation	30 (15)
- Length of operation	238 (95)
- Mechanical ventilation until ICU arrival	330 (106)

Categorical variables are given as absolute number and percentage. Continuous variables are given as median (IQR (interquartile range)). *ICU*, Intensive Care Unit.

3.4. Statistical Analysis of Risk Factors and Outcome Variables

Next, we statistically analyzed potential risk factors for prolonged mechanical ventilation in the ICU (Figure 3).

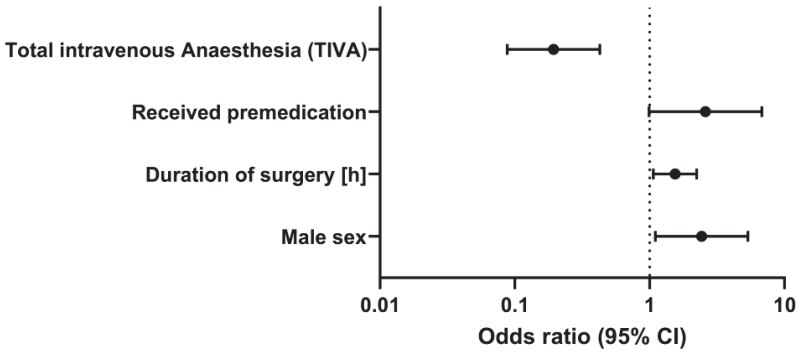

Figure 3. Risk factors for prolonged mechanical ventilation in the ICU.

Multivariable analysis revealed that the factor most strongly associated with delayed extubation in the ICU was premedication with benzodiazepines (odds ratio (OR) 2.60, 95% confidence interval (0.99; 6.81)), followed by the male sex (OR 2.43, 95% confidence interval (1.10; 5.36)), and the duration of surgery (OR 1.54, 95% confidence interval (1.07; 2.23)), whereas the maintenance of general anesthesia with propofol-based TIVA was associated with earlier extubation (OR 0.19, 95% confidence interval (0.09; 0.43)).

4. Discussion

Orthognathic surgery is a common and mostly safe procedure for correcting dentofacial deformities and malocclusions [17]. Risks of surgery include relapse of the jaw, jaw fracture, nerve injury, wound infection, or excessive blood loss, and the patient´s airway may be threatened by obstruction, edema, or intraoral bleeding [18–20]. Kantar et al. have recently shown that, compared with single-jaw surgery, double-jaw osteotomies are associated with significantly higher rates of overall complications. In this study, surgery in the outpatient setting and patient ASA physical status class 3 or higher were identified as independent risk factors for postoperative adverse effects in patients undergoing bimaxillary surgery [6]. Most complications occur early after the operation, and delayed extubation in the ICU has become the standard approach in our institution. While early extubation after bimaxillary surgery is a safe procedure and is associated with reduced ICU length and hospital stay [21], risk factors for prolonged mechanical ventilation and delayed extubation in this patient cohort are poorly defined to date.

In our study, anxiolytic premedication with oral midazolam was associated with prolonged mechanical ventilation and delayed extubation in the ICU despite short elimination half-life midazolam reducing psychomotor performance in healthy volunteers for several hours [22]. Interestingly, until now, there was only low-quality evidence that midazolam reduces anxiety when administered as the sole sedative agent prior to a medical procedure [23]. In geriatric patients undergoing brief surgical procedures, midazolam administration significantly prolonged postanesthesia care unit discharge time [24]. Mohammadi et al. have recently shown that oral premedication with clonidine might have beneficial effects in patients undergoing bimaxillary surgery [25]; in hypertensive patients, dexmedetomidine premedication provides better hemodynamic stability than that of midazolam [26].

In our study, the male sex was associated with delayed extubation in the ICU. The reason for this observation remains unclear. However, there is growing evidence of sex-specific differences in mechanically ventilated patients [27–29], and a retrospective study on hospitalized patients in an ICU showed that women had significantly shorter duration of mechanical ventilation, time to withdrawal of sedation, and time to onset of active exercises [30].

Another result of our study was that, compared to balanced anesthesia with volatile anesthetics, the maintenance of general anesthesia with propofol-based TIVA was associated with a shorter period of mechanical ventilation in the ICU. All patients included in our study were transferred to the ICU with continuous propofol i.v. application. A possible explanation for the observed difference may be that patients undergoing anesthesia with volatile anesthetics may need higher doses of propofol for the transfer to the ICU. Whether causal or not, in the TIVA-group, propofol infusion was continued for transport with a lower target concentration. Other beneficial and advantageous effects of TIVA over inhalational agents in the perioperative setting include reduced PONV and better analgesia, both resulting in greater patient satisfaction and shortened intubation time [31]. Thus, anesthesia maintenance with propofol might be advantageous in patients undergoing bimaxillary surgery.

As one would expect, the type of orthognathic surgery and the amount of mandibular advancement or setback may influence the postoperative mechanical ventilation time. Riekert et al. have recently shown that an early extubation strategy was associated with a shortening of ICU and inhospital stay, whereas postoperative complications such as nausea and vomiting, anemia, or respiratory dysfunction were not increased compared to a delayed extubation strategy in patients undergoing bimaxillary surgery [21]. Another result of this study was that the reduction in pharyngeal airway space did not increase the complication rate in this patient cohort. In our study, the duration of surgery correlated with intubation time in the ICU. This result is consistent with those of previous studies in which prolonged surgery was associated with delayed extubation [32,33]. Surgical procedures represent a potential trigger for systemic inflammation [34], and prolonged

surgery increases the secretion of proinflammatory cytokines and endothelial dysfunction. As a result, postoperative swelling and airway obstruction may occur [35]. Due to a previously published protocol-based evaluation for the feasibility of extubation [16], none of the 195 patients included in our study required reintubation in the ICU.

The potential strengths of the study are that the study cohort consisted of all patients who had undergone bimaxillary orthognathic surgery followed by admission to the ICU between May 2012 and October 2019, and that all operations were performed by a single surgical team. However, our study has several limitations. First, the single-center design with the small sample of patients might limit the generalizability of the results. Second, due to its retrospective character, there might be an absence of data on potential confounding factors. Lastly, our findings are merely an association and cannot imply causation. Further randomized trials should be undertaken to assess predictors for delayed extubation, helping us in identifying patients more likely to undergo prolonged mechanical ventilation.

In conclusion, this study showed that premedication with midazolam, the male sex, and the duration of surgery are associated with prolonged mechanical ventilation and delayed extubation in ICU, whereas the maintenance of general anesthesia with propofol-based TIVA is associated with earlier extubation in patients undergoing bimaxillary orthognathic surgery.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11133829/s1, STROBE checklist.

Author Contributions: Conceptualization, C.I.S., T.L. and M.C.M.; validation, C.I.S. and J.K.; formal analysis, T.R., R.R. and J.K.; data curation, C.I.S., T.R. and M.G.; writing—original draft preparation, C.I.S. and J.K.; writing—review and editing, C.I.S., T.L. and M.C.M.; visualization, T.R. and J.K.; supervision, T.L. and M.C.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This retrospective cohort study was approved by the local Ethics Committee, University of Freiburg, Germany (approval number 200/20). All procedures that were performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

Informed Consent Statement: For this type of retrospective study, formal consent was not required.

Data Availability Statement: Not applicable.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Cascone, P.; di Paolo, C.; Leonardi, R.; Pedulla, E. Temporomandibular disorders and orthognathic surgery. *J. Craniofac. Surg.* **2008**, *19*, 687–692. [CrossRef] [PubMed]
2. Gottsauner-Wolf, S.; Laimer, J.; Bruckmoser, E. Posterior Airway Changes Following Orthognathic Surgery in Obstructive Sleep Apnea. *J. Oral Maxillofac. Surg.* **2018**, *76*, 1093.e1–1093.e21. [CrossRef] [PubMed]
3. Tepecik, T.; Ertas, U.; Akgun, M. Effects of bimaxillary orthognathic surgery on pharyngeal airway and respiratory function at sleep in patients with class III skeletal relationship. *J. Craniomaxillofac. Surg.* **2018**, *46*, 645–653. [CrossRef] [PubMed]
4. Eshghpour, M.; Mianbandi, V.; Samieirad, S. Intra- and Postoperative Complications of Le Fort I Maxillary Osteotomy. *J. Craniofac. Surg.* **2018**, *29*, e797–e803. [CrossRef]
5. Posnick, J.C.; Choi, E.; Chavda, A. Operative Time, Airway Management, Need for Blood Transfusions, and In-Hospital Stay for Bimaxillary, Intranasal, and Osseous Genioplasty Surgery: Current Clinical Practices. *J. Oral Maxillofac. Surg.* **2016**, *74*, 590–600. [CrossRef]
6. Kantar, R.S.; Cammarata, M.J.; Rifkin, W.J.; Alfonso, A.R.; DeMitchell-Rodriguez, E.M.; Noel, D.Y.; Greenfield, J.; Levy-Lambert, D.; Rodriguez, E.D. Bimaxillary Orthognathic Surgery Is Associated with an Increased Risk of Early Complications. *J. Craniofac. Surg.* **2019**, *30*, 352–357. [CrossRef]

7. Brasileiro, B.F.; van Sickels, J.E. Nasal Alar Pressure Ulcer After Orthognathic Surgery: Clinical Presentation and Preventive Recommendations. *J. Craniofac. Surg.* **2019**, *30*, e533–e535. [CrossRef]
8. Pacheco-Lopez, P.C.; Berkow, L.C.; Hillel, A.T.; Akst, L.M. Complications of airway management. *Respir. Care* **2014**, *59*, 1006–1019; discussion 19–21. [CrossRef]
9. Shinn, J.R.; Kimura, K.S.; Campbell, B.R.; Sun Lowery, A.; Wootten, C.T.; Garrett, C.G.; Francis, D.O.; Hillel, A.T.; Du, L.; Casey, J.D.; et al. Incidence and Outcomes of Acute Laryngeal Injury After Prolonged Mechanical Ventilation. *Crit. Care Med.* **2019**, *47*, 1699–1706. [CrossRef]
10. Alpha, C.; O'Ryan, F.; Silva, A.; Poor, D. The incidence of postoperative wound healing problems following sagittal ramus osteotomies stabilized with miniplates and monocortical screws. *J. Oral Maxillofac. Surg.* **2006**, *64*, 659–668. [CrossRef]
11. Posnick, J.C.; Choi, E.; Chavda, A. Surgical Site Infections Following Bimaxillary Orthognathic, Osseous Genioplasty, and Intranasal Surgery: A Retrospective Cohort Study. *J. Oral Maxillofac. Surg.* **2017**, *75*, 584–595. [CrossRef] [PubMed]
12. Zijderveld, S.A.; Smeele, L.E.; Kostense, P.J.; Tuinzing, D.B. Preoperative antibiotic prophylaxis in orthognathic surgery: A randomized, double-blind, and placebo-controlled clinical study. *J. Oral Maxillofac. Surg.* **1999**, *57*, 1403–1406; discussion 6–7. [CrossRef]
13. Vandenbroucke, J.P.; von Elm, E.; Altman, D.G.; Gøtzsche, P.C.; Mulrow, C.D.; Pocock, S.J.; Poole, C.; Schlesselman, J.J.; Egger, M.; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Epidemiology* **2007**, *18*, 805–835. [CrossRef]
14. Semper-Hogg, W.; Fuessinger, M.A.; Dirlewanger, T.W.; Cornelius, C.P.; Metzger, M.C. The influence of dexamethasone on postoperative swelling and neurosensory disturbances after orthognathic surgery: A randomized controlled clinical trial. *Head Face Med.* **2017**, *13*, 19. [CrossRef] [PubMed]
15. Ely, E.W.; Truman, B.; Shintani, A.; Thomason, J.W.; Wheeler, A.P.; Gordon, S.; Francis, J.; Speroff, T.; Gautam, S.; Margolin, R.; et al. Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* **2003**, *289*, 2983–2991. [CrossRef] [PubMed]
16. Schmutz, A.; Dieterich, R.; Kalbhenn, J.; Voss, P.; Loop, T.; Heinrich, S. Protocol based evaluation for feasibility of extubation compared to clinical scoring systems after major oral cancer surgery safely reduces the need for tracheostomy: A retrospective cohort study. *BMC Anesthesiol.* **2018**, *18*, 43. [CrossRef] [PubMed]
17. Al-Moraissi, E.A.; Perez, D.; Ellis, E., 3rd. Do patients with malocclusion have a higher prevalence of temporomandibular disorders than controls both before and after orthognathic surgery? A systematic review and meta-analysis. *J. Craniomaxillofac. Surg.* **2017**, *45*, 1716–1723. [CrossRef]
18. Zaroni, F.M.; Cavalcante, R.C.; Joao da Costa, D.; Kluppel, L.E.; Scariot, R.; Rebellato, N.L.B. Complications associated with orthognathic surgery: A retrospective study of 485 cases. *J. Craniomaxillofac. Surg.* **2019**, *47*, 1855–1860. [CrossRef]
19. Olate, S.; Sigua, E.; Asprino, L.; de Moraes, M. Complications in Orthognathic Surgery. *J. Craniofac. Surg.* **2018**, *29*, e158–e161. [CrossRef]
20. Thiem, D.G.E.; Schneider, D.; Hammel, M.; Saka, B.; Frerich, B.; Al-Nawas, B.; Kämmerer, P.W. Complications or rather side effects? Quantification of patient satisfaction and complications after orthognathic surgery-a retrospective, cross-sectional long-term analysis. *Clin. Oral Investig.* **2021**, *25*, 3315–3327. [CrossRef]
21. Riekert, M.; Kreppel, M.; Schier, R.; Zoller, J.E.; Rempel, V.; Schick, V.C. Postoperative complications after bimaxillary orthognathic surgery: A retrospective study with focus on postoperative ventilation strategies and posterior airway space (PAS). *J. Craniomaxillofac. Surg.* **2019**, *47*, 1848–1854. [CrossRef] [PubMed]
22. Nuotto, E.J.; Korttila, K.T.; Lichtor, J.L.; Ostman, P.L.; Rupani, G. Sedation and recovery of psychomotor function after intravenous administration of various doses of midazolam and diazepam. *Anesth. Analg.* **1992**, *74*, 265–271. [CrossRef] [PubMed]
23. Conway, A.; Rolley, J.; Sutherland, J.R. Midazolam for sedation before procedures. *Cochrane Database Syst. Rev.* **2016**, *2018*, CD009491. [CrossRef] [PubMed]
24. Fredman, B.; Lahav, M.; Zohar, E.; Golod, M.; Paruta, I.; Jedeikin, R. The effect of midazolam premedication on mental and psychomotor recovery in geriatric patients undergoing brief surgical procedures. *Anesth. Analg.* **1999**, *89*, 1161–1166. [CrossRef]
25. Mohammadi, F.; Marashi, M.; Tavakoli, I.; Khakbaz, O. Effects of oral clonidine premedication on hemodynamic status in bimaxillary orthognathic surgery: A double-blind randomized clinical trial. *J. Craniomaxillofac. Surg.* **2016**, *44*, 436–439. [CrossRef] [PubMed]
26. Sezen, G.; Demiraran, Y.; Seker, I.S.; Karagoz, I.; Iskender, A.; Ankarali, H.; Ersoy, O.; Ozlu, O. Does premedication with dexmedetomidine provide perioperative hemodynamic stability in hypertensive patients? *BMC Anesthesiol.* **2014**, *14*, 113. [CrossRef]
27. Kollef, M.H.; O'Brien, J.D.; Silver, P. The impact of gender on outcome from mechanical ventilation. *Chest* **1997**, *111*, 434–441. [CrossRef]
28. Vezzani, A.; Mergoni, M.; Orlandi, P.; Corradi, F.; Volpi, A.; Zasa, M. Gender differences in case mix and outcome of critically ill patients. *Gend. Med.* **2011**, *8*, 32–39. [CrossRef]
29. Mahmood, K.; Eldeirawi, K.; Wahidi, M.M. Association of gender with outcomes in critically ill patients. *Crit. Care* **2012**, *16*, R92. [CrossRef]
30. Daniel, C.R.; de Matos, C.A.; de Meneses, J.B.; Bucoski, S.C.M.; Fréz, A.; Mora, C.T.R.; Ruaro, J.A. Mechanical ventilation and mobilization: Comparison between genders. *J. Phys. Ther. Sci.* **2015**, *27*, 1067–1070. [CrossRef]

31. Schraag, S.; Pradelli, L.; Alsaleh, A.J.O.; Bellone, M.; Ghetti, G.; Chung, T.L.; Westphal, M.; Rehberg, S. Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: A systematic review and meta-analysis. *BMC Anesthesiol.* **2018**, *18*, 162. [CrossRef] [PubMed]
32. Anastasian, Z.H.; Gaudet, J.G.; Levitt, L.C.; Mergeche, J.L.; Heyer, E.J.; Berman, M.F. Factors that correlate with the decision to delay extubation after multilevel prone spine surgery. *J. Neurosurg. Anesthesiol.* **2014**, *26*, 167–171. [CrossRef] [PubMed]
33. Sharma, V.; Rao, V.; Manlhiot, C.; Boruvka, A.; Fremes, S.; Wasowicz, M. A derived and validated score to predict prolonged mechanical ventilation in patients undergoing cardiac surgery. *J. Thorac. Cardiovasc. Surg.* **2017**, *153*, 108–115. [CrossRef] [PubMed]
34. Margraf, A.; Ludwig, N.; Zarbock, A.; Rossaint, J. Systemic Inflammatory Response Syndrome After Surgery: Mechanisms and Protection. *Anesth. Analg.* **2020**, *131*, 1693–1707. [CrossRef] [PubMed]
35. Politis, C.; Kunz, S.; Schepers, S.; Vrielinck, L.; Lambrichts, I. Obstructive airway compromise in the early postoperative period after orthognathic surgery. *J. Craniofac. Surg.* **2012**, *23*, 1717–1722. [CrossRef]

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Factors Associated with Variability in Pulse Wave Transit Time Using Pulse Oximetry: A Retrospective Study

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Abstract: Pulse wave transit time (PWTT) is the time difference between the occurrence of an R-wave on an electrocardiogram and the detection of pulsatile signals on a pulse oximeter, which reflects changes in blood pressure (BP) corresponding to the vessel wall compliance. However, the factors affecting PWTT variability have not been determined. Thus, we investigated the BP changes associated with variations in PWTT and identified the clinical characteristics associated with these variations. Data related to 605 cases of dental procedures performed under intravenous conscious sedation from April 2020 to November 2021 were collected, and 485 cases were enrolled. Heart rate, systolic blood pressure before and after local anesthesia (LA) administration, and crest and trough PWTT waves during LA administration were recorded. Thereafter, PWTT variability was calculated; cases were divided into two groups: large PWTT variability (LPV, n = 357) and small PWTT variability (SPV, n = 128). The index of large PWTT variability could not detect changes in BP. Logistic regression analysis revealed that factors, such as LA use, age, hypertension, and dental treatment phobia were associated with PWTT variability. The use of epinephrine more than 36.25 μg in each LA resulted in PWTT variability of more than 15 ms.

Keywords: pulse wave transit time; ambulatory monitoring; hemodynamic monitoring; local anesthetics

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1. Introduction

Scheduled intermittent measurement of non-invasive blood pressure (NIBP) is important for detecting hemodynamic changes throughout dental procedures performed under intravenous conscious sedation (IVCS) [1]. Nevertheless, NIBP measurements recorded at specific intervals may not be sufficient to detect short-term changes in blood pressure (BP), which are associated with rapid changes in the vascular properties. Particularly in dental procedures, the use of local anesthetic agents containing epinephrine for infiltration anesthesia in addition to various stimuli involving autonomic responses, such as invasive treatments associated with pain and stress, may induce large BP fluctuations within a short period of time.

Epinephrine is commonly contained in local anesthetic agent for routine dental procedures and a potent vasoconstrictor that stimulates α-adrenergic receptors, resulting in immediate BP variations after local anesthesia (LA) administration. This may not be detected by intermittent NIBP measurement and failure to detect BP fluctuations may increase the risk on patients with underlying cardiovascular disease [2,3]. Anesthesiologists can resolve this issue through manual assessments, which may however be subjective. Frequent measurements may also cause discomfort, trauma, and nerve injury to the patient [4].

Various approaches have been investigated as alternatives for continuous BP monitoring [5]. Pulse wave transit time (PWTT) is one of these, and vital monitoring devices that make use of this parameter are commercially available. It calculates the time between the rise of the photoplethysmography (PPG) waveform and the R-wave of the electrocardiogram by using the changes in finger blood volume determined by the PPG [6]. PWTT is affected by

changes in vascular volume, sympathetic nerve activity, and vascular elasticity [3,7]. The pulse wave propagates through the arterial vessel toward the peripheral measurement site, where it appears as a time delay (milliseconds). The length of the PWTT is directly proportional to the BP [4]. When blood volume is high or vessels are constricted, pulse waves travel faster because blood flow reaches the peripheral site with high speed. Variations in PWTT reflect vascular tone increases and subsequent stiffening of the vessel walls [8]. Large variations in PWTT can occur when the vessel wall has a normal ability to constrict under relaxed conditions, especially when it has high elasticity. In contrast, small variations in PWTT might indicate that the vessel wall compliance is limited. This condition can arise from factors such as arteriosclerosis [9]. As a result, the decrease in PWTT is reflected as a steep drop in the graph, showing its changes over time, and the BP increases [10,11]. In this graph, changes in PWTT are indicated by the amplitude width and height. If the vessel wall contracts rapidly, the PWTT drops abruptly; if it contracts severely, the PWTT amplitude increases.

The clinical measurement of PWTT began in recent years. One bedside monitor (Life Scope BSM 3562, Nihon Kohden, Tokyo, Japan) has two settings that automatically trigger NIBP measurement using PWTT; one is when PWTT varies by more than 15 ms, which is assumed to be a change in systolic blood pressure (SBP) of >20 mmHg. The second was when the estimated SBP calculated from this PWTT change exceeded the SBP alarm setpoint for more than 8 s. NIBP measurements are triggered when both conditions are satisfied [12].

Previous studies on the direct relationship between PWTT and BP are often inadequate because of differences in the clinical characteristics of the subjects and the small sample sizes [6,10]. Meanwhile, an investigation of PWTT and BP in newborns showed the ability of PWTT to continuously detect BP changes [11]. To our knowledge, no study has examined the association between changes in BP and variations in PWTT during dental procedures. Therefore, the aim of this study was to investigate whether BP changes can be detected early from the variability in PWTT and the clinical characteristics related to these variations during dental treatment.

2. Materials and Methods

2.1. Participants and Data Sources

We conducted a retrospective study on the changes in PWTT following infiltration anesthesia in adult patients with American Society of Anesthesiologists (ASA) physical status score I–III (I, normal healthy patient; II, indicating patient with mild systemic disease; and III, indicating patient with severe systemic disease with no constant threat to life), who received dental treatment under IVCS between April 2020 and November 2021 in our dental anesthesiology clinic. The ethics committee of our university (No. D2021-017) approved the study procedures for sample collection and analysis. In accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, we substituted the consent form with disclosure of the study details on the hospital website and posting. Patients' background data were acquired from medical records, vital signs including PWTT were collected from anesthesia charts, and bedside monitors at the Dental Anesthesiology Clinic of the TMDU Hospital, respectively. The exclusion patient's criteria were as follows: less than 20 years old, history of frequent arrhythmia or pacemaker use, use of LA without epinephrine, and no LA use.

After standard monitoring was performed, including an electrocardiogram, measurement of NIBP every 5 min, and a pulse oximeter on the index finger of the hand, a peripheral venous catheter was placed in the patient's right arm. In our institution, midazolam 0.03–0.04 mg/kg was administered as a single dose at the usual induction, followed by continuous propofol at 1–4 mg/kg/h, with a target sedation level of 4–5 on the Ramsay sedation scale. Patients received 100% O_2 inhalation through a nasal catheter at a flow rate of 3 mL/min during the treatment. After confirming stable vital signs and achieving the target sedation level, LA was administered. A 2% lidocaine solution with

epinephrine concentration of 1:80,000 (1.8 mL/cartridge) was used as the local anesthetic, and the amount used was decided by the surgeon. Heart rate (HR), SBP, and PWTT were recorded on a bedside monitor from the time of NIBP measurement immediately before LA administration until the next scheduled NIBP measurement, 5 min after completely administering the first dose of LA. The BSM PC Viewer, version 0.04 (Nihon Kohden, Tokyo, Japan) was used to record and extract HR, SBP, and PWTT.

2.2. Clinical Characteristics

We gathered the following patient data from the available medical records and anesthesia charts: sex; age; weight; height; body mass index (BMI) at the time of treatment; obesity classified as BMI $\geq$ 25 [13]; ASA physical status score; dose of epinephrine (μg) in LA solution that was used during the recorded period; preexisting patient history of systemic diseases or mental disorders; patients with history of smoking cigarettes at least 1 d in the past month during medical examination were classified as smokers [14]; and history of alcohol intake in medical records before the treatment classified as alcohol consumption. We recorded the entire history, rather than just a representative one, because patients could have had multiple medical conditions.

2.3. Variables from Recorded Segments

We established the baseline heart rate (HR_{BL}) and baseline systolic blood pressure (SBP_{BL}) at the time of NIBP measurement immediately before LA administration. Maximum heart rate (HR_{LA}) and maximum systolic blood pressure (SBP_{LA}) were recorded at the time of NIBP measurement more than 5 min after finishing LA administration. ΔHR and ΔSBP were obtained from the differences between HR_{BL} and HR_{LA}, and SBP_{BL} and SBP_{LA}, respectively (Figure 1). PWTT variability (ΔPWTT) was calculated as the difference between crest PWTT wave ($PWTT_{MAX}$) and trough PWTT wave ($PWTT_{MIN}$) during the LA administration. The patients were then divided into two groups: a large variation group with ΔPWTT > 15 (LPV) and a small variation group with ΔPWTT < 15 (SPV).

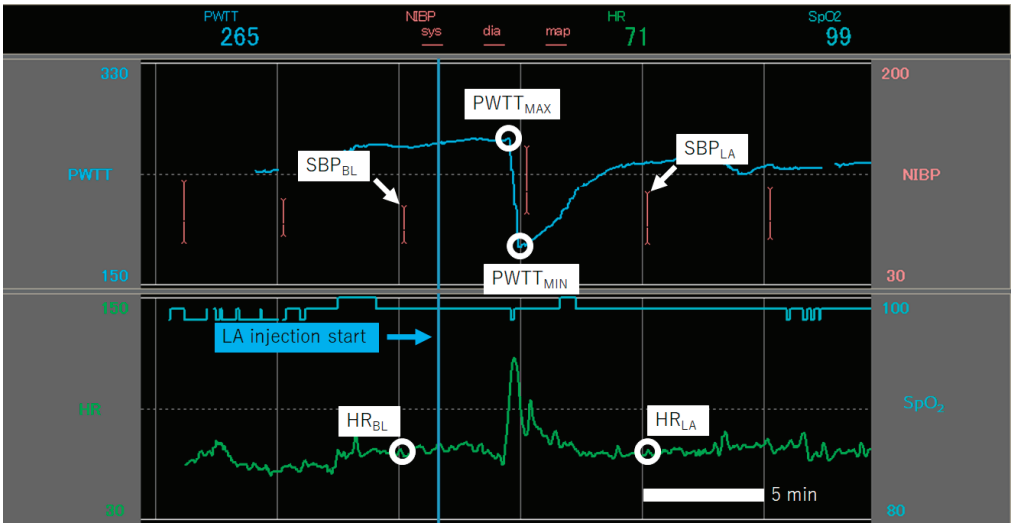

Figure 1. Baseline HR (HR_{BL}) and baseline SBP (SBP_{BL}) immediately before local anesthesia; heart rate after local anesthesia (HR_{LA}); and systolic blood pressure (SBP_{LA}) were also recorded at 5 min after local anesthesia. Value for ΔPWTT. Crest PWTT wave ($PWTT_{MAX}$) value; trough PWTT wave ($PWTT_{MIN}$) value. Unit PWTT in milliseconds (msec), SBP in mmHg, HR in beats per minute (bpm). Abbreviations: HR = heart rate; SBP = systolic blood pressure; PWTT = pulse wave transit time.

2.4. Statistical Analysis

The normality of data distribution on clinical characteristics and variables was examined using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed variables were expressed as the mean ± standard deviation. Non-normally distributed data were presented as medians with interquartile range, minimum, and maximum. The distribution of clinical characteristics and variables from recorded segments was compared between the LPV and SPV groups using *t*-tests or Mann–Whitney U tests for continuous variables and chi-square tests or Fisher's exact tests for categorical data, as appropriate. To evaluate the primary outcome, i.e., the relationship between LPV and ΔSBP, the Mann–Whitney U test was used. Logistic regression was used to determine the associations between clinical characteristics and the LPV group. All statistical analyses were performed using SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Primary Outcome and Summary of Inclusions

Six-hundred-and-five patients who received dental treatment under IVCS were enrolled. Seventy-one patients were excluded based on the exclusion criteria. A total of 534 anesthesia records were reviewed, and in 49 cases, either the PWTT was interrupted or some data were not recorded. Therefore, 485 cases were included in the statistical analyses. Figure 2 presents a flow chart of the case selection process. The included cases were deemed as fit for the analyses, with 357 cases (73.6%) grouped into the LPV group and 128 cases (26.4%) into the SPV group. The average age was 49 ± 17 years old with a sex distribution of 61.2% female and 38.8% male with regard to the total population in this study. There were significant differences in sex, ASA scoring, age, weight, height, BMI, LA, and $PWTT_{MAX}$ between the two groups. In the SPV group, the mean age of the patients was higher. The use of epinephrine in local anesthetic agent was higher in the LPV group. (Table 1).

Table 1. Descriptive and univariate analysis of variables from recorded segments and clinical characteristics from overall reviewed cases.

Variables	Descriptive Analysis	Univariate Analysis		
	Overall Cases (*n* = 485)	LPV (*n* = 357)	SPV (*n* = 128)	*p* Value
Age (year)	49 (17)	48.1 (17)	52.3 (17)	0.018 *
Gender				<0.003 *
Male	188 (38.8%)	122 (64.9%)	66 (35.1%)	
Female	297 (61.2%)	235 (79.1%)	62 (20.9%)	
ASA				0.008 *
I	225 (46.4%)	180 (37.1%)	45 (9.3%)	
II	256 (52.8%)	175 (36.1%)	81 (16.7%)	
III	4 (0.8%)	2 (0.4%)	2 (0.4%)	
Weight (kg)	60.5 (13)	58.5 (13)	62.5 (13)	0.004 *
Height (m)	1.6 (0.1)	1.62 (0.1)	1.64 (0.1)	0.034 *
Body mass index (kg/m^2)	22.5 (4)	22 (4)	23 (4)	0.019 *
Midazolam (mg)	2 (0–5.9)	2 (0–5.9)	2 (0–5)	0.973
Epinephrine use in LA (μg)	43 (20)	49.9 (23)	35.5 (17)	<0.001 *
$PWTT_{MAX}$ (ms)	227 (168–301)	228 (168–301)	220 (179–269)	0.048 *
$PWTT_{MIN}$ (ms)	202 (146–270)	198 (146–270)	212 (168–265)	0.551
SBP_{BL} (mmHg)	115 (85–161)	115 (85–160)	117 (86–182)	0.197
SBP_{LA} (mmHg)	116 (79–182)	117 (86–182)	116 (79–173)	0.536
HR_{BL} (bpm)	72 (42–122)	72 (42–122)	72 (48–102)	0.896
HR_{LA} (bpm)	78 (45–128)	78 (45–128)	77 (45–112)	0.766

* Indicates statistically significant variables $p < 0.05$. Data shown as mean ± standard deviation, counts (percent), or median (interquartile range; minimum and maximum). Abbreviations: ASA = American Society of Anesthesiologists; HR_{BL} = baseline heart rate; HR_{LA} = post local anesthesia heart rate; LA = local anesthesia; LPV = large pulse wave transit time variability group; PWTT = pulse wave transit time; $PWTT_{MAX}$ = crest pulse wave transit time; $PWTT_{MIN}$ = trough pulse wave transit time; SBP_{BL} = baseline systolic blood pressure; SBP_{LA} = post local anesthesia systolic blood pressure; SPV = small pulse wave transit time variability group.

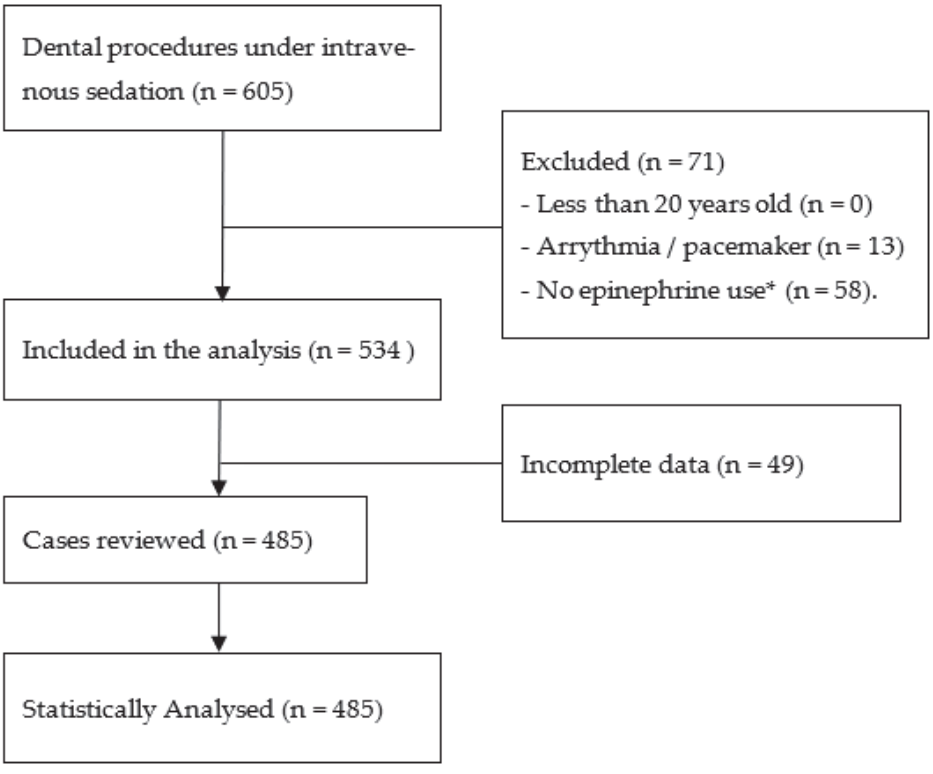

Figure 2. Flow chart of the case selection criteria. * Cases did not receive infiltration anesthesia and infiltration anesthesia without epinephrine.

The median ΔPWTT was distinctively higher in the LPV group, and there was no significant difference between the changes in SBP and PWTT variability over 15 ms, which was the primary outcome of this study. ΔHR was also not significantly different from PWTT variation. (Table 2).

Table 2. Mann–Whitney test of LPV toward ΔSBP and ΔHR.

Variables	LPV (n = 357)	SPV (n = 128)	p Value
ΔPWTT (ms)	31 ((−15)–(−88))	10 ((−14)–6)	<0.001 *
ΔSBP (mmHg)	0 ((−39)–63)	−1 ((−43)–32)	0.072
ΔHR (bpm)	5 ((−36)–180)	3 ((−14)–179)	0.626

* Indicates statistically significant variables $p < 0.05$. Data shown as median (interquartile range; minimum and maximum). Abbreviations: HR = heart rate; LPV = large pulse wave transit time variability group; PWTT = pulse wave transit time; SBP = systolic blood pressure; SPV = small pulse wave transit time variability group.

Regarding variables from the medical histories, there were significant differences in hypertension, cardiac disease, and hepatitis c between the two groups. Hypertension and obesity are more prevalent in the LPV group (Table 3).

3.2. Results from Logistic Regression Analysis

Independent risk factors for LPV were age (odds ratio [OR] = 0.974, 95% confidence interval [CI] = 0.96–0.99), LA cartridge (OR = 2.417, 95% CI = 1.7–3.2), hypertension (OR = 1.896, 95% CI = 1.07–3.5), and dental treatment phobia (OR = 1.74, 95% CI = 1.07–3.03) (Table 4). All clinical characteristics were included as variables in logistic regression analysis using the backward stepwise likelihood method. The probability of exhibiting LPV

increased 2.4-fold for every additional LA cartridge used. Patients with hypertension and dental treatment phobia have a likelihood of more than 1.5 times to establish LPV. However, increasing age was found to be less likely to experience LPV.

Table 3. Descriptive and univariate analysis of medical history variables from overall reviewed cases.

Variables [1]	Descriptive Analysis	Univariate Analysis		
	Overall Cases (*n* = 485)	LPV (*n* = 357)	SPV (*n* = 128)	*p* Value
Hypertension	128 (26.4%)	77 (60.2%)	51 (39.8%)	<0.001 *
Cardiac disease	21 (4.3%)	11 (52.4%)	10 (47.6%)	0.024 *
Hepatitis C	2 (0.4%)	0 (0%)	2 (1.6%)	0.018 *
Cerebral hemorrhage	3 (0.6%)	3 (100%)	0 (0%)	0.298
Cerebral infarction	3 (0.6%)	2 (66.7%)	1 (33.3%)	0.784
Epilepsy	10 (2.1%)	7 (70%)	3 (30%)	0.794
Depression	15 (3.1%)	11 (73.3%)	4 (26.7%)	0.98
Other mental illness	44 (9.1%)	32 (72.7%)	12 (27.3%)	0.69
Asthma	47 (9.7%)	36 (76.6%)	11 (23.4%)	0.619
Emphysema	2 (0.4%)	1 (50%)	1 (50%)	0.448
Other respiratory disease	18 (3.7%)	14 (77.8%)	4 (22.2%)	0.683
Liver/biliary tract disease	1 (0.2%)	1 (100%)	0 (0%)	0.549
Kidney/urinary disease	10 (2.1%)	7 (70%)	3 (30%)	0.797
Obesity [2]	62 (12.7%)	39 (62.9%)	23 (37.1%)	0.041 *
Diabetes	21 (4.3%)	12 (57.2%)	9 (42.8%)	0.08
Other metabolic disease	10 (2.1%)	9 (90%)	1 (10%)	0.235
Gynecological disease	7 (1.4%)	6 (85.7%)	1 (14.3%)	0.464
Dental treatment phobia	214 (44.1%)	156 (72.9%)	58 (27.1%)	0.711
Glaucoma	20 (4.1%)	13 (65%)	7 (35%)	0.372
Hyperactive pharyngeal reflex	46 (9.5%)	32 (69.6%)	14 (30.4%)	0.513
Hyperlipidemia	45 (9.3%)	30 (66.7%)	15 (33.3%)	0.267
Autoimmune disease	13 (2.7%)	12 (92.3%)	1 (7.7%)	0.121
Vasovagal syncope	11 (2.3%)	7 (63.6%)	4 (36.4%)	0.448
Alcohol consumption	141 (29.1%)	103 (73%)	38 (27%)	0.833
Smokers	42 (8.6%)	33 (78.6%)	9 (21.4%)	0.458

* Indicates statistically significant variables $p < 0.05$. Data shown as counts (percent). [1] Medical history are not mutually exclusive because patients can have more than one criterion. [2] body mass index over than 25. Abbreviations: LPV = large pulse wave transit time variability group; SPV = small pulse wave transit time variability group.

Table 4. Logistic regression analysis on clinical characteristic toward LPV.

Characteristics	*B* (sd)	Odds Ratio (95% CI)	*p* Value
Age (years)	−0.025 (0.009)	0.974 (0.96–0.99)	0.006 *
Local anesthesia cartridge (1.8 mL)	0.868 (0.158)	2.417 (1.7–3.2)	<0.001 *
Hypertension (Yes)	0.663 (0.303)	1.896 (1.07–3.5)	0.028 *
Dental treatment phobia (Yes)	0.591 (0.264)	1.74 (1.07–3.03)	0.025 *
Constant	−0.614 (1.221)	0.541 (-)	0.615

* Indicates statistically significant variables $p < 0.05$. Abbreviations: HR = heart rate; LPV = large pulse wave transit time variability group.

Supplementary Analysis

Based on the result that PWTT varies significantly in response to increased LA use, which means increased epinephrine use, we decided to perform an additional analysis of the cut-off values of epinephrine dose at which the PWTT changed by >15 ms, using the receiver operating characteristic curve analysis and Youden index. The results showed that at a dose of 36.25 μg of epinephrine, the PWTT began to fluctuate for >15 ms (Youden index: 1.281, sensitivity: 69.5%) (Figure 3).

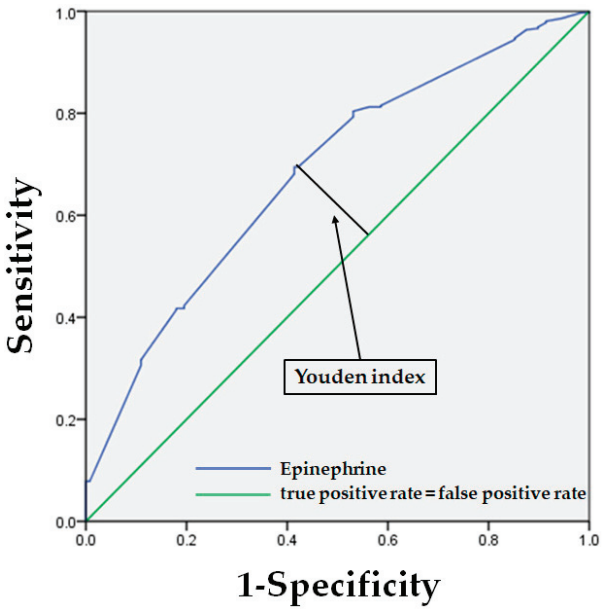

Figure 3. Receiver operating characteristic curves representing epinephrine cut-off value with Youden index.

As a post-hoc analysis, the relationship between ΔPWTT and ΔSBP was determined using Spearman's correlation. This analysis showed a statistically significant positive correlation between PWTT variability and SBP change ($r_s = 0.196$, $p < 0.001$) (Supplementary Table S1).

Furthermore, we used a multiple regression model to confirm the association of ΔPWTT with clinical characteristics, using the same data to confirm the factors influencing ΔPWTT obtained from the logistic regression analysis. Age, LA cartridge, respiratory disease, and phobia were statistically significant factors for PWTT variability (Supplementary Table S2).

4. Discussion

The main outcome of our study was the early detection of changes in BP because of large changes in PWTT. The vital monitor used in this study triggers NIBP measurement in situations when a variation in PWTT of >15 ms is detected and the estimated SBP (a PWTT variation of >15 ms is defined as a 20 mmHg increase in SBP) remains above the alarm limit for more than 8 s [12]. Although we used only this PWTT variation (PWTT variability > 15 ms) as our threshold, it was not sufficient to detect BP changes in this study. A previous study found that PWTT was related to stroke volume (SV) but a change in BP was not related to SV [15]. Therefore, a large PWTT variability that occurs under stimulation does not always reflect BP changes. Another possibility is that because NIBP measurement takes at least 10 s, PWTT changes > 15 ms may reflect NIBP changes only if the change lasts for a certain period of time. However, the association between PWTT and BP changes exists because we found significant positive correlation between PWTT variability and SBP changes from our supplementary analysis (data was not presented, available as Supplementary Materials). Even the slightest PWTT change might reflect changes in SBP; therefore, smaller PWTT thresholds can be considered for detecting BP fluctuations. However, a small change might be an excessive trigger, and it is necessary to reconsider whether these BP fluctuations are clinically meaningful.

We conducted a logistic regression analysis to identify factors related to LPV during dental procedures performed under IVCS and found that increased LA use, younger age, hypertension, and phobia were independent clinical characteristics. As a validation,

multiple regression analysis was performed, and the results were similar to those of logistic regression analysis. These results raised the certainty that ΔPWTT increased with the amount of LA that was administered and presence of dental treatment phobia and decreased with factors such as advanced age, which means that these factors were related to the vessel wall compliance. PWTT reflects vessel wall compliance and is influenced by vascular resistance but not cardiac output [16]. Briefly, epinephrine in local anesthetics changes the somatic vascular resistance via α-action, resulting in increased vascular resistance and shortened PWTT. Moreover, epinephrine increases the HR and SV of the heart, leading to an increase in the cardiac output because of the action on β-adrenergic receptors. However, β-receptor stimulation with low doses of epinephrine dilate arterial vessels in the visceral and skeletal muscles, resulting in lower vascular resistance [17]. This suggests that the increase in BP because of α-action can be attenuated by the β-action. Therefore, the administration of local anesthetics may cause changes in PWTT but may not reflect changes in BP. This may be one of the reasons why we did not find a statistically significant difference between the LPV and ΔSBP in our study.

Vessel wall contraction affects systemic vascular resistance, which is one of the factors that defines BP [18]. However, variations in PWTT associated with local anesthetic injections may reflect not only peripheral vasoconstriction but also SV, i.e., the entire hemodynamic change. Therefore, an additional analysis was performed to determine the cut-off dose of epinephrine, which revealed that a dose of 36.25 μg of epinephrine was the cut-off value. One milliliter of 2% lidocaine with 1:80,000 epinephrine solution contains 12.5 μg of epinephrine, which is approximately equivalent to three 1.8 mL LA cartridges at this cut-off value. Previous studies have indicated that 18–36 μg of epinephrine may have little clinical change in most patients, including those with hypertension or other cardiac diseases, but ≥36 μg epinephrine may have some effect on the circulating system by significantly increasing SV and cardiac output [19–21]. An increase in SV also increases pulse wave propagation; therefore, a large PWTT variability is expected to occur [15]. LPV may not reflect BP changes but may reflect hemodynamic changes that are not reflected in BP.

The incidence of LPV increased in hypertension. A previous study reported that pulse pressure and PWTT are associated with vasoconstriction in adults [22]. Aortic compliance in hypertensive patients decreases with age, resulting in an increase in pulse pressure and SBP, whereas peripheral vessel wall compliance remains relatively unchanged [23]. A higher pulse pressure may lead to a more pronounced anterior pulse pressure wave toward peripheral sites, which is larger in amplitude and steeper in pulse wave elevation, indicating a steeper increase in PWTT [24]. Moreover, under stimuli such as epinephrine, hypertension does not alter peripheral compliance, but decreases the aortic wall compliance. Therefore, hypertension may show large PWTT variability.

Dental treatment phobia in this study was defined as patients who feel fear or anxiety of undergoing dental treatment, which patients usually do not feel. A psychological experiment reported a strong correlation between PWTT and stress [25]. Patients with dental phobia may exhibit increased respiratory rate, HR, vasoconstriction, and BP [26]. These reactions are caused by the activation of the sympathetic nervous system and hormone release, such as epinephrine, which increases PWTT variability. Endogenous release of catecholamines, specifically epinephrine, increases 20–40 times under stress, including anxiety, compared with normal conditions [27]. Circulating epinephrine has been implicated as a contributor to embedding non-conscious emotional memories of fearful or threatening events in the amygdala [28]. When emotional memory is embedded too strongly in the amygdala, it can produce a heightened fear response to external events that is out of proportion to the actual nature of the problems, such as patients with a history of very painful dental treatment developing dental phobia [29]. Since emotional memories stored in the amygdala cannot be consciously controlled, it can be difficult to eradicate or regulate events perceived as stressors. This memory triggers a chronic fear response and places the brain, body, and mind in a constant state of alertness, resulting in a greater release of epinephrine [30]. Endogenous epinephrine in patients with dental phobia may remain in

the body after receiving IVCS, and subsequent administration of LA immediately activates β1 receptors, thereby increasing the intensity of vascular wall contraction [31]. Therefore, large fluctuations in PWTT are likely to occur in patients with dental phobia.

The incidence of LPV is lower in the older population. Repetitive contraction-relaxation with aging is thought to change vessel wall properties, reducing the elastic fibers of the vessel wall [32]. A decrease in vascular wall compliance should result in large PWTT fluctuations during vasoconstrictor stimulation; however, the reason for the opposite result in this study is unclear.

In this study, we found that the threshold of PWTT variations of >15 ms did not reflect changes in NIBP. However, on the basis of the association of ΔPWTT with ΔSBP and the epinephrine cut-off values, it is possible that PWTT variability can detect early hemodynamic changes after the administration of epinephrine-containing LA. Since PWTT is substantially influenced by vessel wall compliance and peripheral arterial resistance, PWTT may reflect fluctuations in not only the blood pressure but also in the circulation following administration of LA. Further, PWTT fluctuations can be observed noninvasively using conventional vital sign measurements. PWTT measurement remains a potential simple and affordable alternative to systemic vascular resistance measurements in patients with systemic diseases who receive dental treatment [33].

This study has certain limitations. The main limitation of this study was its retrospective nature, which makes it susceptible to selection bias. Although we attempted to control for confounding factors by collecting data in a comprehensive manner, there may still be unknown biases, such as differences in surgical management, consciousness level, or sedative agents used. Second, there is a disparity in the interval between LA administration and BP measurement in our study. In addition, we did not classify the arterial stiffness or identify related factors that may have significantly affected the PWTT. Future prospective studies must consider these factors and the measurement of parameters, including PWTT and vital signs, at the same time points.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11143963/s1, Table S1: Spearman's correlation analysis of ΔPWTT and ΔSBP; Table S2: Multiple regression of ΔPWTT with clinical characteristics.

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References

1. Newlin, D.B. Relationships of Pulse Transmission Times to Pre-ejection Period and Blood Pressure. *Psychophysiology* **1981**, *18*, 316–321. [CrossRef] [PubMed]
2. Cassidy, J.P.; Phero, J.C.; Grau, W.H. Epinephrine: Systemic Effects and Varying Concentrations in Local Anesthesia. *Anesth. Prog.* **1986**, *33*, 289–297. [PubMed]

3. Lewington, S.; Clarke, R.; Qizilbash, N.; Peto, R.; Collins, R.; Prospective Studies Collaboration. Age-Specific Relevance of Usual Blood Pressure to Vascular Mortality: A Meta-analysis of Individual Data for One Million Adults in 61 Prospective Studies. *Lancet* **2002**, *360*, 1903–1913. [CrossRef] [PubMed]
4. Elmatite, W.; Mangla, C.; Upadhyay, S.; Yarmush, J. Perioperative Automated Noninvasive Blood Pressure-(NIBP-) Related Peripheral Nerve Injuries: An Anesthetist's Dilemma-A Case Report and Review of the Literature. *Case Rep. Anesthesiol.* **2020**, *2020*, 5653481. [CrossRef]
5. Meidert, A.S.; Saugel, B. Techniques for Non-invasive Monitoring of Arterial Blood Pressure. *Front. Med.* **2017**, *4*, 231. [CrossRef]
6. Schaanning, S.G.; Skjaervold, N.K. Rapid Declines in Systolic Blood Pressure Are Associated with an Increase in Pulse Transit Time. *PLoS ONE* **2020**, *15*, e0240126. [CrossRef]
7. Ochiai, R.; Takeda, J.; Hosaka, H.; Sugo, Y.; Tanaka, R.; Soma, T. The Relationship Between Modified Pulse Wave Transit Time and Cardiovascular Changes in Isoflurane Anesthetized Dogs. *J. Clin. Monit. Comput.* **1999**, *15*, 493–501. [CrossRef]
8. Smith, R.P.; Argod, J.; Pépin, J.L.; Lévy, P.A. Pulse Transit Time: An Appraisal of Potential Clinical Applications. *Thorax* **1999**, *54*, 452–457. [CrossRef]
9. Liu, X.N.; Gao, H.Q.; Li, B.Y.; Cheng, M.; Ma, Y.B.; Zhang, Z.M.; Gao, X.; Liu, Y.; Wang, M. Pulse Wave Velocity as a Marker of Arteriosclerosis and Its Comorbidities in Chinese Patients. *Hypertens. Res.* **2007**, *30*, 237–242. [CrossRef]
10. Liang, Y.; Abbott, D.; Howard, N.; Lim, K.; Ward, R.; Elgendi, M. How Effective Is Pulse Arrival Time for Evaluating Blood Pressure? Challenges and Recommendations from a Study Using the MIMIC Database. *J. Clin. Med.* **2019**, *8*, 337. [CrossRef]
11. Yoneda, B.; Zuiki, M.; Komatsu, H. Utility of Pulse Wave Transit Time to Detect Blood Pressure Changes in Neonates. *J. Jpn. Soc. Perinat. Neonatal Med.* **2021**, *57*, 334–338. [CrossRef]
12. Hiroko, I.; Takehiko, I.; Makoto, T.; Yasuhide, I.; Yoshihiro, S.; Katana, K. Examining the Effectiveness of NIBP Blood Pressure Measurement Using PWTT. In Proceedings of the Japanese Association for Clinical Monitoring, Yokohama, Japan, 17–21 November 2002; p. 41.
13. Examination Committee of Criteria for 'Obesity Disease' in Japan. Japan Society for the Study of Obesity New Criteria for 'Obesity Disease' in Japan. *Circ. J.* **2002**, *66*, 987–992. [CrossRef] [PubMed]
14. Takakura, M.; Miyagi, M.; Kyan, A. Time Trends of Socioeconomic Inequalities in Adolescent Smoking in Okinawa, Japan, 2008–2016: A Repeated Cross-Sectional Study. *Environ. Health Prev. Med.* **2021**, *26*, 24. [CrossRef]
15. Ishihara, H.; Tsutsui, M. Impact of Changes in Systemic Vascular Resistance on a Novel Non-invasive Continuous Cardiac Output Measurement System Based on Pulse Wave Transit Time: A Report of Two Cases. *J. Clin. Monit. Comput.* **2014**, *28*, 423–427. [CrossRef] [PubMed]
16. Tsutsui, M.; Araki, Y.; Masui, K.; Kazama, T.; Sugo, Y.; Archer, T.L.; Manecke, G.R., Jr. Pulse Wave Transit Time Measurements of Cardiac Output in Patients Undergoing Partial Hepatectomy: A Comparison of the esCCO System with Thermodilution. *Anesth. Analg.* **2013**, *117*, 1307–1312. [CrossRef] [PubMed]
17. Sturgill, M.G.; Kelly, M.; Notterman, D.A. Pharmacology of the Cardiovascular System. In *Pediatric Critical Care*, 4th ed.; Elsevier: Philadelphia, PA, USA, 2011; pp. 277–305.
18. Trammel, J.; Sapra, A. Physiology, Systemic Vascular Resistance. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
19. Niwa, H.; Sugimura, M.; Satoh, Y.; Tanimoto, A. Cardiovascular Response to Epinephrine-Containing Local Anesthesia in Patients with Cardiovascular Disease. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* **2001**, *92*, 610–616. [CrossRef]
20. Stratton, J.R.; Pfeifer, M.A.; Ritchie, J.L.; Halter, J.B. Hemodynamic Effects of Epinephrine: Concentration-Effect Study in Humans. *J. Appl. Physiol.* **1985**, *58*, 1199–1206. [CrossRef]
21. Wakita, R.; Ito, T.; Fukayama, H. Small Doses of Adrenaline Contained in The Local Anaesthetic may Result in Prolonged Increased Cardiac Function Even after The Vital Signs Return to Normal. *Adv. Oral Maxillofac. Surg.* **2021**, *3*, 100–104. [CrossRef]
22. Mol, A.; Meskers, C.G.M.; Niehof, S.P.; Maier, A.B.; van Wezel, R.J.A. Pulse Transit Time as a Proxy for Vasoconstriction in Younger and Older Adults. *Exp. Gerontol.* **2020**, *135*, 110938. [CrossRef]
23. Kimoto, E.; Shoji, T.; Shinohara, K.; Inaba, M.; Okuno, Y.; Miki, T.; Koyama, H.; Emoto, M.; Nishizawa, Y. Preferential Stiffening of Central over Peripheral Arteries in Type 2 Diabetes. *Diabetes* **2003**, *52*, 448–452. [CrossRef]
24. Pagoulatou, S.; Adamopoulos, D.; Rovas, G.; Bikia, V.; Stergiopulos, N. Acute and Long-Term Effects of Aortic Compliance Decrease on Central Hemodynamics: A Modeling Analysis. *Front. Physiol.* **2021**, *12*, 701154. [CrossRef] [PubMed]
25. Hey, S.; Gharbi, A.; Haaren, B.v.; Walter, K.; König, N.; Löffler, S. Continuous Noninvasive Pulse Transit Time Measurement for Psychophysiological Stress Monitoring. In Proceedings of the International Conference on Ehealth, Telemedicine, and Social Medicine, Cancun, Mexico, 1–7 February 2009; pp. 113–116. [CrossRef]
26. Susilo, C.W.; Fauziah, E. Respiratory Rate as a Physiological Response to Dental Anxiety. In Proceedings of the 11th International Dentistry Scientific Meeting, Jakarta, Indonesia, 16–17 September 2018. [CrossRef]
27. Dionne, R.A.; Goldstein, D.S.; Wirdzek, P.R. Effects of Diazepam Premedication and Epinephrine-Containing Local Anesthetic on Cardiovascular and Plasma Catecholamine Responses to Oral Surgery. *Anesth. Analg.* **1984**, *63*, 640–646. [CrossRef] [PubMed]
28. McGaugh, J.L. The Amygdala Modulates the Consolidation of Memories of Emotionally Arousing Experiences. *Annu. Rev. Neurosci.* **2004**, *27*, 1–28. [CrossRef] [PubMed]
29. Glannon, W. Psychopharmacology and Memory. *J. Med. Ethics.* **2006**, *32*, 74–78. [CrossRef]
30. Tank, A.W.; Lee Wong, D. Peripheral and Central Effects of Circulating Catecholamines. *Compr. Physiol.* **2015**, *5*, 1–15. [CrossRef]

31. Motiejunaite, J.; Amar, L.; Vidal-Petiot, E. Adrenergic Receptors and Cardiovascular Effects of Catecholamines. *Ann. Endocrinol.* **2021**, *82*, 193–197. [CrossRef] [PubMed]
32. Kim, H.L.; Kim, S.H. Pulse Wave Velocity in Atherosclerosis. *Front. Cardiovasc. Med.* **2019**, *6*, 41. [CrossRef] [PubMed]
33. Schneck, E.; Drubel, P.; Schürg, R.; Markmann, M.; Kohl, T.; Henrich, M.; Sander, M.; Koch, C. Evaluation of Pulse Wave Transit Time Analysis for Non-invasive Cardiac Output Quantification in Pregnant Patients. *Sci. Rep.* **2020**, *10*, 1857. [CrossRef]

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Cerebral Tissue Oxygen Saturation Correlates with Emergence from Propofol-Remifentanil Anesthesia: An Observational Cohort Study

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Abstract: Anesthesia emergence is accompanied by changes in cerebral circulation. It is unknown whether cerebral tissue oxygen saturation ($SctO_2$) could be an indicator of emergence. Changes in $SctO_2$, bispectral index (BIS), mean arterial pressure (MAP), and heart rate (HR) were evaluated during the emergence from propofol-remifentanil anesthesia. At the time of cessation of anesthetic delivery, $SctO_2$, BIS, MAP, and HR values were recorded as baseline. The changes of these parameters from the baseline were recorded as Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR. The behavioral signs (body movement, coughing, or eye opening) and response to commands (indicating regaining of consciousness) were used to define emergence states. Prediction probability (Pk) was used to examine the accuracy of $SctO_2$, BIS, MAP, and HR as indicators of emergence. $SctO_2$ showed an abrupt and distinctive increase when appearing behavioral signs. BIS, MAP, and HR, also increased but with a large inter-individual variability. Pk value of Δ $SctO_2$ was 0.97 to predict the appearance behavioral signs from 2 min before that, which was much higher than the Pk values of Δ BIS (0.81), Δ MAP (0.71) and Δ HR (0.87). The regaining of consciousness was associated with a further increase in the $SctO_2$ value.

Keywords: general anesthesia; cerebral tissue oxygen saturation; near-infrared spectroscopy; emergence

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1. Introduction

Emergence from anesthesia is the final stage of anesthesia with the transition from unconsciousness to wakefulness. Rapid and accurate identification of the emergence state is critical for patient safety and reducing the risk of anesthesia. In clinical practice, anesthesiologists conventionally assess the level of arousal based on the interpretation of clinical signs and symptoms [1]. However, the different experience and the subjectivity of the practitioners could bias the interpretation. In addition, medical conditions, such as motor dysfunction or psychiatric disorders, can also confuse decision-making based on clinical assessment [2,3]. A combination with objective techniques that indicate the state of arousal is therefore essential for a better control of anesthesia emergence and patient's wellbeing.

Currently, electroencephalogram (EEG)-derived brain monitors, such as Bispectral Index (BIS), SEDLine, entropy, narcotrend, and auditory evoked potential (AEP) are used to measure the anesthesia and emergence states [4–7]. Intraoperatively, monitoring of EEG response has been shown to improve the ability of anesthesiologists to titrate anesthetic

drugs and reduce the risk of awareness [8,9]. However, these monitoring systems have limitations when used to indicate the emergence from anesthesia [10]. First, EEG-based algorithms are poor at tracking rapid changes during emergence. BIS and AEP index have weak predictive power with respect to movement in response to noxious stimuli [11]. BIS and entropy showed wide inter-individual variability and thus did not reliably differentiate consciousness from unconsciousness [12]. Second, these EEG monitors do not reflect the hypnotic state consistently. Tiefenthaler et al. [13] have shown that only 20% of BIS, AEP index and entropy values simultaneously categorized the state of anesthesia and wakefulness.

The anesthesia emergence is associated with increased neural activities [14,15], increased cerebral metabolic rate of oxygen ($CMRO_2$), and increased cerebral blood flow (CBF) [16–18]. Currently, there are no clinical monitors that directly assess $CMRO_2$ and CBF. Instead, the $CMRO_2$-CBF balance can be monitored using cerebral oximetry based on near-infrared spectroscopy [19,20]. No studies have reported the change on cerebral tissue oxygen saturation ($SctO_2$) during emergence.

Neuronal activation alters the $CMRO_2$-CBF balance as it typically leads to a more pronounced increase in the CBF than in the $CMRO_2$ due to cerebral coupling [21–23]. Previous studies reported that the concentration of deoxyhemoglobin was reduced during emergence from general anesthesia [24,25], indicating that cerebral oxygen supply may exceed the oxygen extraction. Therefore, in this observational cohort study, we hypothesize that $SctO_2$ increases during anesthesia emergence. Our aim was to compare the pattern of $SctO_2$ change with that of BIS change during emergence from propofol-remifentanil anesthesia, and to evaluate whether $SctO_2$ could be an objective indicator of anesthesia emergence.

2. Methods

2.1. Study Design and Setting

This is an observational cohort study, which was conducted at Xiangya Hospital of Central South University from 15 April 2019 to 10 January 2020. All procedures of this study were approved by the Ethics Committee of Xiangya Hospital of Central South University (IRB No.201904111) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment on the Chinese Clinical Trial Registry (Ref: ChiCTR1900021122, Principal investigator: Changsheng Huang, Date of registration: 29 January 2019). The work has been reported in line with the STROCSS criteria [26].

2.2. Participants

Patients who (1) were going to undergo general anesthesia and patients whose (2) age were 18 yr or older, and (3) ASA classification ranged from I to III were included. Patients who (1) had severe intraoperative organ failure requiring rescue, (2) were going to undergo craniocerebral surgery, (3) were unwilling to participate in the study or had participated in other clinical studies, (4) comorbid with serious diseases, and had a history of central nervous system diseases, cerebrovascular disease, cognitive impairment, mental disorders, and communication disorders were excluded. During the study, participants who had (1) postoperative agitation, (2) postoperative hypoxemia, (3) a deficiency of data and (4) medications that may affect the results (sedatives, central stimulants, etc.) after cessation of anesthetic delivery were eliminated.

2.3. Study Procedures

Anesthesia monitors were applied prior to the start of anesthetic delivery. The monitors included noninvasive blood pressure, electrocardiogram, pulse oximetric oxygen saturation (SpO_2), body temperature, BIS and $SctO_2$. The BIS VISTA monitor (Aspect Medical Systems, Newton, MA, USA) was used and the electrodes were placed on the left side of the patient's forehead in accordance with the manufacturer's instructions. The $SctO_2$ was monitored using a FORE-SIGHT Cerebral Oximeter (CAS Medical Systems,

Branford, CT, USA). The NIRS pads were placed on the right side of the patient's forehead directly over the eyebrow and the signal was adjusted to a full signal state [27] (Supplementary Figure S1).

Anesthesia was induced with midazolam 0.15 mg kg^{-1}, etomidate 0.3 mg kg^{-1}, sufentanil 0.5 μg kg^{-1} and cisatracurium 0.15 mg kg^{-1}, followed by endotracheal intubation. Anesthesia was then maintained using propofol 100–200 μg kg^{-1} min^{-1} and remifentanil 0.05–0.25 μg kg^{-1} min^{-1}. The rate of propofol administration during maintenance of anesthesia was adjusted to keep the BIS value between 40–60. To minimize the influence of residual paralysis on the evaluation of anesthesia recovery during the maintenance period, no muscle relaxants were used or the last injection of muscle relaxants was more than one hour before the end of the operation, provided that the anesthesia management has reached clinical needs.

At the end of the surgery, the delivery of anesthetics was stopped. The mechanical ventilation was kept at a fraction of inspiration oxygen (FiO_2) of 30%, and the ventilation parameters were adjusted to maintain the SpO_2 at 95–100% and the end-tidal carbon dioxide ($EtCO_2$) at 35–40 mmHg. The patients were carefully guarded without intentional disturbance until they showed spontaneously appearing behavioral signs, such as body movement, coughing and eye opening [28–30]. Once the behavioral signs were identified, the patients were tested to determine whether they regained consciousness or not. The regaining of consciousness was defined if the patients was arousable and able to respond to commands, including directed eye movements and hand shaking. The test was repeated at a 2 min interval until the patient regained consciousness. The patients were given neostigmine 0.04 mg kg^{-1} plus atropine 0.01 mg kg^{-1} to reverse residual neuromuscular block. The extubation was performed when the patients maintained $EtCO_2$ < 45 mm Hg and SpO_2 > 95% with spontaneous breathing room air.

The emergence period was defined as the time from the cessation of anesthetic delivery until the patient regained consciousness. At the beginning of emergence, the $SctO_2$, BIS, MAP and HR values were recorded as baseline values. They were continuously recorded thereafter at a 2 min interval during the emergence period. The changes of these parameters over the baseline values were recorded as Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR, as we described above. The Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR were compared at the following time-points during anesthesia emergence, 2 min before the appearance of behavioral signs, appearance of behavioral signs and regaining of consciousness.

2.4. Statistical Analysis

Based on the results of our previous observations, the difference of $SctO_2$ between "2 min before appearance of behavioral signs" and "Appearance of behavioral signs" to detect was 2.2, with a standard deviation of 7.5 in the "Appearance of behavioral signs" and an autocorrelation of 0.665. Therefore, a sample size of 190 was required with power of 90%, and a significance level of 0.05. Taking into account the possible 5% dropout rate, the total sample size required was 200. The "Test for Two Means in a Repeated Measures Design" mode of PASS 11 (NCSS, LIc., Kaysville, UT, USA) was used to perform these calculations.

Data were presented as mean ± SD (standard deviation) or numbers and percentages (%). All statistical analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 7.0 (GraphPad Software Inc., San Diego, CA, USA). Shapiro–Wilk test was used for evaluation of data distribution. To compare normally distributed variables between the two groups, independent *t*-test was used if their variances were equal (using Levene's test to assess the equality of variances), or Welch's *t*-test was used if their variances were not equal. To compare non-normally distributed variables between the two groups, Mann–Whitney U test was used. To compare variables between the two time points within one group of patients, paired *t*-test was used if the variables were normally distributed, and Wilcoxon matched pairs signed rank test was used if the variables were not normally distributed.

The accuracy of Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR to predict the appearance of behavioral signs ("appearance of behavioral signs" versus "2 min before appearance of behavioral signs") was analyzed with the prediction probability (Pk). Pk was calculated for all parameters using a custom spreadsheet macro, PKMACRO, as previously described [31]. A paired t-test was used for the comparison between Pk values of two monitors. A Pk value of 1 means that the value of the predicting variable always correctly predicts the variable to be predicted. A Pk value of 0.5 means that the indicator prediction is no better than chance alone. Pk and its standard error were estimated with the jack-knife method, based on the assumption that all assessments were independent. A receiver operating characteristic (ROC) curve and the associated areas under the curves (AUC) were generated to characterize the sensitivity and specificity of Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR in detecting the appearance of behavioral signs. The comparison between the AUC of ROC curves was performed by the method of DeLong test [32] using MedCalc v. 10.4.7.0 software (MedCalc Software bvba, Mariakerke, Belgium). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Study Population

A total of 218 patients were enrolled in this study. A total of 24 patients among them were eliminated due to data missing (14 patients) or due to hypoxemia or agitation during the period of emergence (10 patients). Eventually, 194 patients completed the study; in addition, 162 of them regained consciousness as soon as the behavioral signs appeared, and the other 32 patients regained consciousness later (Figure 1). The demographic characteristics, types of surgery, intraoperative medications and duration of anesthesia of the patients are shown in Table 1. During the anesthesia emergence, there were no consumption of sedatives, central stimulants, and vasoactive medications.

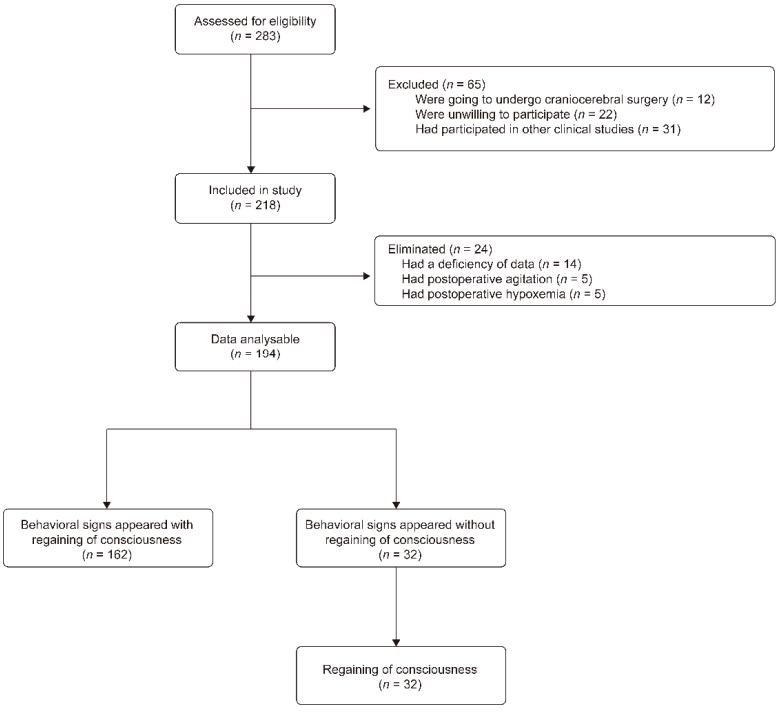

Figure 1. Flow chart of participants' screening and recruitment.

Table 1. Patients' demographic characteristics, types of surgery, intraoperative medications, and duration of anesthesia.

Characteristics	Patients (n = 194)
Age (y)	49.41 ± 12.39
Male, n (%)	91 (46.91)
BMI (kg $(m^{-2})^{-1}$)	23.03 ± 2.86
ASA classification, n (%)	
II	120 (61.86)
III	74 (38.14)
Comorbidities, n (%)	
Hypertension	55 (28.35)
Current smoker	54 (27.84)
Diabetes	29 (14.95)
Coronary artery disease	24 (12.37)
Asthma	21 (10.82)
Chronic obstructive pulmonary disease	12 (6.19)
Obesity [a]	5 (2.58)
Type of surgery, n (%)	
Head and neck	47 (24.23)
General	63 (32.47)
Gynecological	25 (12.89)
Thoracic	18 (9.28)
Orthopedic	8 (4.12)
Spinal	7 (3.61)
Vascular	7 (3.61)
Plastic	5 (2.58)
Other	14 (7.21)
Intraoperative medications	
Midazolam (mg)	7.20 ± 1.99
Sufentanil (μg)	36.88 ± 9.55
Cisatracurium (mg)	16.62 ± 3.80
Etomidate (mg)	22.40 ± 14.60
Propofol (mg kg^{-1})	17.75 ± 9.44
Remifentanil (μg kg^{-1})	25.88 ± 13.84
Duration of anesthesia (min)	134.39 ± 67.20

Values are mean ± SD or numbers and percentages (%). BMI, body mass index; ASA, American Society of Anesthesiologists. [a] Defined as body mass index greater than 30.

3.2. Appearing of Behavioral Signs during Emergence Is Associated with an Abrupt and Distinctive Increase in $SctO_2$ Value

At the beginning of anesthesia emergence, the baseline value of $SctO_2$ was 70 ± 6% and it remained stable during the early stage of anesthesia emergence before the behavioral signs appeared. The Δ $SctO_2$ at 2 min before behavioral signs appeared was 0 ± 1%. At the moment of the appearance of behavioral signs, the Δ $SctO_2$ was 6 ± 3%, which was significantly higher than 2 min before that ($p < 0.001$), demonstrating an abrupt and distinctive increase in $SctO_2$ value within such a short interval (Table 2). Multivariable linear regression analyses showed that there was no association of $SctO_2$ with MAP, HR, SpO_2, or $EtCO_2$ (Supplementary Table S1).

The baseline values of BIS, MAP, and HR are shown in Table 2. At the moment when behavioral signs appeared, the Δ BIS, Δ MAP, and Δ HR were higher than the values 2 min before, although with a large inter-individual variability among the patients ($p < 0.001$, Table 2). The Δ $SctO_2$ showed no correlation with Δ MAP or Δ HR (Supplementary Figure S2), further demonstrating that the $SctO_2$ value was changed independently of the hemodynamic alterations during the emergence.

Table 2. Physiological values from the beginning of emergence to the appearance of behavioral signs.

	Baseline *	Changes over Baseline #		
		2 Min before Appearance of Behavioral Signs &	Appearance of Behavioral Signs	*p* Values $
$SctO_2$ (%)	70 ± 6	0 ± 1	6 ± 3	<0.001
BIS	65 ± 8	6 ± 6	16 ± 9	<0.001
MAP (mmHg)	89 ± 13	1 ± 5	5 ± 7	<0.001
HR (bpm)	60 ± 10	1 ± 5	13 ± 10	<0.001

Data are mean ± SD. $SctO_2$, cerebral tissue oxygen saturation; BIS, bispectral index; MAP, mean arterial pressure; HR, heart rate. * "Baseline" refers to the values of $SctO_2$, BIS, MAP and HR recorded at the beginning of emergence. # "Changes over baseline" refers to the difference between the values of $SctO_2$, BIS, MAP and HR at 2 min before the appearance of behavioral signs or at the moment of appearance of behavioral signs and the baseline values of each variable. & "Behavioral signs" refers to the first appearance of behavioral signs indicating emergence, including body movement, coughing or eye opening. $ The value changes of $SctO_2$, BIS, MAP and HR at "2 min before appearance of behavioral signs" versus "appearance of behavioral signs", $p < 0.001$, using Wilcoxon matched-pairs signed rank test.

3.3. $SctO_2$ Is a Prompt and More Reliable Indicator of Appearing Behavioral Signs during Anesthesia Emergence Than BIS, MAP, and HR

The distinctive increase in $SctO_2$ associated with the appearance of behavioral signs was prominent and could easily be identified in the output graph of the $SctO_2$ monitor (Figure 2A). In contrast, the increase in BIS value at the appearance of behavioral signs was not particularly different when compared with other time points, since the BIS value rose in a relatively steady pattern during the whole process of anesthesia emergence (Figure 2B). Of the total of 194 patients investigated, 193 of them showed an increase in the $SctO_2$ value at the appearance of behavioral signs compared to 2 min before the behavioral signs appeared (Figure 2C), indicating that the increase in $SctO_2$ at the moment of the appearance of behavioral signs was a rather universal phenomenon during the emergence from general anesthesia. However, the changes in individual BIS values were not as consistent as $SctO_2$ when behavioral signs appeared (Figure 2D). Using Pk analysis to evaluate the ability to predict the appearance of behavioral signs based on the changes of these parameters 2 min before, the Pk score of Δ $SctO_2$ was 0.97, which was much higher than Δ BIS (Pk: 0.81), Δ MAP (Pk: 0.72), and Δ HR (Pk: 0.87) ($p < 0.001$, Table 3). The same results were obtained using the ROC analysis and the subsequent DeLong test (Table 3, Supplementary Figure S3). These results demonstrated that $SctO_2$ is a prompt and more reliable indicator of anesthesia emergence than BIS, MAP, and HR, within a 2 min interval before behavioral signs appear.

Table 3. Prediction performance of the four parameters for the appearance of behavioral signs.

	Pk	SE	AUC	95% CI
Δ $SctO_2$	0.97	0.01	0.97	0.95–0.99
Δ BIS	0.81 ***	0.02	0.81 ###	0.77–0.85
Δ MAP	0.72 ***	0.03	0.72 ###	0.67–0.76
Δ HR	0.87 ***	0.02	0.87 ###	0.83–0.90

Pk, prediction probability; SE, standard error; AUC, the associated areas under the receiver operating characteristic (ROC) curves; CI, confidence interval. Δ $SctO_2$, Δ BIS, Δ MAP, and Δ HR refer to the changes of $SctO_2$, BIS, MAP, and HR values over the baseline value of each parameter. The accuracy of Δ $SctO_2$ to predict the appearance of behavioral signs ("appearance of behavioral signs" versus "2 min before appearance of behavioral signs") was higher than that of Δ BIS, Δ MAP, and Δ HR, *** $p < 0.001$, Pk analysis followed by paired *t*-test; ### $p < 0.001$, ROC analysis followed by DeLong test.

We further investigated the changes of $SctO_2$, BIS, MAP and HR in the patients who received a certain type of surgery, including general surgery ($n = 63$), head and neck surgery ($n = 47$) and gynecological surgery ($n = 25$) (Supplementary Table S2), and evaluated the performance of these parameters in predicting anesthesia emergence. The Pk score of Δ $SctO_2$ to predict the appearance of behavioral signs was 0.96 in general surgery patients, 0.99 in head and neck surgery patients and 0.97 in gynecological surgery patients, which were much higher than that of Δ BIS, Δ MAP, and Δ HR ($p < 0.001$, Supplementary Table S3).

Although we did not evaluate the changes of these parameters in the patients who received other types of surgery due to the small number, our results suggested that the increase in $SctO_2$ is a common phenomenon during anesthesia emergence. The $SctO_2$ indicated the appearance of behavioral signs regardless of the type of surgery the investigated patients received in our study.

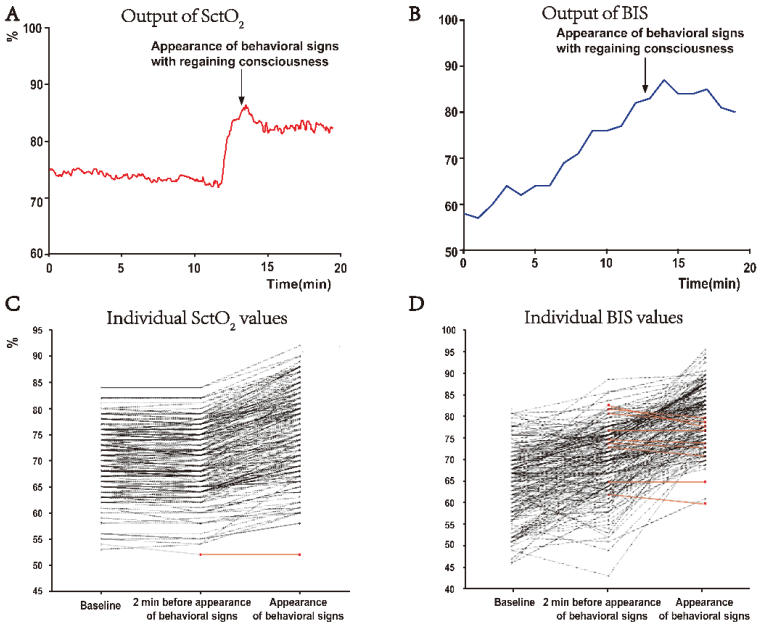

Figure 2. Changes of $SctO_2$ and BIS values from baseline to the appearance of behavioral signs. (**A**,**B**) Representative graphs of monitor output of $SctO_2$ and BIS. At the moment of appearing behavioral signs, the $SctO_2$ value had an obvious peak increase (**A**). The BIS value increased in a relatively stable manner during the emergence period, and there was no special change when the patient had behavioral signs (**B**). (**C**,**D**) Changes of individual $SctO_2$ and BIS values (n = 194). $SctO_2$ value remained relatively stable from the baseline to 2 min before the appearance of behavioral signs, while it was increased in almost every patient when the behavioral signs were appeared (**C**). Changes of BIS value from baseline to the appearance of behavioral signs showed large inter-individual variations (**D**). The black lines represent individual $SctO_2$ or BIS values, which were increased at the moment when the behavioral signs appeared compared to 2 min before, while the red lines represent the individual values decreased or unchanged during this interval.

3.4. The $SctO_2$ Is Further Increased from the Appearance of Behavioral Signs to the Regaining of Consciousness

The 162 patients who regained consciousness as soon as the behavioral signs appeared and the other 32 patients who did not regain consciousness at the same time showed no differences in their demographics, intraoperative medications or duration of anesthesia (Supplementary Table S4). However, at the moment of the appearance of behavioral signs, the Δ $SctO_2$ was higher in the group of the 162 patients who regained consciousness than in the group of the 32 patients who did not regain consciousness ($p < 0.001$, Figure 3A). In these 32 patients, the consciousness returned in 8.25 $\pm$ 6.87 min after the onset of behavioral signs. Interestingly, within these patients, the Δ $SctO_2$ was higher at the moment of regaining consciousness than at the moment when only the behavioral signs appeared ($p < 0.01$, Figure 3B). Multivariable linear regression analyses showed that the $SctO_2$ was not associated with MAP, HR, SpO_2, or $EtCO_2$ (Supplementary Table S1). These results further indicate that the increase in $SctO_2$ correlated with the process of emergence.

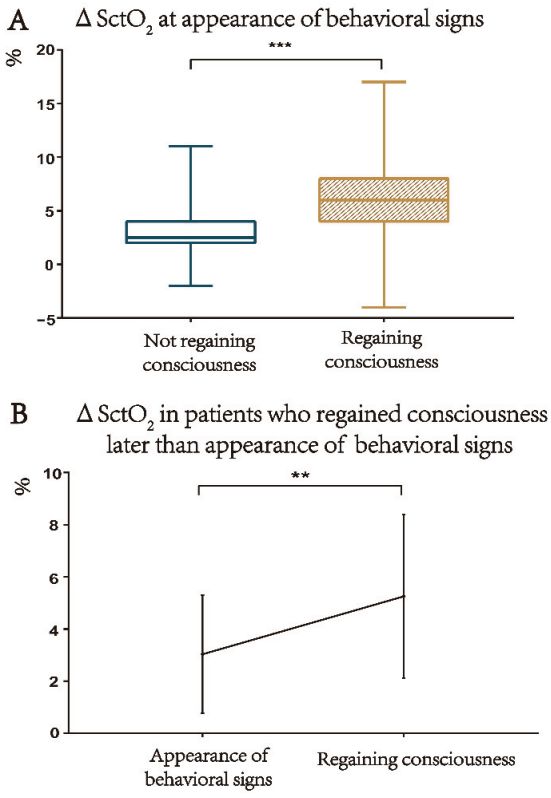

Figure 3. Increase in $SctO_2$ value is related to regaining of consciousness. (**A**) At the moment of the appearance of behavioral signs, the change of $SctO_2$ over the baseline (Δ $SctO_2$) was higher in the patients who also regained consciousness (n = 162) than those who did not regain consciousness (n = 32), *** $p < 0.001$, Mann–Whitney U test. (**B**) Within the 32 patients who regained consciousness later than the appearance of the behavioral signs, the Δ $SctO_2$ was higher at the moment of regaining consciousness than at the moment of behavioral sign appearance, ** $p < 0.01$, paired t-test.

4. Discussion

In this study, we identified an abrupt and distinctive increase in $SctO_2$ as soon as the patient showed behavioral signs during the emergence from propofol-remifentanil anesthesia. The BIS, MAP, and HR values were also increased, but with a relatively high inter-individual variability at the appearance of behavioral signs. The measurement of $SctO_2$ showed a higher accuracy to predict anesthesia emergence than that of BIS, MAP, and HR, within a 2 min interval prior to the appearance of behavioral signs. The regaining of consciousness was associated with a higher $SctO_2$ value than when only behavioral signs appeared, indicating a relationship between the increase in $SctO_2$ and the recovery of consciousness after general anesthesia.

$SctO_2$ monitoring has been extensively used to provide an index of organ ischemia [20]. This study shows for the first time that $SctO_2$ could be an indicator of anesthesia emergence. $SctO_2$ remained stable during the early stage of emergence and was not changed until the behavioral signs appeared. The abrupt and distinctive increase in $SctO_2$ associated with the appearance of behavioral signs could be easily identified by the anesthesia practitioners via the monitor, and then the assessment for extubation could be conducted timely, thus contributing to early tracheal extubation and less man-machine counteraction. In clinical practice, anesthesiologists tend to use behavioral signs to determine the timing

of extubation. However, in some settings, especially when caring for multiple patients awaiting anesthetic awakening and extubation (e.g., in a post-anesthesia care unit), anesthesiologists sometimes do not detect behavioral signs in a timely manner. Therefore, a sudden increase in $SctO_2$ can be a more effective indicator of patient awakening because it is more visible than behavioral signs. Moreover, the increase in $SctO_2$ during emergence was a common phenomenon and was not influenced by the type of surgery. We further showed that changes in the $SctO_2$ value were not related to changes in hemodynamic parameters including MAP and HR. This is consistent with previous reports showing that the emergence-related changes in cerebral circulation were not related to the systemic hemodynamic changes [33]. Taken together, our results suggest that $SctO_2$ could be a prompt and reliable indicator of emergence from anesthesia. However, it should be noticed that several factors may influence cerebral oxygen transport and oxygen saturation including hematocrit, inspiratory oxygenation, and ventilation [34,35]. It is essential to maintain a stable concentration of hemoglobin, FiO_2, SpO_2, and $EtCO_2$ when using the $SctO_2$ to assess the emergence from anesthesia.

The BIS, MAP and HR showed patterns of changes which were different from that of $SctO_2$ during emergence. BIS values were progressively increased from the beginning of emergence and there was no distinctive change at any state of the emergence period. Moreover, the changes of BIS showed a relatively large inter-individual differences among the patients. Thus, different from the increase in $SctO_2$ which indicated the behavioral signs within a 2 min interval, the change of BIS did not rapidly and reliably reflect the transition of emergence state [10,36]. The changes of MAP and HR also showed large individual differences during the emergence, probably due not only to the influence of anesthetics, but also to many other clinical factors that can cause systemic hemodynamic changes [37–39].

It has been accepted that anesthesia emergence does not establish at once but in a bottom-up manner [40]. After ceasing anesthetics, there will be a slow return of brainstem reflexes, eventually leading to uncoordinated body movements that occur shortly before subjects regain consciousness [40,41]. We showed that the regaining of consciousness was associated with a higher $SctO_2$ value than when only behavioral signs appeared. This result further indicates that the increase in $SctO_2$ correlated with the process of emergence. However, the emergence from anesthesia involves a complex interplay of different brain regions that can show different changes in neuronal activity and circulation [17]. Furthermore, it is possible that the NIRS only reflects the $SctO_2$ change in the prefrontal cortex [42,43]. Thus, further studies are needed to better understand the details of cerebral oxygen saturation changes during anesthesia emergence.

The following limitations of the present study should be noted. First, the neuromuscular function was not monitored by the train-of-four during the emergence period. In order to minimize the residual effects of muscle relaxant during the emergence, we included the patients who did not receive muscle relaxant during anesthesia maintenance or who received the last injection of muscle relaxant more than one hour before the end of surgery. However, the potential confounding role of muscle relaxants still could not to be ruled out when evaluating the physical and behavioral signs during the emergence. Second, the data of pre-anesthesia induction and during deep anesthesia state were not collected in the present study. Considering that induction and emergence from general anesthesia are not mirror opposite processes [12,44], we focused on the evaluation of emergence process. The baseline of data was set at the beginning of emergence. This might be appropriate for the measurement of $SctO_2$ which remained stable during the early period of emergence before the appearance of behavioral signs. However, it should be noted that the depth of anesthesia may vary among patients, which may lead to individual differences in baseline and changes in BIS values. Third, the evaluation in this study was only performed in adult patients. Nevertheless, compared with adult patients, the assessment of pediatric anesthesia recovery relies more on objective measurement, because children are usually uncooperative or even nonverbal. Further experiments should be conducted to evaluate whether $SctO_2$ can be used as an indicator of emergence from anesthesia in pediatric

patients. Fourth, the patients who received volatile anesthesia were not included in this study. Further studies will be required to compare the $SctO_2$ between the emergence from anesthesia maintained by total intravenous anesthesia or volatile agents. Fifth, $SctO_2$ monitoring is usually applied in some types of surgery, which have a great impact on cerebral perfusion (e.g., cardiac surgery, carotid endarterectomy). However, most of the surgery types included in this study did not routinely use $SctO_2$ monitoring in clinical practice. It may limit the significance of our findings in clinical practice. Despite all this, through this study, $SctO_2$, as a non-invasive and well performed monitoring, is potentially another valuable index in the emergence from general anesthesia.

5. Conclusions

The increase in $SctO_2$ correlated with the emergence from propofol-remifentanil anesthesia. $SctO_2$ is a more reliable indicator of appearing behavioral signs during anesthesia emergence than BIS, MAP, and HR, within a 2 min interval prior to the appearance of behavioral signs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11164878/s1, Figure S1: The placement of BIS and NIRS. Figure S2: There are no correlations between Δ $SctO_2$ and Δ MAP or Δ HR at appearance of behavioral signs. (A) Δ $SctO_2$ does not correlate with Δ MAP (r = 0.1518, p = 0.0346). (B) Δ $SctO_2$ weakly correlates with Δ HR (r = 0.2159, p = 0.0025). Figure S3: Performance of Δ $SctO_2$, Δ BIS, Δ MAP and Δ HR in predicting the appearance of behavioral signs using the receiver operating characteristic (ROC) curves, n = 194. (A) ROC of Δ $SctO_2$, Δ BIS, Δ MAP and Δ HR for predicting the appearance of behavioral signs. (B,C) Comparison of diagnostic accuracy among Δ $SctO_2$, Δ BIS, Δ MAP and Δ HR for predicting the appearance of behavioral signs using the diagnostic parameters. Table S1: The multivariate analysis of $SctO_2$ at with other parameters ($EtCO_2$, SpO_2, MAP and HR), n = 194. Table S2: Physiological values from the beginning of emergence to the appearance of behavioral signs in patients receiving different types of surgery. Table S3: Performance of Δ $SctO_2$, Δ BIS, Δ MAP and Δ HR in predicting appearance of behavioral signs in patients receiving different types of surgeries. Table S4: Main characteristics of patients who regained consciousness when behavioral signs appeared (n = 162) and those who regained consciousness later than the appearance of behavioral signs (n = 32).

Author Contributions: Conceptualization, J.Z., C.H. and M.K.E.S.; Data curation, Z.C. and Y.T.; Formal analysis, J.Z. and X.Y.; Funding acquisition, C.H.; Investigation, J.Z. and Z.C.; Methodology, J.Z. and Z.C.; Project administration, Z.C.; Resources, C.H. and Q.G.; Supervision, C.H. and Q.G.; Validation, L.W., Y.Z. and X.Y.; Visualization, L.W. and Y.Z.; Writing—original draft, J.Z., Y.T. and X.Y.; Writing—review and editing, C.H. and M.K.E.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by "Medical Ethics Committee of the Xiangya Hospital of Centre South University" (IRB No.201904111; Date of approval, 30 May 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All data included in this study are available upon request by contact with the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Reshef, E.R.; Schiff, N.D.; Brown, E.N. A Neurologic Examination for Anesthesiologists: Assessing Arousal Level during Induction, Maintenance, and Emergence. *Anesthesiology* **2019**, *130*, 462–471. [CrossRef] [PubMed]
2. Goldstein, L.H.; Abrahams, S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: Nature of impairment and implications for assessment. *Lancet. Neurol.* **2013**, *12*, 368–380. [CrossRef]
3. McGuire, J.M.; Burkard, J.F. Risk factors for emergence delirium in U.S. military members. *J. Perianesthesia Nurs. Off. J. Am. Soc. PeriAnesthesia Nurses* **2010**, *25*, 392–401. [CrossRef] [PubMed]
4. Jones, J.H.; Nittur, V.R.; Fleming, N.; Applegate, R.L., 2nd. Simultaneous comparison of depth of sedation performance between SedLine and BIS during general anesthesia using custom passive interface hardware: Study protocol for a prospective, non-blinded, non-randomized trial. *BMC Anesthesiol.* **2021**, *21*, 105. [CrossRef]
5. Chen, W.; Jiang, F.; Chen, X.; Feng, Y.; Miao, J.; Chen, S.; Jiao, C.; Chen, H. Photoplethysmography-derived approximate entropy and sample entropy as measures of analgesia depth during propofol-remifentanil anesthesia. *J. Clin. Monit. Comput.* **2021**, *35*, 297–305. [CrossRef]
6. Puchner, W.F.; Dünser, M.W.; Paulus, P.; Neuner, M.P.; Mayer, C.L.; Pomberger, I.M.; Hackl, R.; Meier, J.M. A comparative study on adequate anesthesia depth: Clinical judgement and the Narcotrend®measurement. *Can. J. Anaesth. = J. Can. D'anesthesie* **2020**, *67*, 664–673. [CrossRef]
7. Kurita, T.; Doi, M.; Katoh, T.; Sano, H.; Sato, S.; Mantzaridis, H.; Kenny, G.N. Auditory evoked potential index predicts the depth of sedation and movement in response to skin incision during sevoflurane anesthesia. *Anesthesiology* **2001**, *95*, 364–370. [CrossRef]
8. Lewis, S.R.; Pritchard, M.W.; Fawcett, L.J.; Punjasawadwong, Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. *Cochrane Database Syst. Rev.* **2019**, *9*, Cd003843. [CrossRef]
9. Dennhardt, N.; Boethig, D.; Beck, C.; Heiderich, S.; Boehne, M.; Leffler, A.; Schultz, B.; Sümpelmann, R. Optimization of initial propofol bolus dose for EEG Narcotrend Index-guided transition from sevoflurane induction to intravenous anesthesia in children. *Paediatr. Anaesth.* **2017**, *27*, 425–432. [CrossRef]
10. Hajat, Z.; Ahmad, N.; Andrzejowski, J. The role and limitations of EEG-based depth of anaesthesia monitoring in theatres and intensive care. *Anaesthesia* **2017**, *72* (Suppl. 1), 38–47. [CrossRef]
11. Recart, A.; Gasanova, I.; White, P.F.; Thomas, T.; Ogunnaike, B.; Hamza, M.; Wang, A. The effect of cerebral monitoring on recovery after general anesthesia: A comparison of the auditory evoked potential and bispectral index devices with standard clinical practice. *Anesth. Analg.* **2003**, *97*, 1667–1674. [CrossRef] [PubMed]
12. Kaskinoro, K.; Maksimow, A.; Långsjö, J.; Aantaa, R.; Jääskeläinen, S.; Kaisti, K.; Särkelä, M.; Scheinin, H. Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, and sevoflurane. *Br. J. Anaesth.* **2011**, *107*, 573–580. [CrossRef] [PubMed]
13. Tiefenthaler, W.; Colvin, J.; Steger, B.; Pfeiffer, K.P.; Moser, P.L.; Walde, J.; Lorenz, I.H.; Kolbitsch, C. How Bispectral Index Compares to Spectral Entropy of the EEG and A-line ARX Index in the Same Patient. *Open Med.* **2018**, *13*, 583–596. [CrossRef] [PubMed]
14. Mashour, G.A.; Palanca, B.J.; Basner, M.; Li, D.; Wang, W.; Blain-Moraes, S.; Lin, N.; Maier, K.; Muench, M.; Tarnal, V.; et al. Recovery of consciousness and cognition after general anesthesia in humans. *eLife* **2021**, *10*, e59525. [CrossRef] [PubMed]
15. Kelz, M.B.; García, P.S.; Mashour, G.A.; Solt, K. Escape From Oblivion: Neural Mechanisms of Emergence From General Anesthesia. *Anesth. Analg.* **2019**, *128*, 726–736. [CrossRef]
16. Xie, G.; Deschamps, A.; Backman, S.B.; Fiset, P.; Chartrand, D.; Dagher, A.; Plourde, G. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: A positron emission tomography study. *Br. J. Anaesth.* **2011**, *106*, 548–557. [CrossRef]
17. Hudetz, A.G. General anesthesia and human brain connectivity. *Brain Connect.* **2012**, *2*, 291–302. [CrossRef]
18. Drummond, J.C.; Dao, A.V.; Roth, D.M.; Cheng, C.R.; Atwater, B.I.; Minokadeh, A.; Pasco, L.C.; Patel, P.M. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. *Anesthesiology* **2008**, *108*, 225–232. [CrossRef]
19. Jöbsis, F.F. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* **1977**, *198*, 1264–1267. [CrossRef]
20. Murkin, J.M.; Arango, M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br. J. Anaesth.* **2009**, *103* (Suppl. 1), i3–i13. [CrossRef]
21. Leontiev, O.; Dubowitz, D.J.; Buxton, R.B. CBF/CMRO2 coupling measured with calibrated BOLD fMRI: Sources of bias. *NeuroImage* **2007**, *36*, 1110–1122. [CrossRef] [PubMed]
22. Leithner, C.; Royl, G. The oxygen paradox of neurovascular coupling. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* **2014**, *34*, 19–29. [CrossRef] [PubMed]
23. Koch, K.U.; Zhao, X.; Mikkelsen, I.K.; Espelund, U.S.; Aanerud, J.; Rasmussen, M.; Meng, L. Correlation Between Cerebral Tissue Oxygen Saturation and Oxygen Extraction Fraction During Anesthesia: Monitoring Cerebral Metabolic Demand-supply Balance During Vasopressor Administration. *J. Neurosurg. Anesthesiol.* **2021**. [CrossRef] [PubMed]
24. Hernandez-Meza, G.; Izzetoglu, M.; Osbakken, M.; Green, M.; Abubakar, H.; Izzetoglu, K. Investigation of optical neuro-monitoring technique for detection of maintenance and emergence states during general anesthesia. *J. Clin. Monit. Comput.* **2018**, *32*, 147–163. [CrossRef] [PubMed]

25. Leon-Dominguez, U.; Izzetoglu, M.; Leon-Carrion, J.; Solís-Marcos, I.; Garcia-Torrado, F.J.; Forastero-Rodríguez, A.; Mellado-Miras, P.; Villegas-Duque, D.; Lopez-Romero, J.L.; Onaral, B.; et al. Molecular concentration of deoxyHb in human prefrontal cortex predicts the emergence and suppression of consciousness. *NeuroImage* **2014**, *85 Pt 1*, 616–625. [CrossRef]
26. Agha, R.; Abdall-Razak, A.; Crossley, E.; Dowlut, N.; Iosifidis, C.; Mathew, G. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. *Int. J. Surg.* **2019**, *72*, 156–165. [CrossRef]
27. Davie, S.N.; Grocott, H.P. Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. *Anesthesiology* **2012**, *116*, 834–840. [CrossRef]
28. Cornelissen, L.; Donado, C.; Lee, J.M.; Liang, N.E.; Mills, I.; Tou, A.; Bilge, A.; Berde, C.B. Clinical signs and electroencephalographic patterns of emergence from sevoflurane anaesthesia in children: An observational study. *Eur. J. Anaesthesiol.* **2018**, *35*, 49–59. [CrossRef]
29. Ledowski, T.; Bromilow, J.; Paech, M.J.; Storm, H.; Hacking, R.; Schug, S.A. Skin conductance monitoring compared with Bispectral Index to assess emergence from total i.v. anaesthesia using propofol and remifentanil. *Br. J. Anaesth.* **2006**, *97*, 817–821. [CrossRef]
30. Ledowski, T.; Paech, M.J.; Storm, H.; Jones, R.; Schug, S.A. Skin conductance monitoring compared with bispectral index monitoring to assess emergence from general anaesthesia using sevoflurane and remifentanil. *Br. J. Anaesth.* **2006**, *97*, 187–191. [CrossRef]
31. Smith, W.D.; Dutton, R.C.; Smith, N.T. Measuring the performance of anesthetic depth indicators. *Anesthesiology* **1996**, *84*, 38–51. [CrossRef] [PubMed]
32. DeLong, E.R.; DeLong, D.M.; Clarke-Pearson, D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* **1988**, *44*, 837–845. [CrossRef] [PubMed]
33. Grillo, P.; Bruder, N.; Auquier, P.; Pellissier, D.; Gouin, F. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. *Anesth. Analg.* **2003**, *96*, 1145–1149. [CrossRef]
34. Chai, C.; Wang, H.; Chu, Z.; Li, J.; Qian, T.; Mark Haacke, E.; Xia, S.; Shen, W. Reduced regional cerebral venous oxygen saturation is a risk factor for the cognitive impairment in hemodialysis patients: A quantitative susceptibility mapping study. *Brain Imaging Behav.* **2020**, *14*, 1339–1349. [CrossRef] [PubMed]
35. Picton, P.; Dering, A.; Alexander, A.; Neff, M.; Miller, B.S.; Shanks, A.; Housey, M.; Mashour, G.A. Influence of Ventilation Strategies and Anesthetic Techniques on Regional Cerebral Oximetry in the Beach Chair Position: A Prospective Interventional Study with a Randomized Comparison of Two Anesthetics. *Anesthesiology* **2015**, *123*, 765–774. [CrossRef] [PubMed]
36. Zanner, R.; Pilge, S.; Kochs, E.F.; Kreuzer, M.; Schneider, G. Time delay of electroencephalogram index calculation: Analysis of cerebral state, bispectral, and Narcotrend indices using perioperatively recorded electroencephalographic signals. *Br. J. Anaesth.* **2009**, *103*, 394–399. [CrossRef]
37. Kwak, H.J.; Kim, J.Y.; Lee, K.C.; Kim, H.S.; Kim, J.Y. Effect of mild hypocapnia on hemodynamic and bispectral index responses to tracheal intubation during propofol anesthesia in children. *J. Clin. Monit. Comput.* **2015**, *29*, 29–33. [CrossRef]
38. Channabasappa, S.M.; Shankarnarayana, P. A comparative study of hemodynamic changes between prone and supine emergence from anesthesia in lumbar disc surgery. *Anesth. Essays Res.* **2013**, *7*, 173–177. [CrossRef]
39. Paloheimo, M.P.; Sahanne, S.; Uutela, K.H. Autonomic nervous system state: The effect of general anaesthesia and bilateral tonsillectomy after unilateral infiltration of lidocaine. *Br. J. Anaesth.* **2010**, *104*, 587–595. [CrossRef]
40. Långsjö, J.W.; Alkire, M.T.; Kaskinoro, K.; Hayama, H.; Maksimow, A.; Kaisti, K.K.; Aalto, S.; Aantaa, R.; Jääskeläinen, S.K.; Revonsuo, A.; et al. Returning from oblivion: Imaging the neural core of consciousness. *J. Neurosci. Off. J. Soc. Neurosci.* **2012**, *32*, 4935–4943. [CrossRef]
41. Brown, E.N.; Lydic, R.; Schiff, N.D. General anesthesia, sleep, and coma. *N. Engl. J. Med.* **2010**, *363*, 2638–2650. [CrossRef] [PubMed]
42. Meex, I.; Vundelinckx, J.; Buyse, K.; Deburggraeve, F.; De Naeyer, S.; Desloovere, V.; Anné, L.; Truijen, J.; Vander Laenen, M.; Heylen, R.; et al. Cerebral tissue oxygen saturation values in volunteers and patients in the lateral decubitus and beach chair positions: A prospective observational study. *Can. J. Anaesth.* **2016**, *63*, 537–543. [CrossRef]
43. Suehiro, K.; Okutai, R. Cerebral desaturation during single-lung ventilation is negatively correlated with preoperative respiratory functions. *J. Cardiothorac. Vasc. Anesth.* **2011**, *25*, 127–130. [CrossRef] [PubMed]
44. Kelz, M.B.; Sun, Y.; Chen, J.; Cheng Meng, Q.; Moore, J.T.; Veasey, S.C.; Dixon, S.; Thornton, M.; Funato, H.; Yanagisawa, M. An essential role for orexins in emergence from general anesthesia. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 1309–1314. [CrossRef] [PubMed]

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Systematic Review

Use of the Thyromental Height Test for Prediction of Difficult Laryngoscopy: A Systematic Review and Meta-Analysis

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Abstract: The thyromental height test (TMHT) has been proposed as a novel single clinical test for predicting difficult laryngoscopy (DL), though consequent studies have put forward various estimates when verifying its reliability. This systematic review and meta-analysis aimed to provide a comprehensive evaluation of the predictive value of TMHT for DL. A computerized search of CNKI, CQVIP, EBSCO, PubMed, SinoMed, and Wanfang Data was conducted on 1 June 2022. Prospective cohort studies reporting diagnostic properties of TMHT in relation to Cormack and Lehane grading in patients aged more than 16 years, either sex, scheduled for surgery under general anesthesia, requiring tracheal intubation with direct laryngoscopy were included in this analysis. Data was extracted or calculated, and meta-analysis was done by the Stata MIDAS module. A total of 23 studies with 5896 patients were included in this analysis. Summary estimates of all included studies are as follows: sensitivity 74% (95% CI, 68–79%); specificity 88% (95% CI, 81–92%); diagnostic odd ratio, 20 (95% CI, 10–40); positive likelihood ratio, 5.9 (95% CI, 3.6–9.6); and negative likelihood ratio, 0.30 (95% CI, 0.23–0.39). Summary sensitivity and specificity for studies with a prespecified threshold were 82% (95% CI, 71–89%) and 94% (95% CI, 87–98%), respectively. The estimated area under curve (AUC) was 85% (95% CI, 81–88%). There was no significant threshold effect but significant heterogeneity in both sensitivity and specificity. Heterogeneity in sensitivity became insignificant after removing two outliers of sensitivity analysis. It is concluded that THMT has an overall optimal predictive value for DL in adult patients with diverse ethnicity and various risk factors, displaying better predictive values in a large patient population comparing to other recent reported bedside assessments and a previous meta-analysis. As significant heterogeneity brought by un-standardized application of external laryngeal manipulations in the included studies may have biased the results of this meta-analysis, the actual predictive value of TMHT for DL still awaits further studies with good designs and large sample sizes for better determination.

Keywords: thyromental height test; laryngoscopy; airway management; systematic review; meta-analysis

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1. Introduction

A difficult airway is the clinical situation in which a conventionally trained anesthesiologist experiences difficulty with facemask ventilation, laryngoscopy and intubation, supraglottic airway ventilation, extubation, or invasive airway [1]. Adverse airway events resulting from unanticipated difficult laryngoscopy (DL) or intubation (DI), such as airway injury, esophageal intubation, and aspiration, are major causes of anesthesia-related perioperative morbidity and mortality [2,3]. Although not exactly equivalent to DI, DL is currently the reliable clinical predictor that signals a warning for high risk of DI. Thus, a reliable airway assessment test with a high accuracy as the predictor for DL is vital for the safety of clinical anesthesia.

Most airway assessment tests, such as upper lip bite test (ULBT), modified Mallampati test (MMT), and thyromental distance (TMD), have been recommended for preoperative prediction of DL, but recent robust evidence indicates that no any single airway assessment test can reliably predict the occurrence of DL [4–7]. To improve predictive accuracy, different combinations of airway assessment tests have been suggested [4,8,9]. A recent study showed that the combination of ULBT and MMT had the best predictive ability for DL, with a sensitivity of 88.9% and a specificity of 93.2% [10]. Thus, it is still necessary to continuously explore airway assessment tests with a good predictive ability for DL.

The thyromental height test (TMHT) was first proposed as a clinical test by Etezadi et al. in 2013 [11], and it showed a surprisingly high predictive value for DL at a 5 cm threshold based on a relatively small sample study. In the original study of Etezadi et al. [11], thyromental height (TMH) was defined as the height between the anterior border of the thyroid cartilage (on the thyroid notch just between the 2 thyroid laminae) and the anterior border of the mentum (on the mental protuberance of the mandible), with the patient lying supine with her/his mouth closed. Subsequently, several studies evaluated the actual performance of TMHT as a single predictor for DL in different populations [11–20]. In 2021, moreover, Carvalho et al. [21] performed a meta-analysis that included eight studies and showed that TMHT was a good predictor of DL with a better performance than most previously reported bedside airway assessment tests. In the meta-analysis of Carvalho et al. [21], however, exclusion of non-English language studies may have resulted in the absence of some important studies. Most importantly, several new works assessing the performance of TMHT for prediction of DL have been published after their meta-analysis [22–27]. To further determine the actual performance of TMHT as a single predictor of DL, we performed this systematic review and meta-analysis including all 23 studies in the available literature.

2. Methods

2.1. Protocol and Registration

This systematic review and meta-analysis of diagnostic test accuracy was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [28,29]. The review protocols had been designed before literature screening, registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO, accessed on 1 April 2022, registration number: CRD42022319323), and followed throughout the entire work.

2.2. Eligibility Criteria

For this systematic review of diagnostic test accuracy, we included only studies of prospective cohort design or randomized controlled trials with full reports which met the following criteria: (1) Languages: studies published in languages restricted to English, Chinese, and Portuguese; (2) Populations: patients recruited were $\geq$16 years of age, either sex, scheduled for surgery requiring endotracheal intubation by direct laryngoscopy under general anesthesia. No restrictions were placed on patients' American Society of Anesthesiologists (ASA) physical status classification, other specific health conditions, the healthcare setting, or the healthcare professionals involved.

Index test: a study was included as long as both the measuring method and reported data for TMHT were consistent and complete for all patients. However, the studies about the predictive accuracy of modified thyromental height test (MTMHT) for DL were excluded, as TMH was measured in a similar but different manner.

Reference standard test: The laryngoscopy view of glottis was determined by the classical Cormack and Lehane (CL) grading system, where grade 3 (only epiglottis visible) and grade 4 (neither glottis nor epiglottis visible) are considered as DL [1]. Studies presenting data on DL based on other tests and other ranges of CL grading systems were excluded.

Data: Numbers of cases for true positive (TP), false positive (FP), false negative (FN), and true negative (TN) were reported, respectively; otherwise, sensitivity and

specificity along with total sample size and the number of DL should be provided for manual calculation.

2.3. Information Sources and Search Strategy

The following databases were searched on 1 June 2022: CNKI, CQVIP, EBSCO, PubMed, SinoMed, and Wanfang Data. Reference lists of included studies were also searched and those potentially relevant to TMH were retrieved.

2.4. Selection Process

First round screening of literature was performed merely on titles and abstracts for relevancy, followed by a second round screening, where full texts of all remaining papers were assessed against eligibility criteria and study quality. Both rounds of screening were conducted independently by two reviewers (WXC and TT). Uncertainties and disagreements were resolved by their discussion.

2.5. Data Collection Process and Data Items

One reviewer (WXC) independently extracted and calculated the data of interest through a standardized form in Microsoft Excel from each included study, and it was then verified by another reviewer (TT). Uncertainties and disagreements were resolved by their discussion. The key items included in the data chart are: authors, year of publication, design of study, age, gender, height, weight, body mass index (BMI), total sample size, sample size of DL groups, mean TMH, and cut-off values of TMH, TP, FP, FN, TN, sensitivity, and specificity. When data for more than one threshold or laryngoscopy manipulations were provided in a single study, they were considered as different data groups and displayed separately.

2.6. Study Risk of Bias Assessment

Both risk of bias and applicability concerns were assessed independently by two reviewers (WXC and TT), using a revised tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [30]. Each study was coded as 'high', 'low', or 'unclear' risk/concern, according to the corresponding answers of several signaling questions about: (1) patient selection; (2) index test; (3) reference standard, and (4) patient flow and timing. The answers could be chosen from 'yes', 'no', and 'unclear', where a single 'no' leads to 'high' risk/concern, and only 'yes' for all questions leads to 'low' risk/concern. The assessing process was conducted in the Review Manager (RevMan, London, UK, v5.3.5) [31]. Uncertainties and disagreements were resolved by discussion.

2.7. Diagnostic Accuracy Measures

Sensitivity and specificity of TMHT for DL, which was defined by grades 3 and 4 of the CL grading system, were the primary outcomes of this study. Diagnostic odd ratio (DOR), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were also calculated for further detailed analysis.

2.8. Synthesis Methods

The statistical analysis for this study was performed in Stata (StataMP, release 16, Lakeway, TX, USA) with the module for meta-analytical integration of diagnostic test accuracy studies (MIDAS) [32]. Diagnostic properties, including TP, FP, FN, and TN were either collected or calculated, which enabled the production of forest plots for sensitivity and specificity of TMHT for diagnosis of DL. Forest plots for diagnostic odd ratio (DOR), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) were also depicted. Overall heterogeneity was evaluated by the Cochran's Q test along with the Spearman correlation test for the presence of diagnostic threshold effect. When heterogeneity was present ($I^2 > 50\%$), sensitivity analysis was performed and a forest plot for estimates was built to evaluate the contribution of each study to the overall heterogeneity. Studies that

were the most responsible for heterogeneity were then eliminated before further analysis. Summary receiver operating characteristic curves (SROC) were also generated in Stata MIDAS module [32] by which summary sensitivity and specificity, and the area under curve (AUC) were calculated. Furthermore, summary sensitivity and specificity were estimated for studies with a same TMHT cut-off value (5 cm) and with a prespecified cut-off value.

2.9. Publication Bias Assessment

Publication bias was assessed by the Deek's funnel plot asymmetry test in Stata with MIDAS module, which performed the linear regression of log odds ratios on inverse root of effective sample sizes as a test for funnel plot asymmetry. A p value of less than 0.10 was set for the significance threshold [32].

3. Results

3.1. Study Selection

After computerized research through several databases, 93 papers were identified, but only 54 remained after eliminating 39 duplications. A PubMed search strategy is displayed in Supplementary Table S1. First round literature screening was conducted on titles and abstracts of these 54 articles, 26 of which were further excluded for to two reasons: (1) retrospective evaluation, literature review, and letter (6 articles); and (2) irrelevance to our study objectives (20 articles). Full texts of all 28 remaining articles were retrieved before the second-round screening process. Careful assessment was performed with thorough reading and application of the eligible criteria. As a result, a total of 5 articles were excluded because of the following reasons: (1) DL identification methods other than the CL grading system (2 articles); (2) missing or inconsistent data (2 articles); (3) different measuring procedures for TMH (1 article). A PRISMA diagram [28] for the complete study selection process is shown in Figure 1. After the study selection process, all included studies were in either English or Chinese.

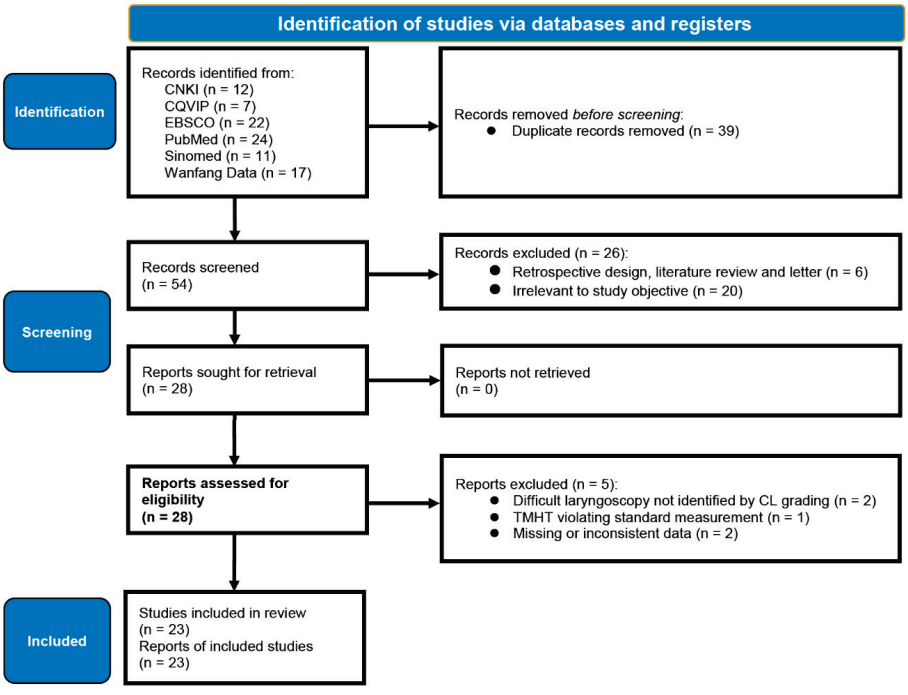

Figure 1. The PRISMA flow diagram of systematic review for included and excluded studies.

3.2. Study Characteristics

Important characteristics of each included study are summarized in Table 1. Among 23 independent studies including 5896 patients, a total of 615 patients were reported as DL according to the CL grading system. The incidence of DL in the included studies ranged from 1% to 31%. These prospective cohort observational studies took place in Australia, Bangladesh, China, Egypt, India, Iran, Japan, Nepal, and Turkey. Patients undergoing elective surgeries under general anesthesia requiring tracheal intubation were recruited. All studies included only patients without obvious airway abnormalities and malformations. One study [12] included only patients scheduled for coronary artery bypass surgery, two [19,26] only elderly patients ($\geq$65 years), and another two [22,25] only obese patients with a BMI > 30 kg/m^2.

As for the TMH measurement during preoperative assessment, 17 studies mentioned the use of either digital gauges (10 articles) [11–13,16,18,20,22,25–27] or regular rulers (7 articles) [14,15,17,19,23,24,33], while 6 studies failed to specify their measurement tools. Patients were placed in sniffing position for direct laryngoscopy and intubation in 14 studies [11,12,14,16–20,23,26,27,33–35]. During the direct laryngoscopy, a Macintosh blade was used in 17 studies in which one [31] used only size 3, 7 [12,16–18,20,23,26] used size 3 or 4, 2 [11,25] used only size 4, and 1 [13] used size 4 or 5. Only one study [11] mentioned the use of a Miller blade instead of a Macintosh when no laryngeal view was achieved and a second attempt was needed. Almost all laryngoscopy procedures were conducted by experienced anesthesiologists, except for one study [11] by residents and two [36,37] without mentioning. Application of external laryngeal manipulation showed inconsistency among studies, and its application or applicable condition lacked clear statements in most of the studies. The CL grading system was applied in all studies as for the eligible criteria. The CL grade 3 or 4 was the most approved diagnostic standard for DL, while only two [16,26] used the CL classification 2b or higher as their standard for DL.

Table 1. Characteristics of included studies.

Authors	Years	Countries	Mean Age; Years	Male; %	Female; %	Mean Height; cm	Mean Weight; kg	Mean BMI	Total Sample Size	DL; n (%)	Thresholds; cm
Etezadi	2013	Iran	44.5	47.5	52.5	166.1	72.0	25.8	314	23 (7.3)	5
Cao	2016	China	43.0	56.7	43.3	NA	NA	24.2	120	5 (4.2)	5
Cao	2017	China	42.0	58.0	42.0	NA	NA	25.2	200	8 (4)	5
Jain	2017	India	56.7	NA	NA	162.6	65.3	24.7	345	32 (9.3)	5
Selvi	2017	Turkey	48.5	51.0	49.0	NA	77.7	NA	451	37 (8.2)	5 4.35
Si	2017	China	51.4	NA	NA	165.0	NA	25.8	300	22 (7.3)	4.9
Cao	2018	China	44.6	56.0	44.0	NA	61.3	NA	200	24 (12)	4.9
Majigoudar	2018	India	39.8	53.3	46.7	NA	NA	21.3	60	4 (6.7)	5
Nurullah	2018	Bangladesh	45.4	50.4	49.6	NA	NA	NA	139	43 (31)	5
Rao	2018	Australia	43.4	47.2	52.8	162.6	62.0	23.4	316	26 (8.2)	5
Yang	2018	China	47.0	43.3	56.7	161.0	NA	23.0	263	24 (10)	3.92
Panjiar	2019	India	37.2	43.6	56.4	158.4	61.1	24.5	550	55 (10)	5
Yabuki	2019	Japan	50.2	18.0	82.0	159.6	58.6	22.9	609	6 (1)	5 with BURP 5.4 with BURP
										73 (12)	5 without BURP 5.4 without BURP
Luo	2020	China	49.9	38.4	61.6	160.6	62.4	NA	263	13 (4.9)	3.9
Mostafa	2020	Egypt	68.0	57.0	43.0	NA	NA	27.1	120	15 (12)	5.7
Rawal	2020	Nepal	35.8	44.3	55.7	158.0	60.9	24.1	246	7 (2.8)	5
Ahmed	2021	Egypt	38.3	78.1	21.9	NA	NA	43.7	105	23 (21.9)	4.7
Bhanushali	2021	India	51.7	40.4	59.6	162.4	NA	NA	109	16 (14.7)	5
Chhatrapati	2021	India	36.8	53.3	46.7	NA	55.2	NA	150	50 (30)	5
Kheirabadi	2021	Iran	41.3	32.1	67.9	NA	NA	35.7	196	48 (24.5)	4.8
Li	2021	China	NA	52.0	48.0	NA	NA	NA	400	53 (13.25)	4.805
Panjiar	2021	India	69.4	48.4	58.6	154.1	54.2	23.1	140	35 (25)	5.5
Prakash	2021	India	40.9	60.7	39.3	162.4	60.3	22.9	300	46 (15.3)	5 4.4

BMI: body mass index (kg/M^2); DL: difficult laryngoscopy.

3.3. Risk of Bias in Studies

As displayed in Figure 2 for methodological quality assessment by the QUADAS-2 tool, risk of bias in individual studies mainly came from patient selection, index test, and reference standard. Inappropriate exclusion criteria proposed in 13 studies [12,14–16,18,20,22–25,27,34,37] accounted for the high risk of bias in terms of patient selection. There was high concern that the test accuracy reported by these 13 studies could be positively affected by the fact that they removed patients with obesity, pregnancy, and other factors potentially increasing the possibility of DL. The provenance of bias related to the index test was straightforward: inability to preset a diagnostic TMHT threshold [11–13,17–19,22,25–27,33,36,37]. Bias regarding the reference standard was basically due to the absence of blindness [12,14,22,24,25,36,38,39] and the un-standardized application of external laryngeal manipulation [11,12,16,18–20,22,26,36]. All studies showed a low risk/concern for flow and timing and applicability.

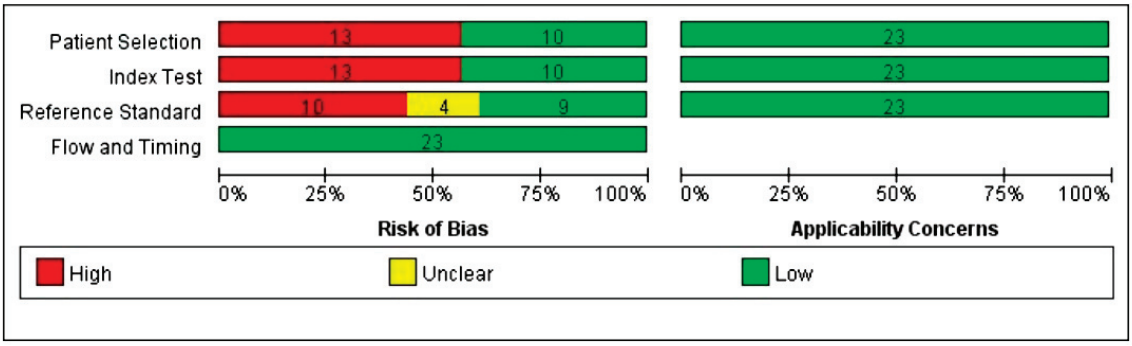

Figure 2. Risk of bias and applicability concerns review with authors' judgments about each domain presented as percentages across included studies.

3.4. Results of Syntheses

The Stata codes used for this meta-analysis are displayed in Supplementary Table S2. All figures were direct outputs of Stata (StataMP, release 16) [32] and Review Manager (RevMan, London, UK, v5.3.5) [31]. As shown in Figure 3, sensitivity and specificity of TMHT for prediction of DL reported in all 23 studies ranged from 39% to 95%, and 53% to 100%, respectively. The ranges for other diagnostic accuracy measurements were as follows: DOR, 1.33 to 721.29 (Figure 4A); LR+, 1.17 to 149; LR−, 0.05 to 0.87 (Figure 4B).

Analysis was first conducted with data from all included studies, resulting in a summary sensitivity of 74% (95% CI, 68–79%) and a specificity of 88% (95% CI, 81–92%) (Figure 3). Other summary estimates included: DOR, 20 (95% CI, 10–40) (Figure 4A); LR+, 5.9 (95% CI, 3.6–9.6); and LR−, 0.30 (95% CI, 0.23–0.39) (Figure 4B). The estimated area under curve (AUC) for the SROC curve was 85% (95% CI, 81–88%) (Figure 5).

After removing two studies [18,27] of high heterogeneity, the same analytical procedure was conducted again, which will be elaborated in the next section. The summary sensitivity and specificity were 77% (95% CI, 72–81%) and 90% (95% CI, 84–94%), respectively, after their removal (Supplementary Figure S1).

A total of 14 studies [11–18,20,23,24,27,38,39] with the same TMHT threshold (5 cm) showed a summary sensitivity of 75% (95% CI, 66–83%) and a specificity of 91% (95% CI, 82–95%) (Supplementary Figure S2). A total of 10 studies [14–16,20,23,24,34,35,38,39] with prespecified TMHT thresholds showed a summary sensitivity of 82% (95% CI, 71–89%), a specificity of 94% (95% CI, 87–98%) (Supplementary Figure S3), and an AUC of 92% (95% CI, 90–94%) (Supplementary Figure S4).

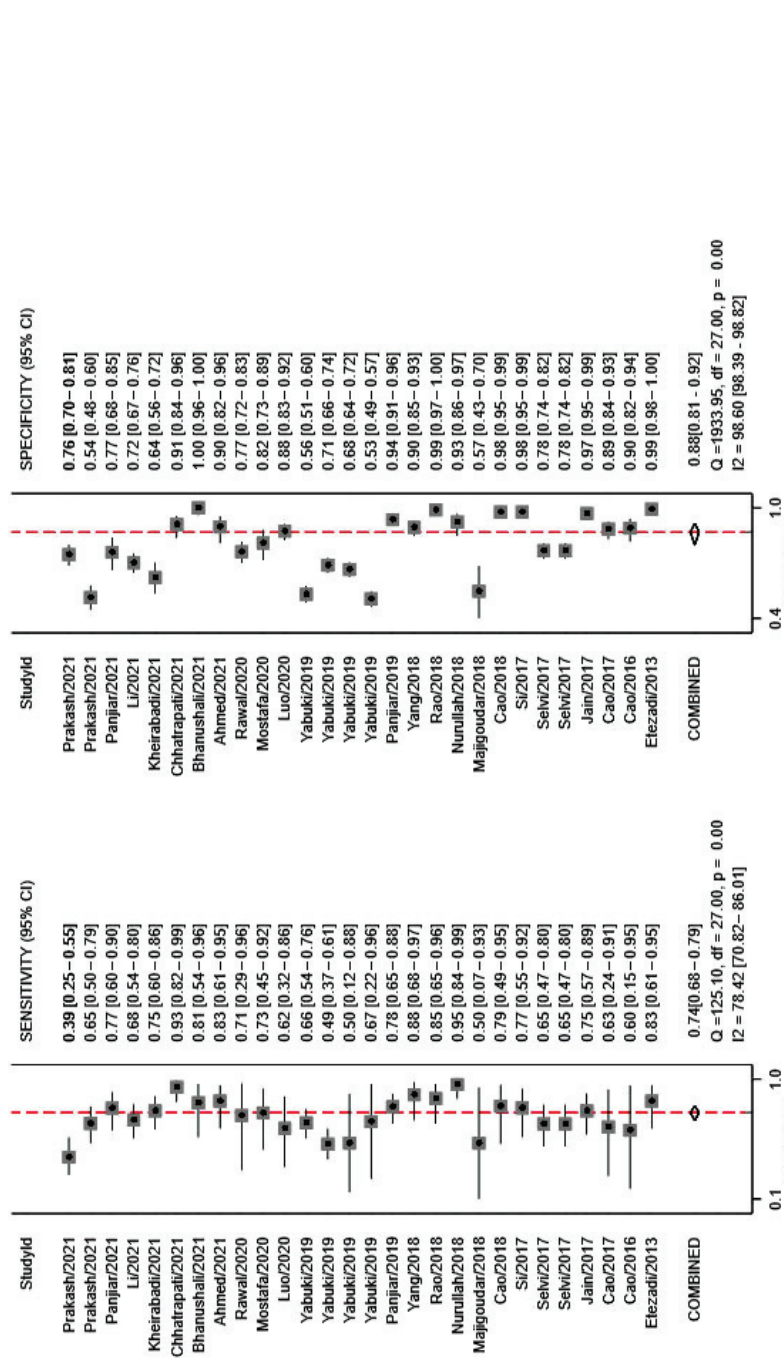

Figure 3. Forest plots of the analysis about the prediction value of TMHT for DL in terms of sensitivity and specificity with the data of all 23 studies. Square symbols represent the sensitivity or specificity of each study according to the Study ID shown on the y-axis, while the short lines cutting through represent the relative 95% CI. The diamond symbols refer to the combined sensitivity or specificity, which was automatically calculated and displayed by Stata software. A "COMBINED" label coordinating to the diamond symbol is shown on the y-axis underneath all Study ID.

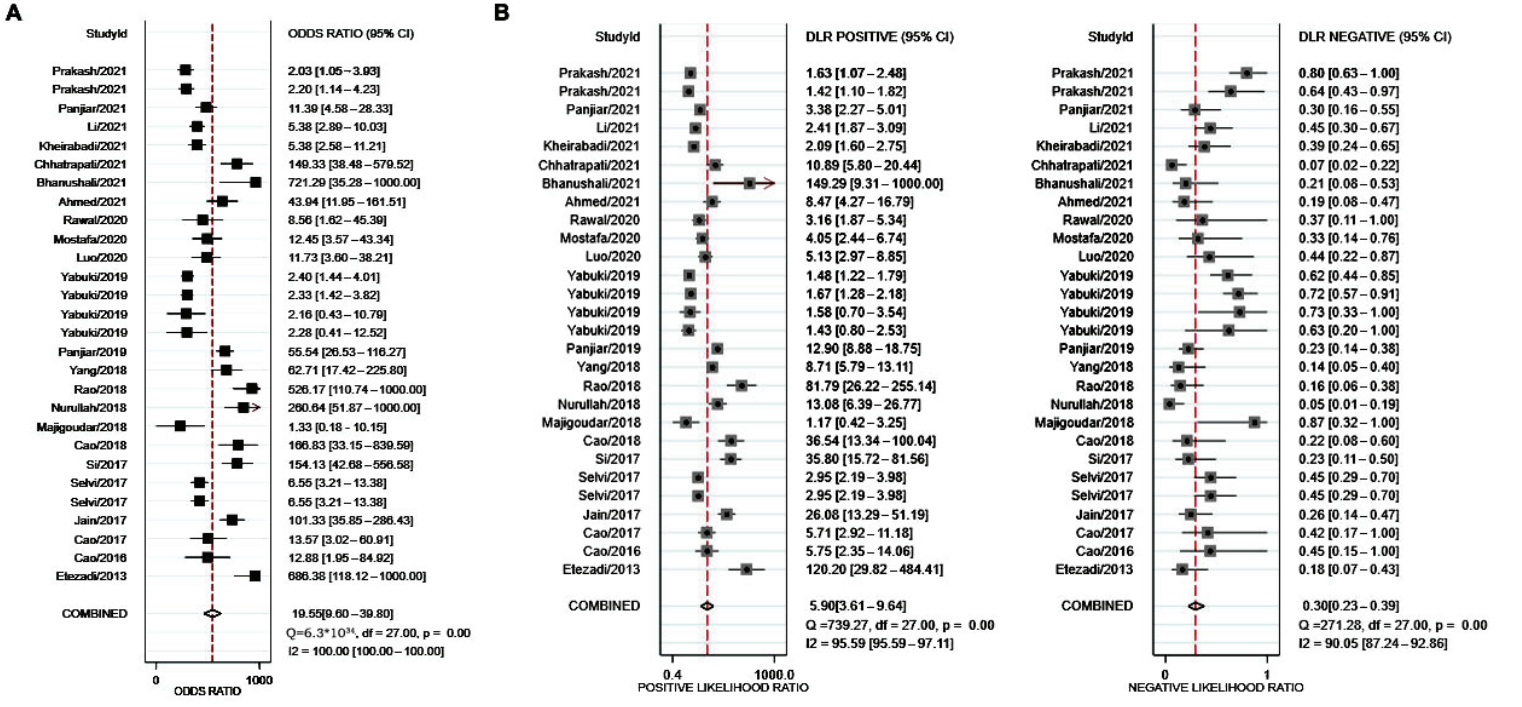

Figure 4. Forest plots of the analysis about the prediction value of TMHT for DL in terms of diagnostic odd ratio (DOR, (**A**)), positive likelihood ratio and negative likelihood ratio (LR+, LR−, (**B**)) with the data of all 23 studies. Square symbols represent the sensitivity or specificity of each study according to the Study ID shown on the y-axis, while the short lines cutting through represent the relative 95% CI. The diamond symbols refer to the combined sensitivity or specificity, which was automatically calculated and displayed by Stata software. A "COMBINED" label coordinating to the diamond symbol is shown on the y-axis underneath all Study ID.

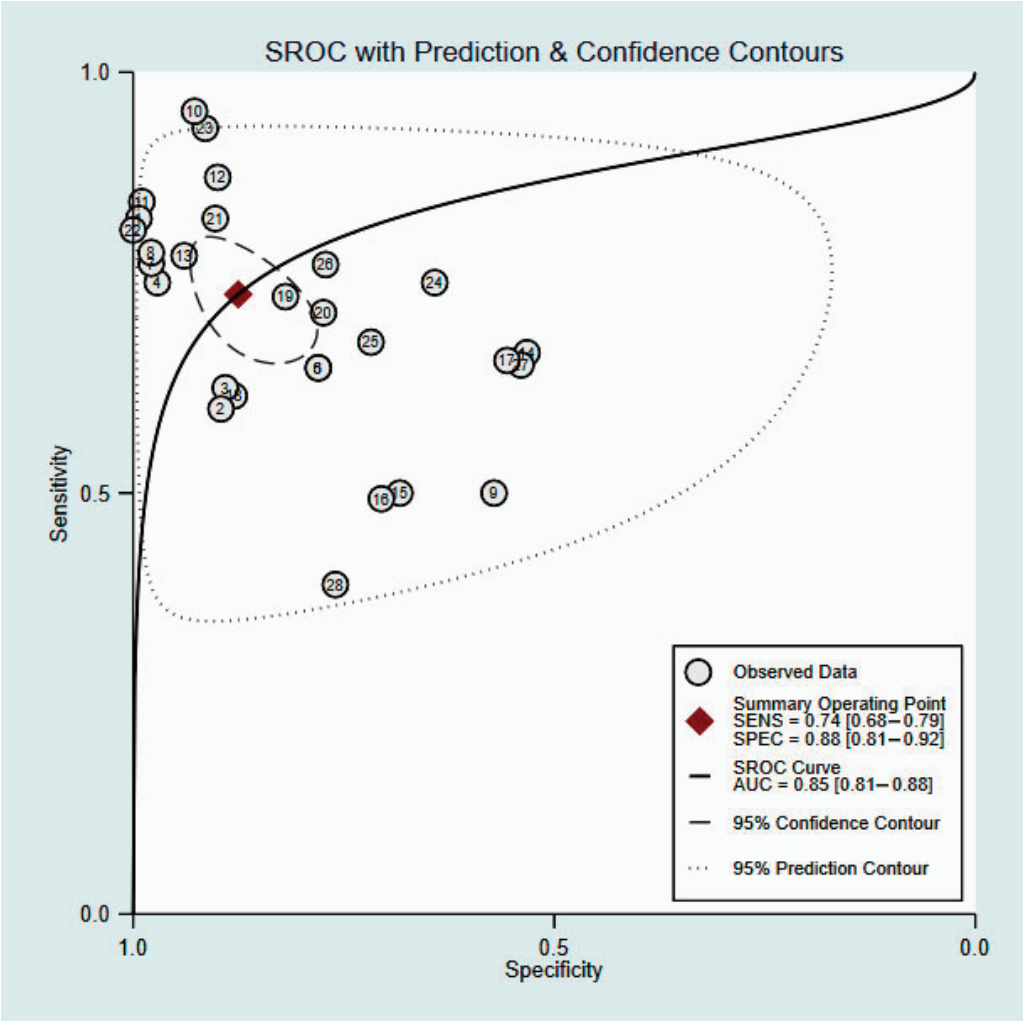

Figure 5. SROC of sensitivity and specificity of TMHT for prediction of DL with the data of all 23 included studies.

3.5. Reporting Biases

Threshold effect: There was no a significant threshold effect building up to the heterogeneity of this study (Spearman correlation estimate 0.70, $p = 0.49$).

Heterogeneity and sensitivity analysis: There were significant heterogeneities in both sensitivity ($p < 0.001$, $I^2 = 78.42$) and specificity ($p < 0.001$, $I^2 = 98.60$) of TMHT for prediction of DL (Figure 3). Sensitivity analysis was therefore conducted, and it showed two main sources of heterogeneity [18,27] (Supplementary Figure S5). After removing the data of these two studies and repeating the Cochran's Q test, the heterogeneity in sensitivity ($p = 0.001$, $I^2 = 44.48$) was no longer significant but the specificity ($p < 0.001$, $I^2 = 98.51$) remained the same. Other possible factors contributing to the heterogeneous significance might be related to the concerns for the reference standard as previously mentioned in methodological quality assessment. Different TMHT thresholds, preoperative threshold specification, standardization of external laryngeal manipulation (backward, upward,

rightward pressure, BURP), blade sizes, neuromuscular blockage, and operators' experience were the potential candidates for our heterogeneity.

Publication bias: Deek's funnel plot asymmetry test provided a chance for visual inspection and statistical calculation at the same time, both suggesting a low risk of publication bias ($p = 0.19$) (Supplementary Figure S6).

4. Discussion

The prediction of difficult airways has always been a crucial task for anesthesiologists in terms of airway management. Systematic reviews have been performed on various preoperative assessment methods, but inconsistent conclusions have been drawn [40–42]. According to the summary estimates of our review and analysis, the overall predictive value of TMHT for DL seems optimistic, with a sensitivity of 74%, a specificity of 88%, and an AUC of 85%. For all that, uncertainties are still present and should be addressed with caution. Especially, significant heterogeneity, relatively large 95% CI, and un-standardized application of external laryngeal manipulation during laryngoscopy are the potential weaknesses that need further discussion.

Among all 23 studies, the reported incidence of DL varied from 1% to 31%. Furthermore, the reported sensitivity and specificity of TMHT for prediction of DL ranged from 39% to 95%, and 53% to 100%, respectively. Although significant variability in sensitivity and specificity was reported, TMHT had an overall impressive specificity, and high sensitivity in these included studies. In total, 10 out of 23 studies had a specificity of above 90% [11,12,15–17,22–24,34,35], emphasizing an outstanding value of TMHT in differentiating non-DL patients from the others. In total, 16 [11–13,15–17,19,20,22–26,33–35] out of 23 studies reported a sensitivity of more than 70% comparing to the CL grading system, and 3 [13,15,24] among them over 90%, depicting a rather promising prediction of true DL. When a 5 cm threshold was set in the study, as proposed by Etezadi et al. [11], increased sensitivity and specificity were obtained, indicating the rationality and necessity of a 5 cm threshold.

This analysis showed that compared to other major predictors studied in recent literatures [5,7,40–42], TMHT had a satisfying predictive potential for DL with stability, comprehensiveness and independence. A systematic review and meta-analysis on various airway ultrasound predictors, such as the distance from skin to epiglottis (DSE), the distance from skin to hyoid bone (DSHB), and the distance from skin to vocal cords (DSVC), showed that DSE was the best imaging predictor, with a sensitivity of 82% (95% CI, 74–87%), a specificity of 79% (95% CI, 70–87%), and an AUC of 87% (95% CI, 84–90%) [40]. As patients with a history of previous difficult intubation or expected difficult laryngoscopy have been excluded from the above analysis of airway ultrasound predictors, the overall quality of evidence is low/very low and there is a high concern of bias [40]. In our analysis, however, TMHT demonstrated a higher specificity, which is the ability to accurately identify non-DL patients. Aside from the imaging airway test, other bedside airway tests have also been assessed in other systematic reviews [5,41,42]. Both MMT and ULBT showed a relatively high specificity of 84% [41] and 92% [5], respectively, but both tests showed relatively poor results for sensitivity (MMT 55% [41] and a ULBT of 67% [5]. Another meta-analysis on ULBT shared similar results [42]. Other bedside airway tests examined by Roth et al. [5], including a Wilson risk score, TMD, sternomental distance, and mouth opening, all displayed the similar pattern, i.e., a high specificity but a poor sensitivity. With similar, if not higher sensitivity and specificity, our results proved that TMHT is a rather comprehensive single predictor for DL, as most of the other predictors showed an unbalanced relation between sensitivity and specificity in other meta-analysis [5].

Last but not least, a prespecified threshold value plays an important role in reducing bias, and leads to a more impartial result [30]. Thus, in our study, a subgroup analysis containing 10 studies [14–16,20,23,24,34,35,38,39] with prespecified TMHT thresholds was conducted and showed a great predictive value by hitting the highest level of all tests and studies, with a summary sensitivity of 82% (95% CI, 71–89%), a specificity of 94% (95% CI,

87–98%) (Supplementary Figure S3), and an AUC of 92% (95% CI, 90–94%) (Supplementary Figure S4). That is to say, after reducing the existing bias to a certain degree, the outstanding predictive values from subgroup analysis were those that best represented the actual reliability of TMHT in predicting DL, confirming its excellent predictive potential.

The meta-analysis conducted by Carvalho et al. [21] in 2021 reported similar but somewhat limited results. In their analysis, summary sensitivity and specificity for studies with a common threshold were 82.6% (95% CI, 74–88.8%) and 93.5% (95% CI, 79–98.2%), respectively [21]. Obviously, there are numeral differences in both sensitivity and specificity between their analyses and ours. However, what needs to be kept in mind is the significant enlargement for the number of studies and total sample size/range included in our analysis. A total of 23 studies with 5896 patients were included, almost doubling the sample size, compared to 8 studies with 2844 patients as reported by Carvalho et al. [21]; especially, three of the most recent studies [22,25,26], which are all included, are aimed at the predictive performance of TMHT for DL in specific populations with risk factors of difficult airways, such as obesity, an age over 65 years, and others. Knowing that these factors are directly associated with the prevalence of DL and were considered as exclusion criteria in Carvalho et al.'s [21] work, the current study faces an extra challenge in the process of analysis and gains an extra validity in the results. Eight studies [20,33–39] conducted on the Chinese and Nepalese populations were included in our analysis, contributing to the ethnic diversity of patients. In total, the current study included 2355 Mongoloid subjects [18,33–39], 3225 Indian Mediterranean type Caucasian subjects [11–15,17,19,20,22–27], and 316 Baltic Sea type Caucasian subjects [16]. Baltic Sea type Caucasian subjects could be under-represented. No African type subjects were included in this meta-analysis. None of all 23 included studies in our analysis were eliminated during meta-analysis whether or not sharing the same threshold. These characteristics allowed a more comprehensive and representative population, bringing down the concern for bias and bolstering the credibility. Moreover, if a common 5 cm threshold was set, our data showed a summary sensitivity of 76% (95% CI, 66–83%) and a specificity of 91% (95% CI, 82–95%), almost at the same level with Carvalho et al.'s results [21]. Publication bias, not occurring in the current analysis, was suggested to be present in Carvalho et al.'s analysis [21], which also brought positive impact to their summary estimates. Thus, the results of the current study concurred with those of Carvalho et al.' analysis [21] but take a step forward, i.e., providing a more valid proof for the ability of TMHT in predicting DL.

5. Limitations and Implications

In spite of the already impressive potential of TMHT, the summary estimates of TMHT for all 23 studies, sensitivity 74% and specificity 88%, in fact failed to reach expectation, possibly due to the impact of un-standardized application of external laryngeal manipulation across studies. External laryngeal manipulation, known as BURP, referring to external, backward, upward, and rightward pressure, can be applied when the designated airway assessor estimates the laryngeal view of the patient for the purpose of predicting difficult airway [18,22]. Helping the practitioner to get a better view, it is worthwhile to combine BURP with the CL grading system to better determine DL. However, the presence of BURP would modify the final CL grading, affecting the final determination of DL. Moreover, the lack of proper principles and consistent indications for BURP application in the included studies would have caused confusion in the screening process, as some studies applied BURP on all patients [22], while other studies applied it only on the second attempt [11,12] or only on poor CL grades of [16,18,20,36]. The consistency of the reference standard test CL grading was therefore perturbed, bringing significant heterogeneity. A fact worth mentioning is that the largest study included in this analysis also presented the lowest incidence of DL and the worst predictive performance of TMHT for DL among all included studies, with non-BURP evaluation showing a slightly better accuracy (68.1% versus 53.4%) [18]. This brought up the idea that the BURP manipulation might result in unintended stringent CL grading and conflict with TMHT, thus the predictive value of THMT in our analysis, on the

whole, seemed unsatisfying when at least 9 [11,12,16,18–20,22,26,36] out of 23 studies mentioned the presence of BURP. That is to say, TMHT anticipates an even better performance in DL prediction whenever a consistent BURP policy is announced.

The ideal evidence for the current study, in fact, would be the studies with both low risk-of-bias and 5 cm threshold. Unfortunately, however, only two of the studies [13,17] included in this meta-analysis matched these conditions. Thus, there is not enough data for conducting such a sub-group meta-analysis. As TMHT is a novel single parameter and relevant study design still awaits improvement, we believe that more and more precise results about the predictive value of THMT for DL would be obtained in future studies and clinical practice. On the premise of the outcomes of current studies, with growing attention and more well-designed future clinical trials, TMHT may become a widely accepted indicator for prediction of DL among anesthesiologists.

6. Conclusions

Our analysis demonstrates that the predictive value of THMT for DL, on the whole, is more reliable than other imaging and bedside airway tests available in current practice. However, the significant heterogeneity and the uncertain influence brought by unstandardized BURP application indicate that further studies with a good design and a large sample size are still needed to determine the actual predictive value of TMHT for DL.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11164906/s1, Figure S1: Forest plots of the analysis about the prediction value of TMHT for DL in terms of sensitivity and specificity after removing heterogeneous studies; Figure S2: Forest plots of the analysis about the prediction value of TMHT for DL in terms of sensitivity and specificity with the data of only studies consisting of a 5 cm threshold; Figure S3: Forest plots of the analysis about the prediction value of TMHT for DL in terms of sensitivity and specificity with the data of only studies consisting of a prespecified threshold; Figure S4: SROC for sensitivity and specificity of TMHT for prediction of DL with the data of studies consisting of a prespecified threshold; Figure S5: Forest plot of sensitivity analysis of all studies selected from literature review; Figure S6: Deek's funnel plot asymmetry test for publication bias of all studies selected from literature review; Table S1: PubMed search strategy; Table S2: Stata code used for meta-analysis.

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References

1. Apfelbaum, J.L.; Hagberg, C.A.; Connis, R.T.; Abdelmalak, B.B.; Agarkar, M.; Dutton, R.P.; Fiadjoe, J.E.; Greif, R.; Klock, P.A.; Mercier, D.; et al. 2022 American Society of Anesthesiologists Practice Guidelines for Management of the Difficult Airway. *Anesthesiology* **2022**, *136*, 31–81. [CrossRef] [PubMed]
2. Honarmand, A.; Safavi, M.; Ansari, N. A comparison of between hyomental distance ratios, ratio of height to thyromental, modified Mallamapati classification test and upper lip bite test in predicting difficult laryngoscopy of patients undergoing general anesthesia. *Adv. Biomed. Res.* **2014**, *3*, 166. [PubMed]
3. Apfelbaum, J.L.; Hagberg, C.A.; Caplan, R.A.; Blitt, C.D.; Connis, R.T.; Nickinovich, D.G.; Hagberg, C.A.; Caplan, R.A.; Benumof, J.L.; Berry, F.A.; et al. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* **2013**, *118*, 251–270. [PubMed]

4. Chhina, A.K.; Jain, R.; Gautam, P.L.; Garg, J.; Singh, N.; Grewal, A. Formulation of a multivariate predictive model for difficult intubation: A double blinded prospective study. *J. Anaesthesiol. Clin. Pharmacol.* **2018**, *34*, 62–67. [PubMed]
5. Roth, D.; Pace, N.L.; Lee, A.; Hovhannisyan, K.; Warenits, A.M.; Arrich, J.; Herkner, H. Bedside tests for predicting difficult airways: An abridged Cochrane diagnostic test accuracy systematic review. *Anaesthesia* **2019**, *74*, 915–928. [CrossRef]
6. Vannucci, A.; Cavallone, L.F. Bedside predictors of difficult intubation: A systematic review. *Minerva Anestesiol.* **2016**, *82*, 69–83.
7. Detsky, M.E.; Jivraj, N.; Adhikari, N.K.; Friedrich, J.O.; Pinto, R.; Simel, D.L.; Wijeysundera, D.N.; Scales, D.C. Will This Patient Be Difficult to Intubate? The Rational Clinical Examination Systematic Review. *JAMA* **2019**, *321*, 493–503. [CrossRef]
8. Yıldırım, İ.; İnal, M.T.; Memiş, D.; Turan, F.N. Determining the Efficiency of Different Preoperative Difficult Intubation Tests on Patients Undergoing Caesarean Section. *Balkan Med. J.* **2017**, *34*, 436–443. [CrossRef]
9. Nørskov, A.K. Preoperative airway assessment—Experience gained from a multicentre cluster randomised trial and the Danish Anaesthesia Database. *Dan. Med. J.* **2016**, *63*, B5241.
10. Dawood, A.S.; Talib, B.Z.; Sabri, I.S. Prediction of difficult intubation by using upper lip bite, thyromental distance and Mallampati score in comparison to Cormack and Lehane classification system. *Wiad Lek.* **2021**, *74*, 2305–2314. [CrossRef]
11. Etezadi, F.; Ahangari, A.; Shokri, H.; Najafi, A.; Khajavi, M.R.; Daghigh, M.; Moharari, R.S. Thyromental height: A new clinical test for prediction of difficult laryngoscopy. *Anesth. Analg.* **2013**, *117*, 1347–1351. [CrossRef]
12. Jain, N.; Das, S.; Kanchi, M. Thyromental height test for prediction of difficult laryngoscopy in patients undergoing coronary artery bypass graft surgical procedure. *Ann. Card Anaesth.* **2017**, *20*, 207–211.
13. Selvi, O.; Kahraman, T.; Senturk, O.; Tulgar, S.; Serifsoy, E.; Ozer, Z. Evaluation of the reliability of preoperative descriptive airway assessment tests in prediction of the Cormack-Lehane score: A prospective randomized clinical study. *J. Clin. Anesth.* **2017**, *36*, 21–26. [CrossRef] [PubMed]
14. Majigoudar, S.S.; Revappa, K.B. Comparison of thyromental height test (TMH) with modified mallampati test and thyromental distance for prediction of difficult laryngoscopy: A prospective study. *Indian J. Clin. Anaesth.* **2017**, *4*, 238–241.
15. Nurullah, M.; Alam, M.S.; Hossen, M.; Shahnawaz, M. Prediction of difficult airway by thyromental height test-a comparison with modified mallampati test. *Bangladesh J. Med. Sci.* **2018**, *17*, 455–461. [CrossRef]
16. Rao, K.V.N.; Dhatchinamoorthi, D.; Nandhakumar, A.; Selvarajan, N.; Akula, H.R.; Thiruvenkatarajan, V. Validity of thyromental height test as a predictor of difficult laryngoscopy: A prospective evaluation comparing modified Mallampati score, interincisor gap, thyromental distance, neck circumference, and neck extension. *Indian J. Anaesth.* **2018**, *62*, 603–608. [PubMed]
17. Panjiar, P.; Kochhar, A.; Bhat, K.M.; Bhat, M.A. Comparison of thyromental height test with ratio of height to thyromental distance, thyromental distance, and modified Mallampati test in predicting difficult laryngoscopy: A prospective study. *J. Anaesthesiol. Clin. Pharmacol.* **2019**, *35*, 390–395. [CrossRef]
18. Yabuki, S.; Iwaoka, S.; Murakami, M.; Miura, H. Reliability of the thyromental height test for prediction of difficult visualisation of the larynx: A prospective external validation. *Indian J. Anaesth.* **2019**, *63*, 270–276. [CrossRef]
19. Mostafa, M.; Saeed, M.; Hasanin, A.; Badawy, S.; Khaled, D. Accuracy of thyromental height test for predicting difficult intubation in elderly. *J. Anesth.* **2020**, *34*, 217–223. [CrossRef]
20. Rawal, P.; Shrestha, S.M. The Evaluation of Thyromental Height Test as a Single, Accurate Predictor of Difficult Laryngoscopy. *J. Nepal Health Res. Counc.* **2020**, *18*, 271–276. [CrossRef]
21. Carvalho, C.C.; Santos Neto, J.M.; Orange, F.A. Predictive performance of thyromental height for difficult laryngoscopies in adults: A systematic review and meta-analysis. *Braz. J. Anesthesiol.* **2021**. [CrossRef] [PubMed]
22. Ahmed, A.M.; Zaky, M.N.; El-Mekawy, N.M.; Ollaek, M.A.; Sami, W.M.; Mohamed, D.M. Evaluation of thyromental height test in prediction of difficult airway in obese surgical patients: An observational study. *Indian J. Anaesth.* **2021**, *65*, 880–885. [CrossRef] [PubMed]
23. Bhanushali, A.; Date, A. Evaluation of upper lip bite test and thyromental height test for prediction of difficult laryngoscopy: A prospective observational study. *Airway* **2021**, *4*, 185–190.
24. Chhatrapati, S.; Bloria, S.; Singh, N.; Paul, S.; Luthra, A.; Kataria, K.K.; Vithani, S.; Omar, S.; Nayanar, V.K.N. Comparison of modified Mallampati test and thyromental height test for preoperative airway assessment: A prospective observational study. *Indian Anaesth. Forum* **2021**, *22*, 47–52.
25. Kheirabadi, D.; Honarmand, A.; Rasouli, M.R.; Safavi, M.R.; Maracy, M.R. Comparison of airway assessment tests for prediction of difficult intubation in obese patients: Importance of thyromental height and upper lip bite test. *Minerva Anestesiol.* **2021**, *88*, 114–120. [CrossRef]
26. Panjiar, P.; Bhat, K.M.; Yousuf, I.; Kochhar, A.; Ralli, T. Study comparing different airway assessment tests in predicting difficult laryngoscopy: A prospective study in geriatric patients. *Indian J. Anaesth.* **2021**, *65*, 309–315. [CrossRef]
27. Prakash, S.; Mullick, P.; Singh, R. Evaluation of thyromental height as a predictor of difficult laryngoscopy and difficult intubation: A cross-sectional observational study. *Braz. J. Anesthesiol.* **2021**. [CrossRef]
28. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
29. Page, M.J.; Moher, D.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ* **2021**, *372*, n160. [CrossRef]

30. Whiting, P.F.; Rutjes, A.W.; Westwood, M.E.; Mallett, S.; Deeks, J.J.; Reitsma, J.B.; Leeflang, M.M.; Sterne, J.A.; Bossuyt, P.M.; QUADAS-2 Group. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* **2011**, *155*, 529–536. [CrossRef]
31. The Cochrane Collaboration. *Review Manager (RevMan), Version 5.4.1*; The Cochrane Collaboration: London, UK, 2020.
32. StataCorp LLC. *StataCorp, Stata Statistical Software: Release 16*; StataCorp LLC: College Station, TX, USA, 2019.
33. Yang, Y.; Chen, M.; Shi, J.; Mo, H.Z.; Wu, Y.M.; Zou, X.H. Accuracy of modified thyromental height in predicting difficult laryngoscopy. *Chin. J. Anesth.* **2018**, *38*, 466–469.
34. Si, Y.N.; Wang, X.L.; Shi, L. Comparison of predictive capability of different methods for difficult laryngoscopy. *J. Clin. Anesthesiol.* **2017**, *33*, 11–14. (In Chinese)
35. Cao, J. Analysis of the effectiveness of different methods for predicting difficult airway laryngoscope intubation. *Med. Inform.* **2018**, *31*, 186–188. (In Chinese)
36. Luo, J.Y.; Yang, Q.; He, F.F.; Liu, L.Y.; Ou-Yang, J. Accuracy of modified thyromental height test in predicting difficult laryngoscopy. *J. Reg. Anat. Oper. Surg.* **2020**, *29*, 836–839. (In Chinese)
37. Li, M. The Effectiveness of Ultrasound Measurement of Upper Airway Anatomical Parameters in Predicting Difficult Airway. Master's Thesis, China National Knowledge, Online. 2021. [CrossRef]
38. Cao, Y.H.; Zhao, Y.X.; Chi, P. The value of thyromental height in predicting of difficult laryngoscopy. *Beijing Med. J.* **2016**, *38*, 880–882.
39. Cao, Y.H.; Chi, P.; He, H.L. Diagnostic accuracy of ratio of height to thyromental distance for difficult laryngoscopy in Chinese population. *Chin. J. Clin.* **2017**, *45*, 81–83. (In Chinese)
40. Carsetti, A.; Sorbello, M.; Adrario, E.; Donati, A.; Falcetta, S. Airway Ultrasound as Predictor of Difficult Direct Laryngoscopy: A Systematic Review and Meta-analysis. *Anesth. Analg.* **2022**, *134*, 740–750. [CrossRef]
41. Lee, A.; Fan, L.T.; Gin, T.; Karmakar, M.K.; Ngan Kee, W.D. A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. *Anesth. Analg.* **2006**, *102*, 1867–1878. [CrossRef]
42. Faramarzi, E.; Soleimanpour, H.; Khan, Z.H.; Mahmoodpoor, A.; Sanaie, S. Upper lip bite test for prediction of difficult airway: A systematic review. *Pak. J. Med. Sci.* **2018**, *34*, 1019–1023. [CrossRef]

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Forecasting Postoperative Delirium in Older Adult Patients with Fast-and-Frugal Decision Trees

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Abstract: Postoperative delirium (POD) is associated with increased complication and mortality rates, particularly among older adult patients. However, guideline recommendations for POD detection and management are poorly implemented. Fast-and-frugal trees (FFTrees), which are simple prediction algorithms, may be useful in this context. We compared the capacity of simple FFTrees with two more complex models—namely, unconstrained classification trees (UDTs) and logistic regression (LogReg)—for the prediction of POD among older surgical patients in the perioperative setting. Models were trained and tested on the European BioCog project clinical dataset. Based on the entire dataset, two different FFTrees were developed for the pre-operative and postoperative settings. Within the pre-operative setting, FFTrees outperformed the more complex UDT algorithm with respect to predictive balanced accuracy, nearing the prediction level of the logistic regression. Within the postoperative setting, FFTrees outperformed both complex models. Applying the best-performing algorithms to the full datasets, we proposed an FFTree using four cues (Charlson Comorbidity Index (CCI), site of surgery, physical status and frailty status) for the pre-operative setting and an FFTree containing only three cues (duration of anesthesia, age and CCI) for the postoperative setting. Given that both FFTrees contained considerably fewer criteria, which can be easily memorized and applied by health professionals in daily routine, FFTrees could help identify patients requiring intensified POD screening.

Keywords: fast-and-frugal decision trees; postoperative outcomes; postoperative delirium; clinical data prediction; medical decision making

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1. Introduction

Postoperative delirium (POD) is an acute and sudden change in the mental state, characterized by fluctuating levels of attention, consciousness and cognition [1,2]. The occurrence of POD is associated with increased complication and mortality rates [3,4] and may be related to the development of long-term cognitive disorders [5–7]. Incidence depends on predisposing and precipitating risk factors [8–10] and ranges from 10–50% [11,12], and older people are particularly susceptible to POD [13].

Given the risks associated with undetected postoperative delirium, it is important to have tools available to detect POD reliably and in a timely manner. According to the recommendations of the evidence-based and consensus-based guidelines on postoperative delirium [11], screening for delirium should be performed once per shift, at least twice

a day, for 5 days after surgery in all patients, and predisposing and precipitating risk factors should be attenuated whenever possible. However, the implementation of these measures requires a considerable allocation of personnel resources and time, and it may thus come as no surprise that these guideline recommendations are poorly implemented [14]. Furthermore, a number of predictive models have been developed in the past to guide the prediction of POD; however, these also often require extensive assessment, and their clinical implications remain unclear [15–20]. These examples suggest that a detection tool that would be supportive of use in clinical care needs to be simple to keep the number of personnel and the time costs of the assessment as low as possible. Fast-and-frugal trees (FFTrees)—binarizing prediction algorithms based on limited information search—can provide such a simple structure and have demonstrated the capacity to facilitate accurate decisions in a variety of medical domains [21–25]. For instance, when predicting whether a patient presenting with chest pain should be admitted to the coronary care unit or to a normal ward, an FFTree consisting of only three yes-or-no questions performed comparably with a dedicated decision support tool (heart disease predictive instrument (HDPI)) requiring 50 pieces of information. These findings likely go against the common assumption that "more information is always better", particularly in the medical domain, where most professionals may feel that, to make a good prediction or diagnosis, gathering more rather than less information reduces the risk of error. However, the relation between the amount of information and the quality of prediction is often an inverse U-shaped curve [26,27], specifically when situational uncertainty is high, as is the case in most medical situations including the prediction of POD. When situational uncertainty is high, model robustness is key [28,29]. Complex models, by using as much information as possible, fit "noise" and idiosyncrasies in the presented dataset that do not generalize to a new sample of patients. The result is "overfitting", which conflicts with the robustness of a model and, thus, with the accuracy of prediction. Furthermore, it is important to note that the POD risk detected at admission (predisposing factors) increases substantially during the operation, and the impact of anesthesia and surgery (precipitating factors, such as trauma, stress, medication, depth of anesthesia, blood pressure fluctuations, transfusions) warrant the reassessment of risk. This means that models for POD must be adaptable and must include the conditions associated with surgery.

The aim of this work was to examine if FFTrees are able to sufficiently predict POD. To address the requirements of perioperative medicine, we built a pre-operative FFTree based on pre-operative parameters and further built a postoperative FFTree with modeling that additionally considered intraoperative parameters. Moreover, we compared the ability to predict unseen cases in the two FFTree construction methods [22]—which are based on limited information search—with those of two compensatory models; namely, unconstrained classification trees (based on the classification and regression trees (CART) algorithm) and logistic regression.

2. Materials and Methods

2.1. Overview of the Present Study

The work reported herein was performed on data initially acquired via the BioCog project, a prospective multicenter observational study conducted at the Charité–Universitätsmedizin Berlin, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany, and the University Medical Center Utrecht, Department of Intensive Care Medicine, Utrecht, the Netherlands. This work was a secondary analysis performed for the purpose of generating FFTrees considering various influencing variables from the BioCog database generated at the study site Charité–Virchow Klinikum (n = 394, see Figure 1) in relation to the development of POD. The secondary analysis was approved by the local Ethics Committee (ref: EA2_048_18, 16 July 2020) and conducted in accordance with the Declaration of Helsinki.

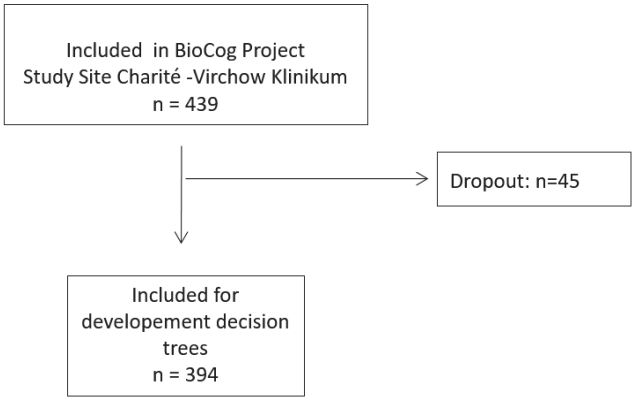

Figure 1. Flow chart.

The BioCog dataset was based on patients aged ≥ 65 years who were scheduled for elective surgery and presented with a Mini-Mental-State-Examination (MMSE) score of 23 points or higher (for detailed inclusion and exclusion criteria, see [30]).

2.2. Assessment of Postoperative Delirium

The models of this work inferred whether each respondent was at risk of POD as defined by the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [31]. Patients were considered delirious if they met any one of the following criteria:

- ≥2 cumulative points on the Nursing Delirium Screening Scale (Nu-DESC) and/or a positive Confusion Assessment Method (CAM) score;
- a positive CAM score for the Intensive Care Unit (CAM-ICU);
- a patient chart review that showed descriptions of delirium (e.g., confused, agitated, drowsy, disorientated, delirious, received antipsychotic therapy).

Delirium screening was started in the recovery room and repeated twice per day at 08:00 and 19:00 (±1 h) for up to seven days after surgery. Delirium assessment was conducted independently of the routine hospital procedures by a research team that was trained and supervised by psychiatrists and delirium experts.

2.3. Cues

We aimed to develop two different models predicting a patient's POD status based on (i) pre-operative cues alone and (ii) both pre-operative and intraoperative cues.

For the pre-operative model, each model was meant to categorize a patient as being or not being at risk of POD based on the following cues: age; sex; body height; body mass index; physical status according to the American Society of Anesthesiologists (ASA PS); Charlson Comorbidity Index (CCI) [32]; comorbidities, such as arterial hypertension, coronary artery disease, diabetes mellitus, stroke or transient ischemic attack, in medical history; education according to International Standard Classification of Education (ISCED) [33]; MMSE; pre-operative cognitive impairment (for details, see Supplementary Information S1); impaired activities of daily living according to Barthel (ADL) [34], as well as Lawton and Brody (IADL) [35]; malnutrition according to the Mini-Nutritional Assessment (MNA) [36]; pre-operative frailty status (for details, see Supplementary Information S2); depression according to the geriatric depression scale (GDS) [37,38]; pre-operative long-term medication with benzodiazepines; hazardous alcohol consumption based on the AUDIT score [39]; current smoker status; pack years and site of surgery (intracranial vs. intrathoracic, intra-abdominal or pelvic vs. peripheral). The postoperative model used, in addition to these

pre-operative pieces of information, the duration of anaesthesia and the administration of premedication before surgery (benzodiazepines, clonidine, antihistaminergics, etc.).

2.4. Model Comparison

Two FFTree construction algorithms (the ifan algorithm (FFTi) and the dfan algorithm (FFTd)) [22] were compared with logistic regression and an unconstrained classification tree algorithm (UDT) based on CART [39] for the pre-operative and the complete dataset separately. We chose a maximum number of five cues for the FFTi algorithm and a maximum number of four cues for the FFTd algorithm. The criteria for ifan and dfan were set to balanced accuracy. For UDT, we weighted misclassifications of positive cases higher than the misclassification of negative cases (based on the ratio of negative to positive cases in the training set) to aim for good performance in terms of balanced accuracy. We used the rpart package in R for UDT [40], which implements most of the CART algorithms [39] (with the minimum splitting size set to 20 and the complexity parameter to 0.00001). For the binary logistic regression model (LogReg), cues that were provided to the corresponding tree models were included in the regression model. To target the criterion of balanced accuracy, we set the threshold to transform probability estimates into predictions to the base rate observed in the training set. We used the implementation of logistic regression in the glm command in R.

2.4.1. Training and Test Set

In order to estimate the predictive performance of each model, the dataset was repeatedly randomly split into training and test (prediction set) sets, with an equal number of cases in each. Trees were constructed and parameters estimated based on the training set, and performance was measured based on the test set alone. The performance measure used was balanced accuracy—the mean of sensitivity and specificity—and models were estimated with the aim of achieving high values on this measure. Based on the model comparison, a tree construction algorithm was chosen to build two final trees (pre- and postoperative) based on the full dataset (n = 394). All analyses were run in R (version 4.1.2) [41].

2.4.2. Model Comparison Procedure

In preparing the dataset, missing values were replaced before starting the model comparison. For the following variables, a missing value was replaced by the sample median: ISCED, GDS, pack years, duration of anaesthesia. For categorical variables, missing values were replaced by the mode, which was 0 (no impairment) in the case of arterial hypertension, coronary artery disease, diabetes mellitus, stroke or transient ischemic attack in medical history, pre-operative cognitive impairment, ADL, IADL and the administration of premedication before surgery and 3 (no impairment) in the case of MNA.

In each trial of the model comparison, the full dataset was randomly split into training and test sets with an equal number of cases (n = 197). Models were estimated using the training set and performance (sensitivity, specificity and balanced accuracy) was measured using the test set alone. This procedure was repeated 1000 times for the more time-intensive FFTree construction algorithm (FFTd) and 10,000 times for all others. In each trial, the same training-test split was applied for each model, with FFTd being restricted to the first 1000 splits.

3. Results

3.1. Patient Characteristics

Altogether, we used data for 394 older adult surgical patients; 99 patients (25.1%) fulfilled the criteria for POD (see Table 1 for patient characteristics).

Table 1. Patient characteristics (n = 394).

Characteristic	POD (n = 99) 25.10%	Non POD (n = 295) 74.90%	*p*
		n = 394	
Age (years)	74 [71;77]	72 [68;76]	0.004 [a]
Sex			
Female	51 (41.5%)	145 (49.2%)	0.684 [b]
ASA PS			
1–2	43 (43.4%)	203 (68.8%)	<0.001 [b]
3–4	56 (56.6%)	92 (31.2%)	
Charlson Comorbidity Index	2.14 ±1.5 [c]	1.43 ± 1.6 [c]	<0.001 [a]
Frailty status			
Pre-frail	50 (51.0%)	143 (49.1%)	<0.001 [b]
frail	30 (30.6%)	30 (10.3%)	
Site of surgery			
intracranial	2 (2.0%)	7 (2.4%)	<0.001 [b]
intrathoracic, intra-abdominal or pelvic	67 (67.7%)	122 (41.4%)	
peripheral	30 (30.3%)	166 (56.3%)	
Duration of Anaesthesia (min)	360 [220;495]	157 [100;260]	<0.001 [b]

Data are expressed as medians [25th quartile; 75th quartile] except for categorical data, which are expressed as frequencies (percentages). *p*-values are with respect to Mann–Whitney U test ([a]) or Chi-squared test ([b]) between patients with or without POD. Additionally, data for Charlson Comorbidity Index are presented as means ± SD ([c]). $p \leq 0.05$ was considered as statistically significant. SD—standard deviation, POD—postoperative delirium, ASA PS—physical status according to the American Society of Anesthesiologists, min—minutes.

3.2. Model Comparison

For each model comparison, we report the mean performance of the four algorithms for the training and test sets and present visualizations of the distribution of prediction results across trials.

3.2.1. Performance of Pre-Operative Models

The model performance for all four models is summarized in Table 2. Performance for the training set represents the ability to predict criterion values based on already known cue values. The table reports sensitivity, specificity and balanced accuracy (the average of sensitivity and specificity).

Unconstrained decision trees exhibited the best average balanced accuracy (0.803), followed by logistic regression and the two FFTree models. The difference between the best and worst model was over 0.11. The standard error for FFTd models was higher due to the smaller number of trials (1000 vs. 10,000). It should be noted that the standard error for balanced accuracy was lower than that for sensitivity and specificity: Models tended to trade off sensitivity against specificity across trials, resulting in more stable values for the average. The performance of unconstrained decision trees suffered the most, changing the order of performance in the test set.

The distribution of results across trials (see Figure 2) demonstrated the variability across trials and put the average differences into context. Further analysis showed that the LogReg model outperformed the FFTi model in 76.0% of the trials, but it was outperformed by the FFTi model in 23.9% of the trials.

Table 2. Average performance for algorithms across trials with pre-operative information. The table presents means and standard errors separately for the four algorithms with the training set (fitting) and test set (prediction). For each combination, the table reports the mean and standard error of the mean for sensitivity, specificity and balanced accuracy across trials. FFTi, UDT and LogReg were tested in 10,000 trials and FFTd in the first 1000 of these only.

		Training			Prediction		
		Sensitivity	**Specificity**	**Bal. Accuracy**	**Sensitivity**	**Specificity**	**Bal. Accuracy**
FFTi	M	0.693	0.682	0.688	0.578	0.644	0.611
	SE	(0.0013)	(0.0013)	(0.0002)	(0.0015)	(0.0014)	(0.0003)
FFTd	M	0.751	0.689	0.720	0.562	0.625	0.593
	SE	(0.0037)	(0.0037)	(0.0007)	(0.0044)	(0.0040)	(0.0011)
UDT	M	0.868	0.738	0.803	0.52	0.626	0.573
	SE	(0.0006)	(0.0006)	(0.0002)	(0.0010)	(0.0007)	(0.0004)
LogReg	M	0.737	0.747	0.742	0.581	0.692	0.637
	SE	(0.0004)	(0.0003)	(0.0003)	(0.0007)	(0.0004)	(0.0003)

M—mean, SE—standard error of the mean, FFTi—fast-and-frugal tree construction using the ifan algorithm, FFTd—fast-and-frugal tree construction using the dfan algorithm, UDT—unconstrained decision trees based on the CART algorithm, LogReg—logistic regression.

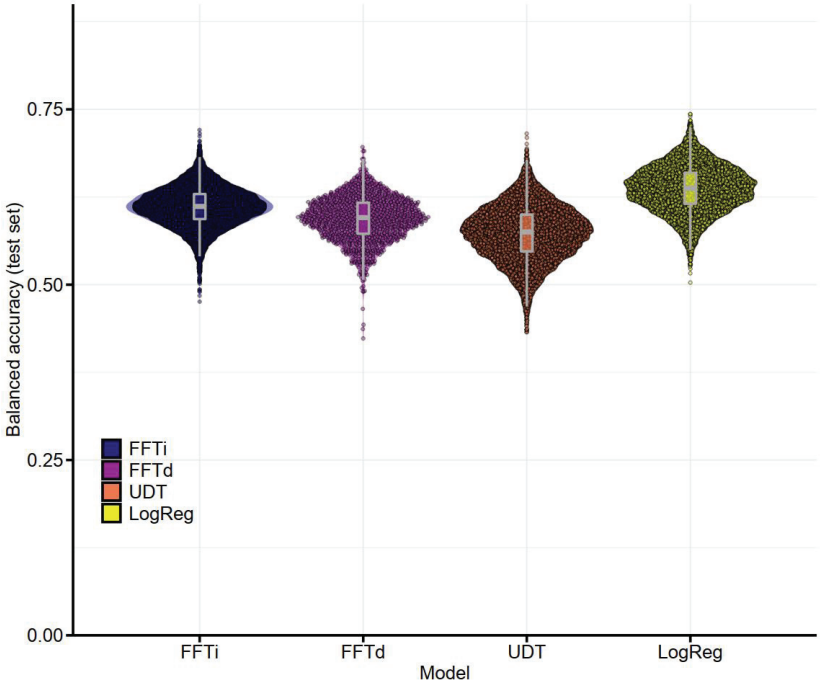

Figure 2. Balanced accuracy in the test set (prediction task) for the four algorithms across trials with pre-operative cues only. The graph shows boxplots and violin plots, with dots representing the results of individual trials (10,000 trials for FFTi, UDT and LogReg; 1000 trials for FFTd). FFTi—fast-and-frugal tree construction using the ifan algorithm, FFTd—fast-and-frugal tree construction using the dfan algorithm, UDT—unconstrained decision tree based on the CART algorithm, LogReg—logistic regression.

3.2.2. Performance of Postoperative Models

Adding the postoperative variables improved the performance of all models, both in fitting the training set and predicting the test set (see Table 3).

Table 3. Average performance of algorithms across trials with full information. The table presents means and standard errors separately for the four algorithms with the training set (fitting) and test set (prediction). For each combination, the table reports the mean and standard error of the mean for sensitivity, specificity and balanced accuracy across trials. FFTi, UDT and LogReg were tested in 10,000 trials and FFTd in the first 1000 of these only.

		Training			Prediction		
		Sensitivity	**Specificity**	**Bal. Accuracy**	**Sensitivity**	**Specificity**	**Bal. Accuracy**
FFTi	M	0.767	0.723	0.745	0.698	0.695	0.696
	SE	(0.0008)	(0.0008)	(0.0002)	(0.0011)	(0.0009)	(0.0003)
FFTd	M	0.815	0.756	0.786	0.698	0.71	0.704
	SE	(0.0025)	(0.0024)	(0.0007)	(0.0032)	(0.0028)	(0.0010)
UDT	M	0.896	0.784	0.840	0.625	0.694	0.660
	SE	(0.0005)	(0.0005)	(0.0002)	(0.0010)	(0.0007)	(0.0004)
LogReg	M	0.792	0.803	0.798	0.632	0.749	0.690
	SE	(0.0004)	(0.0003)	(0.0003)	(0.0007)	(0.0004)	(0.0003)

M—mean, SE—standard error of the mean, FFTi—fast-and-frugal tree construction using the ifan algorithm, FFTd—fast-and-frugal tree construction using the dfan algorithm, UDT—unconstrained decision tree based on the CART algorithm, LogReg—logistic regression.

Again, the order of performance changed between fitting and prediction, with unconstrained decision trees showing the best fitting performance (0.840) and the worst prediction performance (0.660). In contrast to the previous comparison, the FFTrees outperformed both alternative models in prediction. The FFTd algorithm showed a better average balanced accuracy in prediction (0.704) than the FFTi algorithm (0.696). FFTi performed better than LogReg in 56.1% of the trials, and FFTd performed better than LogReg in 61.9% of the trials and better than FFTi in 56.2% of the trials. The distribution of balanced accuracy in the prediction task is shown in Figure 3. Thus, these differences were not generated by outliers but by a general tendency to outperform the competitors.

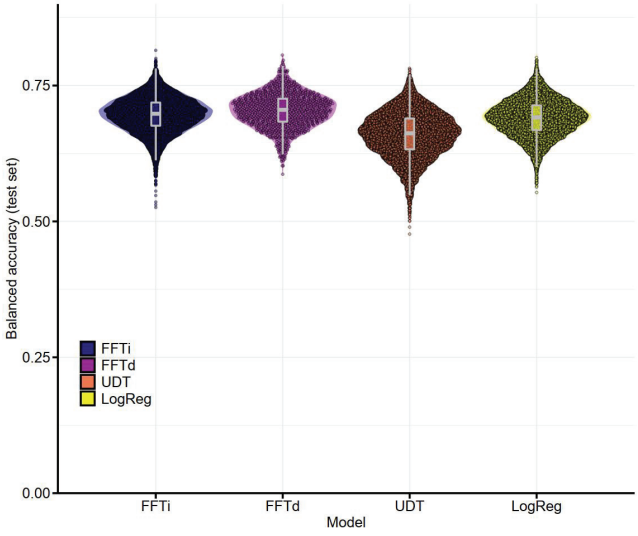

Figure 3. Balanced accuracy in the test set (prediction task) for the four algorithms across trials with all cues: The graph shows boxplots and violin plots, with dots representing the results of individual trials (10,000 trials for FFTi, UDT and LogReg; 1000 trials for FFTd). FFTi—fast-and-frugal tree construction using the ifan algorithm, FFTd—fast-and-frugal tree construction using the dfan algorithm, UDT—unconstrained decision tree based on the CART algorithm, LogReg—logistic regression.

3.3. Decision Trees Based on Full Dataset

Based on the results of the model comparison, we estimated two fast-and-frugal trees based on the full dataset, one for the pre-operative set of variables and one for the complete, postoperative set of variables. We present visualizations of the resulting trees and report performance statistics based on the full dataset (n = 394).

3.3.1. Pre-Operative FFTree

The first (pre-operative decision tree) was based on pre-operative data. Following the results of the model comparison, we chose the ifan algorithm to construct the tree. The resulting pre-operative decision tree contained four cues (CCI, site of surgery, ASA PS and frailty status) and indicated a sensitivity of 0.84 and a specificity of 0.46 with a balanced accuracy of 0.65 (see Figure 4). On average, 1.8 cue values had to be looked up to make a decision for the cases in the dataset, and 93% of the provided information was ignored on average. Over 52% of all cases were classified as positive after the first question (with a CCI larger than 1), and 71 of the 99 positive cases were in this group. The tree achieved a higher sensitivity at the cost of specificity (the unweighted accuracy was 0.56).

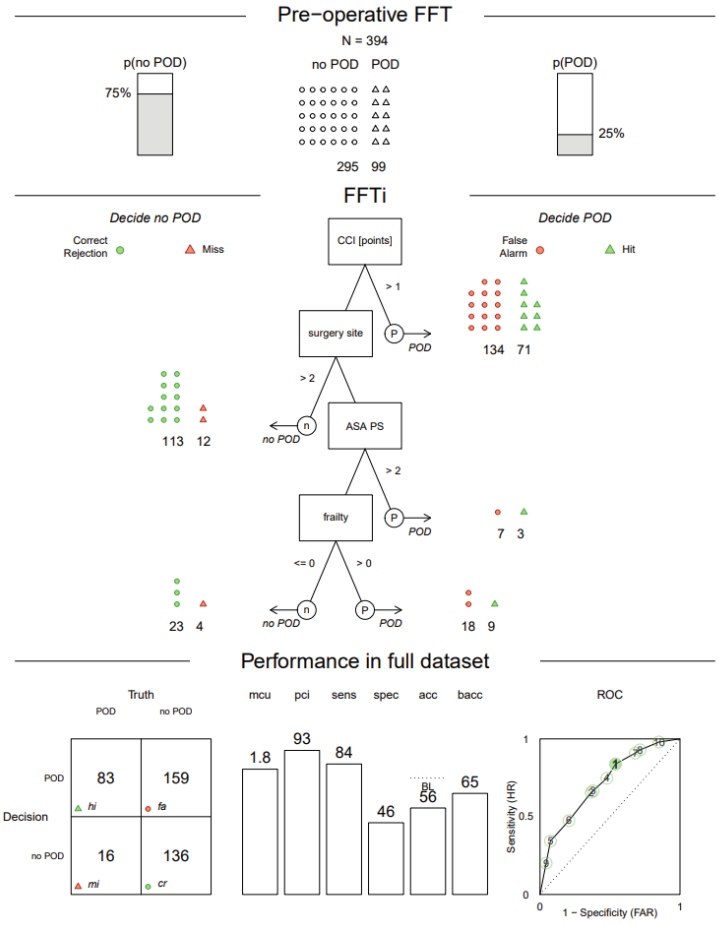

Figure 4. Pre-operative fast-and-frugal tree estimated with the ifan algorithm. POD—postoperative delirium, p(POD)—probability of POD a priori (base rate), p (no POD)—complement of p(POD),

FFTi—fast-and-frugal tree construction using the ifan algorithm, CCI—Charlson Comorbidity Index, surgery site > 2—peripheral, ASA PS—physical status according to the American Society of Anesthesiologists, frailty <= 0—robust, frailty > 0—pre-frail/frail, mcu—mean cues used, pci—percent cues ignored, sens—sensitivity, spec—specificity, acc—unweighted accuracy, back—balanced accuracy (sensitivity + specificity)/2, BL—probable BL (the base rate of 75% that could be achieved by classifying all cases as negative), ROC—receiver operating characteristic (shows the performance of all compared trees using the same cue order numbered according to their resulting balanced accuracy (in the training set), each data point shows the false alarm rate (FAR) on the *x*-axis and sensitivity/hit rate (HR) on the *y*-axis), hi—hit, mi—miss, cr—correct rejection.

3.3.2. Postoperative FFTree

The construction of the second decision tree (postoperative decision tree) took intraoperative parameters into account in addition to the pre-operative data. Following the results of the model comparison, we chose the dfan algorithm for tree construction in this case. The postoperative decision tree contained three cues (duration of anesthesia, age and CCI). While the maximum depth was set to four cues, the algorithm did not find an improvement by adding an additional layer to the tree, generating a truncated tree (see also [29]).

The decision tree demonstrated a sensitivity of 0.81, a specificity of 0.72 and a balanced accuracy of 0.76 (see Figure 5). It used 2.1 cues on average to make a classification, and it ignored 92% of the provided information on average. The tree was more balanced than the pre-operative tree and achieved an unweighted accuracy of 0.74.

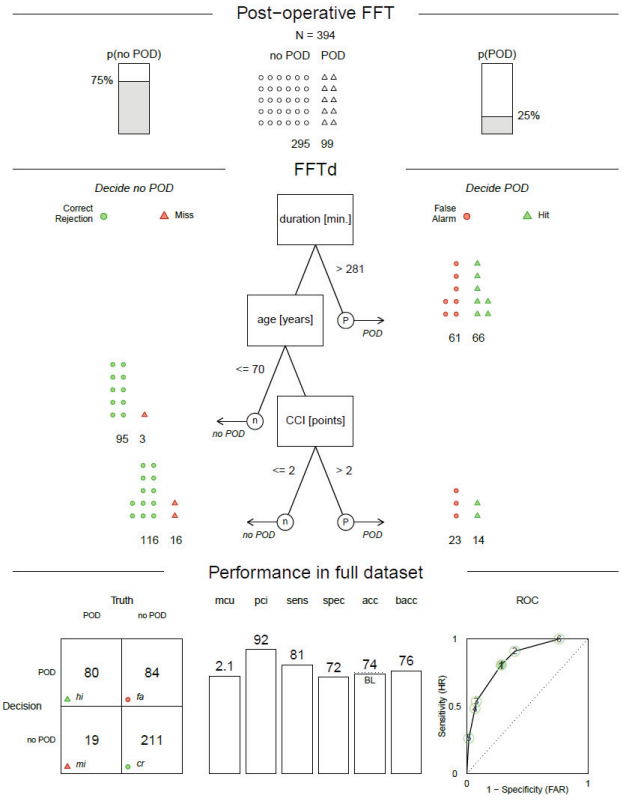

Figure 5. Postoperative fast-and-frugal tree estimated with the dfan algorithm. POD—postoperative delirium, p(POD)—probability of POD a priori (base rate), p (no POD)—complement of p(POD),

FFTd—fast-and-frugal tree construction using the dfan algorithm, duration—duration of anesthesia, CCI—Charlson Comorbidity Index, mcu—mean cues used, pci—percent cues ignored, sens—sensitivity, spec—specificity, acc—unweighted accuracy, back—balanced accuracy (sensitivity + specificity)/2, BL—probable BL (the base rate of 75% that could be achieved by classifying all cases as negative), ROC—receiver operating characteristic (shows the performance of all compared trees using the same cue order numbered according to their resulting balanced accuracy (in the training set), each data point shows the false alarm rate (FAR) on the *x*-axis and sensitivity/hit rate (HR) on the *y*-axis), hi—hit, mi—miss, cr—correct rejection.

4. Discussion

The aim of this work was to develop decision trees that can be used to estimate the risk of developing POD both pre-operatively and postoperatively in older adult patients. We were able to create two decision trees that differed in the parameters included. The pre-operative decision tree contained four cues (CCI, site of surgery, ASA PS and frailty status) and the postoperative contained three cues (duration of anesthesia, age and CCI). Before estimating fast-and-frugal trees (FFTrees), we compared two methods of FFTree construction (the ifan algorithm (FFTi) and the dfan algorithm (FFTd)) with unconstrained classification trees (UDTs, based on CART) and logistic regression. Fast-and-frugal trees are minimal binary classification trees that are constrained in terms of their structure. Various algorithms have been proposed for the construction of fast-and-frugal trees [22,25,29,42]. Here, we chose two algorithms that have been proved most competitive in achieving a high balanced accuracy [22], the ifan algorithm (FFTi) and the dfan algorithm (FFTd). A natural comparison for highly constrained fast-and-frugal trees are unconstrained classification trees (UDTs). Furthermore, we compared FFTrees with binary logistic regression models (LogReg), which predict the probability of an older adult patient being at risk for POD based on a weighted integration of all provided cues. It should be noted that, due to the relatively smaller number of positive cases in the sample, models aimed at achieving a high unweighted accuracy would, in contrast, likely sacrifice sensitivity for specificity, which would not be in line with the aims for the decision tool.

The results were in line with previous model comparisons [22,25,29]. More flexible models generally outperform less flexible models in this type of fitting performance. In line with this, unconstrained decision trees exhibited the best average balanced accuracy in the training set in the pre-operative model comparison, followed by logistic regression and the two FFTree models. The distribution of results across trials demonstrated the variability across trials and put the average differences into context. In the testing set with pre-operative modeling, logistic regression showed the highest balanced accuracy, closely followed by fast-and-frugal trees constructed with the ifan algorithm. All models showed worse performance in the testing set when predicting cases that were not part of the sample used to estimate their parameters. The inflation of predictive accuracy when predicting familiar cases has also been termed "overfitting", and it is usually more pronounced in more complex and flexible models. As expected, the performance of unconstrained decision trees suffered the most, changing the order of performance in the testing set.

Adding the postoperative variables improved the performance of all models, both in fitting the training set and predicting the test set. Again, the order of performance changed between fitting and prediction, with unconstrained decision trees showing the best fitting performance and the worst prediction performance. In contrast to the previous comparison, the fast-and-frugal trees outperformed both alternative models in prediction. Based on these model comparisons, we chose the ifan algorithm for pre-operative testing and the dfan algorithm for FFTree construction. It should be noted that the model comparison used 50% of the full dataset, providing a training sample that was smaller than the full sample. The advantage of this method is that training samples were less correlated. However, larger sample sizes tend to make logistic regression and CART more competitive. Based on our results for model comparison, we argue that FFTrees performed similarly to logistic regression and were not necessarily superior. From our point of view, the choice of method could be

guided by the availability of data: the more data there are, the better the case for using more complex methods to achieve better predictive capability. In smaller (and often typical) datasets, the case is stronger for FFTrees. Moreover, FFTrees are simpler to apply, easier to communicate and requires less information, but they are competitive in predicting cases.

For all the cues included in the FFTrees, there is strong evidence in the literature [11,43–45] that they are independent risk factors in the development of POD and have to be considered in perioperative care according to guideline recommendations. The fact that age was not considered in the pre-operative decision tree may reflect the relevance of biological age rather than chronological age. In the pre-operative decision trees, this is represented by frailty status. Duration of anesthesia had a strong impact in decision tree development. It can be regarded as a surrogate for extent of surgery and associated inflammation, toxicity of anesthesia or intraoperative complications, such as bleeding or organ damage. All of these factors influence the risk for developing POD. The evaluation of this simple surrogate (duration of anesthesia) is significant for clinical applicability.

To the best of our knowledge, this is the first time decision trees were created for the risk stratification of POD. In the past, more emphasis has been placed on developing predictive models with clinical implications that remain unclear. A number of prediction models have been developed but primarily to predict delirium risk (not POD risk) [17] or for ICU patients [15,18,20,46]. A simple translation to surgical patients is problematic, as the needs of surgical patients are not addressed. Although surgical patients have a baseline risk of developing POD, surgery is such a relevant incident that it requires reassessment of risk. This means that models for POD must be adaptable and must include the conditions associated with surgery.

The oldest prediction model for delirium, developed in the 1990s, included the evaluation of vision and cognitive impairment, severe illness and high urea nitrogen/creatinine ratio [17]. Prediction models for ICU delirium include—besides age parameters, which are primarily related to intensive care treatment, such as for coma—use of sedatives and morphine [46], respiratory failure [20], vasoactive medication use and requirement of continuous renal replacement therapy and mechanical ventilation [15]. Some of them were developed through retrospective analysis [15,18].

There are three noteworthy studies that address modeling for POD risk prediction that have been recently published. A nine-item model for predicting POD risk with an area under the curve (AUC) of 0.77 was developed in a cohort of patients with acute hip fracture [47]. In this model, ASA PS was also considered, as well as functional dependence and pre-operative use of mobility aids, which are surrogates for frailty. Although this model was based on an extensive dataset, there was a crucial limitation, as POD was not determined prospectively but retrospectively by means of a chart review. Another seven-item model with an AUC of 0.82 was developed in older adult orthopedic patients in the ICU [19]. POD was determined prospectively, which reduced the sample size accordingly. Here, intraoperative parameters could be considered. For example, in addition to age, major hemorrhage was also included in the score. This score appears promising but also has the limitations that it is a very specific patient group, not all of the parameters are routine parameters (level of interleukin-6) and pre-operative application of the score is not appropriate (three intraoperative parameters are included). These scores have in common the limitation that eight or nine criteria may be too extensive for routine daily use. In this regard, a score based on four items with an AUC of 0.83 for cardiac surgery patients is more feasible for clinical application [16]. This score includes age, evaluation of MMSE, insomnia needing medical treatment and low physical activity, which is equivalent to one item in our frailty definition. Here, an automatic calculator, which calculates the risk, is actually available. Nevertheless, intraoperative parameters are not considered in this approach either.

We were able to solve this challenge by developing both a tree for pre-operative use and a tree for postoperative use. Furthermore, the datasets for development of the decision trees included both parameters for which there is strong evidence regarding the association with POD and parameters for which there are only hypotheses. With our work,

we were able to select the most relevant parameters and rank them. It has been shown that only parameters with existing strong evidence were relevant in our analysis. Sensitivity appeared to be adequate in both trees. Specificity was very low in the pre-operative tree at 0.46. This does not matter considering how these trees will be applied in clinical care. In theory, all patients should receive a complete delirium screening and predisposing and precipitating factors should be anticipated. Since this is not implemented across the board for various reasons, the application of decision trees was intended to fill this gap, at least for those patients who should receive screening and special attention in any case. There is no disadvantage in giving special attention pre-operatively to a probably higher number of patients with misclassified increased risk of delirium. The postoperative decision tree has a higher specificity, which is relevant for clinical application, since POD screening requires personnel resources that are supposed to be extensive. The next steps include validation of the decision trees and verification of clinical practicability.

Strength and Limitations

A key strength of this study is the prospective design of the POD assessment. POD was assessed through a comprehensive, standardized and validated assessment. While the use of routine data for modeling, as in many of the previously discussed models, has the great advantage that extensive datasets are available, this must be viewed very critically, especially in the case of the clinical picture of postoperative delirium. Especially due to its fluctuating characteristics and the frequent occurrence of hypoactive forms, a comprehensive validated screening is essential. As described above, there is a large gap in POD coverage, so it cannot be assumed that POD screening is implemented adequately. This raises doubts about the quality of the analysis of routine data.

The study database contained extensive information on both parameters for which there is strong evidence regarding the association with POD and parameters for which there are only hypotheses. In addition, we were able to develop the decision trees based on a dataset of patients covering a wide range of surgical disciplines (see Supplementary Table S1), which reflects the conditions that apply to the perioperative risk evaluation settings in clinical practice and gives the translation approach a bit more feasibility.

Nevertheless, some important limitations must be considered. Even though our dataset was very high quality and extensive, the sample size was small. Therefore, the model comparison used 50% of the full dataset, providing a training sample that was smaller than the full sample. Larger sample sizes tend to make unconstrained classification trees and logistic regression more competitive whereas smaller sample sizes do the opposite. Therefore we would like to argue that the choice of method should be guided by the availability of data: the more data there are, the better the case for using more complex methods to achieve a better predictive capability. In smaller (and often typical) datasets, the case is stronger for the FFTrees. Finally, we were able to provide initial insights with our analysis, but these still need to be validated.

5. Conclusions

Within the pre-operative setting, FFTrees outperformed the more complex UDT algorithm with respect to their predictive balanced accuracy, nearing the prediction level of logistic regression. Within the postoperative setting, FFTrees outperformed both complex models. Applying the best-performing algorithms to the full datasets we propose an FFTree using four cues (CCI, site of surgery, ASA PS and frailty status) for the pre-operative setting and an FFTree containing only three cues (duration of anesthesia, age and CCI) for the postoperative setting. Given that both FFTrees contain considerably fewer criteria, which can be easily memorized and applied by health professionals in daily routine, FFTrees could help identify patients requiring intensified POD screening.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11195629/s1, Supplementary Information S1: Assessment of

pre-operative cognitive impairment. Supplementary Information S2: Assessment of frailty status. Supplementary Information S3: Further information on the models applied. Supplementary Table S1: Overview of surgical sites of the surgical procedures (n = 394). References [48–54] are cited in the supplementary materials.

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References

1. Hewer, W.; Thomas, C.; Drach, L.M. *Delir Beim Alten Menschen*; W. Kohlhammer GmbH: Stuttgart, Germany, 2016; Volume 1.
2. Rengel, K.F.; Pandharipande, P.P.; Hughes, C.G. Postoperative delirium. *Presse Med.* **2018**, *47 Pt 2*, e53–e64. [CrossRef] [PubMed]
3. Bickel, H.; Gradinger, R.; Kochs, E.; Forstl, H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement. Geriatr. Cogn. Disord.* **2008**, *26*, 26–31. [CrossRef] [PubMed]
4. Moskowitz, E.E.; Overbey, D.M.; Jones, T.S.; Jones, E.L.; Arcomano, T.R.; Moore, J.T.; Robinson, T.N. Post-operative delirium is associated with increased 5-year mortality. *Am. J. Surg.* **2017**, *214*, 1036–1038. [CrossRef] [PubMed]
5. Davis, D.H.; Muniz Terrera, G.; Keage, H.; Rahkonen, T.; Oinas, M.; Matthews, F.E.; Cunningham, C.; Polvikoski, T.; Sulkava, R.; MacLullich, A.M.; et al. Delirium is a strong risk factor for dementia in the oldest-old: A population-based cohort study. *Brain A J. Neurol.* **2012**, *135*, 2809–2816. [CrossRef]
6. Daiello, L.A.; Racine, A.M.; Yun Gou, R.; Marcantonio, E.R.; Xie, Z.; Kunze, L.J.; Vlassakov, K.V.; Inouye, S.K.; Jones, R.N.; Alsop, D.; et al. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. *Anesthesiology* **2019**, *131*, 477–491. [CrossRef]
7. Sprung, J.; Roberts, R.O.; Weingarten, T.N.; Nunes Cavalcante, A.; Knopman, D.S.; Petersen, R.C.; Hanson, A.C.; Schroeder, D.R.; Warner, D.O. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *Br. J. Anaesth.* **2017**, *119*, 316–323. [CrossRef]
8. Wang, J.; Li, Z.; Yu, Y.; Li, B.; Shao, G.; Wang, Q. Risk factors contributing to postoperative delirium in geriatric patients postorthopedic surgery. *Asia-Pac. Psychiatry Off. J. Pac. Rim Coll. Psychiatr.* **2015**, *7*, 375–382. [CrossRef]
9. Berian, J.R.; Zhou, L.; Russell, M.M.; Hornor, M.A.; Cohen, M.E.; Finlayson, E.; Ko, C.Y.; Rosenthal, R.A.; Robinson, T.N. Postoperative Delirium as a Target for Surgical Quality Improvement. *Ann. Surg.* **2017**, *268*, 93–99. [CrossRef]
10. Inouye, S.K. Predisposing and precipitating factors for delirium in hospitalized older patients. *Dement. Geriatr. Cogn. Disord.* **1999**, *10*, 393–400. [CrossRef]
11. Aldecoa, C.; Bettelli, G.; Bilotta, F.; Sanders, R.D.; Audisio, R.; Borozdina, A.; Cherubini, A.; Jones, C.; Kehlet, H.; MacLullich, A.; et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur. J. Anaesthesiol.* **2017**, *34*, 192–214. [CrossRef]
12. Ho, M.H.; Nealon, J.; Igwe, E.; Traynor, V.; Chang, H.R.; Chen, K.H.; Montayre, J. Postoperative Delirium in Older Patients: A Systematic Review of Assessment and Incidence of Postoperative Delirium. *Worldviews Evid. Based Nurs.* **2021**, *18*, 290–301. [CrossRef] [PubMed]
13. Maldonado, J.R. Neuropathogenesis of delirium: Review of current etiologic theories and common pathways. *Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry* **2013**, *21*, 1190–1222. [CrossRef]

14. Saller, T.; Hofmann-Kiefer, K. Kenntnis und Umsetzung der S3-Leitlinie zum Delirmanagement in Deutschland. *Anaesthesist* **2016**, *65*, 755–762. [CrossRef] [PubMed]
15. Cherak, S.J.; Soo, A.; Brown, K.N.; Ely, E.W.; Stelfox, H.T.; Fiest, K.M. Development and validation of delirium prediction model for critically ill adults parameterized to ICU admission acuity. *PLoS ONE* **2020**, *15*, e0237639. [CrossRef] [PubMed]
16. de la Varga-Martínez, O.; Gómez-Pesquera, E.; Muñoz-Moreno, M.F.; Marcos-Vidal, J.M.; López-Gómez, A.; Rodenas-Gómez, F.; Ramasco, F.; Álvarez-Refojo, F.; Tamayo, E.; Gómez-Sánchez, E. Development and validation of a delirium risk prediction preoperative model for cardiac surgery patients (DELIPRECAS): An observational multicentre study. *J. Clin. Anesth.* **2021**, *69*, 110158. [CrossRef] [PubMed]
17. Inouye, S.K.; Viscoli, C.M.; Horwitz, R.I.; Hurst, L.D.; Tinetti, M.E. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann. Intern. Med.* **1993**, *119*, 474–481. [CrossRef]
18. Pagali, S.R.; Miller, D.; Fischer, K.; Schroeder, D.; Egger, N.; Manning, D.M.; Lapid, M.I.; Pignolo, R.J.; Burton, M.C. Predicting Delirium Risk Using an Automated Mayo Delirium Prediction Tool: Development and Validation of a Risk-Stratification Model. *Mayo Clin. Proc.* **2021**, *96*, 1229–1235. [CrossRef]
19. Wang, G.; Zhang, L.; Qi, Y.; Chen, G.; Zhou, J.; Zhu, H.; Hao, Y. Development and Validation of a Postoperative Delirium Prediction Model for Elderly Orthopedic Patients in the Intensive Care Unit. *J. Healthc. Eng.* **2021**, *2021*, 9959077. [CrossRef]
20. Wassenaar, A.; van den Boogaard, M.; van Achterberg, T.; Slooter, A.J.; Kuiper, M.A.; Hoogendoorn, M.E.; Simons, K.S.; Maseda, E.; Pinto, N.; Jones, C.; et al. Multinational development and validation of an early prediction model for delirium in ICU patients. *Intensive Care Med.* **2015**, *41*, 1048–1056. [CrossRef]
21. Green, L.; Mehr, D. What alters physicians' decisions to admit to the coronary care unit? *J. Fam. Pract.* **1997**, *45*, 219–226.
22. Phillips, N.; Neth, H.; Woike, J.K.; Gaissmaier, W. FFTrees: A toolbox to create, visualize, and evaluate fast-and-frugal decision trees. *Judgm. Decis. Mak.* **2017**, *12*, 344–368.
23. Wegwarth, O. Deciding the Fast & Frugal Way on the Application of Pharmacodiagnostic Tests in Cancer Care? A Comparative Study of Oncologists', Pathologists', and Cancer Patients' Decision Making in Germany and the USA. Ph.D. Thesis, Humboldt University, Berlin, Germany, 2007.
24. Wegwarth, O.; Day, R.W.; Gigerenzer, G. Decisions on pharmacogenomic tests in the USA and Germany. *J. Eval. Clin. Pract.* **2011**, *17*, 228–235. [CrossRef] [PubMed]
25. Woike, J.K.; Hoffrage, U.; Martignon, L. Integrating and testing natural frequencies, naïve Bayes, and fast-and-frugal trees. *Decision* **2017**, *4*, 234–260. [CrossRef]
26. Pitt, M.A.; Myung, I.J.; Zhang, S. Toward a method of selecting among computational models of cognition. *Psychol. Rev.* **2002**, *109*, 472–491. [CrossRef] [PubMed]
27. Gigerenzer, G.; Todd, P.M. *The ABC Research Group. Simple Heuristics that Makes Us Smart*; Oxford University Press: Oxford, UK, 1999.
28. Gigerenzer, G.; Goldstein, D.G. Reasoning the fast and frugal way: Models of bounded rationality. *Psychol. Rev.* **1996**, *103*, 650–669. [CrossRef] [PubMed]
29. Martignon, L.; Katsikopoulos, K.V.; Woike, J.K. Categorization with limited resources: A family of simple heuristics. *J. Math. Psychol.* **2008**, *52*, 352–361. [CrossRef]
30. Heinrich, M.; Müller, A.; Lammers-Lietz, F.; Borchers, F.; Mörgeli, R.; Kruppa, J.; Zacharias, N.; Winterer, G.; Slooter, A.J.C.; Spies, C.D. Radiological, Chemical, and Pharmacological Cholinergic System Parameters and Neurocognitive Disorders in Older Presurgical Adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **2021**, *76*, 1029–1036. [CrossRef]
31. American Psychiatric Association Publishing. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; American Psychiatric Association Publishing: Washington, DC, USA, 2013. [CrossRef]
32. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **1987**, *40*, 373–383. [CrossRef]
33. UNESCO Institute for Statistics. *International Standard Classification of Education ISCED 2011*; UNESCO Institute for Statistics: Montreal, QC, Canada, 2012. Available online: http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf (accessed on 2 May 2020).
34. Mahoney, F.I.; Barthel, D.W. Functional evaluation: The barthel index. *Md. State Med. J.* **1965**, *14*, 61–65.
35. Lawton, M.P.; Brody, E.M. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **1969**, *9*, 179–186. [CrossRef]
36. Guigoz, Y.; Vellas, B.; Garry, P.J. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr. Rev.* **1996**, *54*, S59–S65. [CrossRef] [PubMed]
37. Yesavage, J.A.; Brink, T.L.; Rose, T.L.; Lum, O.; Huang, V.; Adey, M.; Leirer, V.O. Development and validation of a geriatric depression screening scale: A preliminary report. *J. Psychiatr. Res.* **1982**, *17*, 37–49. [CrossRef]
38. Saunders, J.B.; Aasland, O.G.; Babor, T.F.; de la Fuente, J.R.; Grant, M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption—II. *Addiction* **1993**, *88*, 791–804. [CrossRef]
39. Breiman, L.; Friedman, J.H.; Olshen, R.A.; Stone, C.J. *Classification and Regression Trees*, 1st ed.; Routledge: London, UK, 1984. [CrossRef]
40. Therneau, T.; Atkinson, B. Recursive Partitioning and Regression Trees. R Package Version 4.1-16. 2019. Available online: https://CRAN.R-project.org/package=rpart (accessed on 2 May 2020).

41. R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2020. Available online: https://www.R-project.org/ (accessed on 2 May 2020).
42. Luan, S.; Schooler, L.J.; Gigerenzer, G. A signal-detection analysis of fast-and-frugal trees. *Psychol. Rev.* **2011**, *118*, 316–338. [CrossRef]
43. Radtke, F.M.; Franck, M.; MacGuill, M.; Seeling, M.; Lütz, A.; Westhoff, S.; Neumann, U.; Wernecke, K.D.; Spies, C.D. Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. *Eur. J. Anaesthesiol.* **2010**, *27*, 411–416. [CrossRef]
44. Robinson, T.N.; Raeburn, C.D.; Tran, Z.V.; Angles, E.M.; Brenner, L.A.; Moss, M. Postoperative delirium in the elderly: Risk factors and outcomes. *Ann. Surg.* **2009**, *249*, 173–178. [CrossRef]
45. Marcantonio, E.R.; Goldman, L.; Mangione, C.M.; Ludwig, L.E.; Muraca, B.; Haslauer, C.M.; Donaldson, M.C.; Whittemore, A.D.; Sugarbaker, D.J.; Poss, R.; et al. A clinical prediction rule for delirium after elective noncardiac surgery. *Jama* **1994**, *271*, 134–139. [CrossRef] [PubMed]
46. van den Boogaard, M.; Pickkers, P.; Slooter, A.J.; Kuiper, M.A.; Spronk, P.E.; van der Voort, P.H.; van der Hoeven, J.G.; Donders, R.; van Achterberg, T.; Schoonhoven, L. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: Observational multicentre study. *BMJ* **2012**, *344*, e420. [CrossRef]
47. Kim, E.M.; Li, G.; Kim, M. Development of a Risk Score to Predict Postoperative Delirium in Patients With Hip Fracture. *Anesth. Analg.* **2020**, *130*, 79–86. [CrossRef]
48. Rasmussen, L.S.; Larsen, K.; Houx, P.; Skovgaard, L.T.; Hanning, C.D.; Moller, J.T. The assessment of postoperative cognitive function. *Acta Anaesthesiol. Scand.* **2001**, *45*, 275–289. [CrossRef]
49. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M156. [CrossRef] [PubMed]
50. Vellas, B.; Guigoz, Y.; Garry, P.J.; Nourhashemi, F.; Bennahum, D.; Lauque, S.; Albarede, J.L. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* **1999**, *15*, 116–122. [CrossRef]
51. Ensrud, K.E.; Ewing, S.K.; Cawthon, P.M.; Fink, H.A.; Taylor, B.C.; Cauley, J.A.; Dam, T.-T.; Marshall, L.M.; Orwoll, E.S.; Cummings, S.R.; et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *J. Am. Geriatr. Soc.* **2009**, *57*, 492–498. [CrossRef]
52. Rockwood, K.; Andrew, M.; Mitnitski, A. A comparison of two approaches to measuring frailty in elderly people. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2007**, *62*, 738–743. [CrossRef]
53. Siscovick, D.S.; Fried, L.; Mittelmark, M.; Rutan, G.; Bild, D.; O'Leary, D.H. Exercise intensity and subclinical cardiovascular disease in the elderly. The Cardiovascular Health Study. *Am. J. Epidemiol.* **1997**, *145*, 977–986. [CrossRef] [PubMed]
54. Podsiadlo, D.; Richardson, S. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* **1991**, *39*, 142–148. [CrossRef] [PubMed]

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Perioperative Outcomes in Patients Who Received Spinal Chloroprocaine for Total Hip or Knee Arthroplasty—Consecutive Case Series Study

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Abstract: Spinal anaesthesia is an established component of perioperative management for fast-track lower limbs arthroplasty. Short-acting local anaesthetics may present an interesting option for primary non-complicated knee (TKA) and hip (THA) arthroplasty. We describe the perioperative outcomes in patients operated under fixed 50 mg spinal chloroprocaine for total hip and knee replacement. In this retrospective case series study, 65 patients were analysed (median age 65 years, 55% females, benefit from THA (n = 31), TKA (n = 25), and unicompartmental knee arthroplasty (n = 9)). In all cases, anaesthesia duration (87 min) was sufficient for successful surgery (52 min). Up to 45% of patients (THA and less in TKA) developed postoperative pain in the post-anaesthesia care unit (PACU), requiring intravenous morphine titration (up to 7.5 mg). One patient developed severe breakthrough pain requiring advanced regional analgesia. The median PACU stay was up to 97 min (less in TKA), and the incidence of nausea and urinary retention was low. All patients were able to start physical therapy on the same day of surgery. These findings encourage the use of a short-acting agent for spinal anaesthesia in patients with primary non-complicated arthroplasty; however, the relay analgesia should be systematically implemented to avoid breakthrough pain in PACU.

Keywords: arthroplasty; chloroprocaine; perioperative outcome; spinal anaesthesia

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1. Introduction

Although the best choice of anaesthesia technique for major orthopaedic surgery is a matter of debate, spinal anaesthesia is an established component of perioperative management for fast-track lower limb arthroplasty [1,2].

Bupivacaine is one of the most common options for spinal anaesthesia in total hip (THA) or total knee (TKA) arthroplasty. It produces a well-known dose-dependent long-acting anaesthesia and analgesia, associated with postoperative urinary retention and delayed motor function recovery, which have led to multiple studies looking for a minimally effective dose, with non-compromising anaesthesia safety and fast-track protocols [3,4]. However, even lower doses of bupivacaine were not constantly associated with a significant improvement in the term of events, precluding the meeting of fast-track protocol requirements [5].

The development of modern approaches in hip and knee arthroplasty—such as anterior access in hip surgery, the sub-vastus/medial parapatellar approach in knee surgery, and robot-assisted techniques for both procedures—allowed for a significant reduction in surgical trauma (associated with bleeding, tissue damage, pneumatic tourniquet, and postoperative pain) and procedure time (shortening of surgical time by less than 60 min) [6,7]. A

one-night stay or ambulatory setting has become a daily practice in patients with scheduled THA and TKA. Postoperative anaesthesia and analgesia, adapted to the particularities of the patients, surgical trauma, and operating time, must maximize the principles of early rehabilitation and preserve functional capacity.

The arsenal of local anaesthetics used for spinal anaesthesia in orthopaedic surgery includes chloroprocaine, a short-acting local anaesthetic, particularly interesting for scheduled short-duration orthopaedic surgery. The advantages of this molecule include the motor and sensory block of rapid installation, the duration of analgesia allowing surgery of 60 min, and the low rate of adverse effects associated with spinal anaesthesia compared to that with conventional agents (bupivacaine) (hypotension, urinary retention, delay in lifting sensory block).

Spinal anaesthesia with 50 mg of chloroprocaine produces surgical anaesthesia of 60 ± 15 min [8] with respect to outpatient surgery criteria [9]. In our centre, we use spinal chloroprocaine anaesthesia in selected patients scheduled for TKA or THA, and in whom the duration and course of surgery are short and predictable. To date, only one team has recently reported their positive experience of using spinal anaesthesia with chloroprocaine in the context of hip surgery [10].

In this paper, we describe the perioperative outcomes of such patients based on our experience. Our report will be an addition to the literature, to develop anaesthesia techniques adapted to the patient's journey and integrate surgical particularities.

The main objective of our retrospective study was to analyse the safety and efficacy of short-term spinal anaesthesia (with chloroprocaine) in selected patients who benefit from hip or knee arthroplasty. The secondary objectives were to analyse the characteristics of postoperative analgesia related to the anaesthetic technique, and the events related to this anaesthesia during the postoperative 24 h.

2. Materials and Methods

A retrospective study on patients who received spinal anaesthesia for total knee or hip surgery during the years 2020–2021 in a French regional referral centre was performed.

Through the institutional health records system, we identified patients who received spinal anaesthesia with chloroprocaine for elective primary knee or hip arthroplasty. For that, we solicited an Institutional Review Board and sent all identified patients an informed consent form. According to French legislation, if there was no negative response to the use of data for the research, patients were included in the analysed cohort.

We extracted demographic data (age, sex, body mass index, American Society of Anesthesiologists (ASA) status, prostate hypertrophy history), perioperative data (time from spinal anaesthesia to incision, surgical time, blood loss, surgical incidents, the tourniquet use), anaesthesia-related data (level of spinal puncture, sensitive bloc level, time to the motor block, intraoperative need for sedation, bradycardia (heart rate less than 60 per minute), hypotension (mean blood pressure less than 60 or the use of vasopressors)), postoperative data (duration of motor block, the need of supplementary analgesia in post-anaesthesia care unit (PACU), the incidence of moderate to severe pain in PACU, the length of stay (LOS) in PACU, the incidence of postoperative urinary retention and nausea/vomiting in first 24 h), and failure to initiate physical therapy at day 0.

2.1. Standard Institutional Protocol for Perianesthesia Management

All patients scheduled for arthroplasty undergo a standard institutional pre-anaesthesia evaluation at least 3 weeks before surgery. Spinal anaesthesia (hyperbaric bupivacaine and sufentanyl), combined with optional regional anaesthesia (such as a single shot or continued adductor canal block for UKA/TKA or ilioinguinal/lateral cutaneous nerve block), and perioperative comfort choice (stepwise choice of sound-isolating earphones, music, distracting virtual reality, or light propofol sedation) is a common approach, used in more than 90% of cases at our institution. A prilocaine–lidocaine patch is systematically used for local analgesia of the lumbar puncture site [11]. Optional anxiolysis, based on

Amsterdam Anxiety and Information Scale (APAIS) or a single numeric score, may be administered at the patient's admission to the hospital or pre-anaesthesia room [12,13].

After surgery, patients are admitted to the post-anaesthesia care unit. Additional analgesics are administered as needed. This includes a stepwise administration of acetaminophen, ketoprofen, and morphine titration *pro re nata*. The volume of the bladder is systematically assessed with a bedside ultrasound device (Bladderscan®, Verathon Medical BV, Amsterdam, The Netherlands). An evacuator urinary catheter is placed if the bladder volume is more than 500 mL after the failure of spontaneous urination. Discharge criteria are based on the Aldrete score [14], and the Bromage scale [15] is used to assess the resolution of motor block after spinal anaesthesia.

2.2. Choice of Patients for Spinal Anesthesia with Chloroprocaine

Patients are systematically informed about the choice of local anaesthetics during the pre-anaesthesia clinics. The ultimate decision to use spinal chloroprocaine is made by an anaesthesiologist after a discussion with the operating surgeon. The following criteria are taken into account: (1) the absence of anticipated surgical difficulties for scheduled primary arthroplasty, (2) compensated comorbidities, and (3) patient compliance. We use a single 50 mg dose of chloroprocaine (Clorotekal®, Nordic Group BV, Hoofddorp, The Netherlands) without additives.

2.3. Surgical Procedures for TKA, UKA and THA

Total knee arthroplasty is performed using the medial parapatellar approach. THA is performed through the anterior approach. In all cases, a local anaesthetic infiltration (LIA) is used. In TKA/UKA a three times infiltration with Ropivacaine 0.2% is used according to the Kerr and Kohan technique [16]. In THA pericapsular and fascia iliaca infiltration is used with Ropivacaine 0.2%. All arthroplasties were performed by senior surgeons.

2.4. Outcomes

The primary outcome was the proportion of patients with successful anaesthesia technique using chloroprocaine. Anaesthesia was deemed to be successful if there was no need to convert spinal anaesthesia to general intraoperatively, to use deep sedation and/or remifentanil for the patient's discomfort in the surgical site (pain in the surgical site) during the procedure course.

Secondary outcomes were the need for advanced analgesia techniques for the breakthrough pain in PACU (strong opioids and/or regional block, e.g., fascia iliaca compartment or saphenous), and the incidence of PONV and UR in the first 24 h postoperatively.

2.5. Statistical Considerations

This is a retrospective non-probability sampling cohort descriptive study where no hypothesis to test was stated. Descriptive quantitative and qualitative statistics are used, data are presented as median [interquartile range, IRQ] or frequency (percentage) as appropriate; non-parametric statistic methods are used for comparisons. A p-value less than 0.5 indicates statistical significance. Statistical analyses were performed using JMP 11 (SAS, Cary, NC, USA) software.

2.6. Ethics Consideration

Our work received the approval of the institutional ethic committee, CSE-HCL-IRB 00013204, with the reference number 22-729, 25 January 2022, and communicated to the French National Commission on Informatics and Liberty (CNIL), report N 22-5729. All patients included in this study received informed consent for their medical data use. In accordance with French legislation, a written patient's agreement was not required for any part of the study.

3. Results

From 2020 through 2021, sixty-eight patients who received chloroprocaine for THA/TKA/UKA were identified. One month after informed consent was sent, two patients expressed their unwillingness to participate. Medical data for 66 patients were extracted; in one patient spinal anaesthesia failed before the surgery due to a technical problem; finally, 65 patients were included and analysed. Table 1 illustrates patients' characteristics, principal and supplementary anaesthesia techniques used before the surgery, the onset of anaesthesia, surgical timing, and blood loss.

Table 1. Demographic, medical, and surgical characteristics (total, breakdown by THA, TKA, UKA).

	Total	**THA**	**TKA**	**UKA**
	***n* = 65**	***n* = 31**	***n* = 25**	***n* = 9**
Age	65 [59 to 72]	62.6 [56 to 71]	67 [59.8 to 76]	68 [65 to 71]
Sex, Females	36 (55%)	16 (52%)	17 (68%)	3 (33%)
BMI	24 [21 to 29]	24.3 [20.8 to 28]	23.6 [21.4 to 31]	23.8 [21 to 29]
ASA III	8 (12%)	4 (13%)	3 (12%)	1 (11%)
Hospitalization type (outpatients)	44 (68%)	24 (77%)	14 (56%)	6 (67%)
BPH (males, n = 29)	11 (38%)	2 (13%)	5 (62%)	4 (66%)
LP level	L3-L4 36 (55%) L4-L5 29 (45%)	L3-L4 13 (42%) L4-L5 18 (58%)	L3-L4 17 (68%) L4-L5 8 (32%)	L3-L4 6 (67%) L4-L5 3 (33%)
Level of block, Th	10 [8 to 11]	10 [7 to 11]	10 [8 to 11]	10 [8.5 to 11]
Preoperative regional anaesthesia	27 (42%)	3 (10%)	19 (76%)	4(33%)
ACB		n/a	9 (36%)	4 (33%)
C-ACB		n/a	10 (40%)	0 (11%)
LCNB		3 (10%)	n/a	n/a
Time to surgical block	8 [6 to 10]	8 [6 to 10]	7 [6 to 10]	7 [5.5 to 10]
Time to incision	16 [13 to 19.5]	17 [14 to 22]	14 [11 to 18]	14 [11.5 to 16.5]
Length of surgery	52 [44.5 to 57.5]	44 [41 to 48]	55 [52.5 to 62]	58 [51.5 to 66]
Tourniquet use	10 (15.6%)	n/a	1 (4%)	9 (100%)
Blood loss, mL	200 [150 to 300]	200 [105 to 300]	250 [150 to 300]	100 [75 to 225]

THA—total hip arthroplasty; TKA—total knee arthroplasty; UKA—unicompartmental knee arthroplasty. BMI—body mass index; BPH—benign prostatic hyperplasia; LP—lumbar puncture, Th—thoracic level; ACB—adductor canal block; C-ACB—continuous adductor canal block; LCNB—lateral cutaneous nerve block. Data are presented as median [IQR] and frequency (percentage).

3.1. Primary Outcome

No failed spinal anaesthesia regarding the surgical timing was observed. Sixty-five patients were operated under a single spinal 50 mg chloroprocaine dose without the need for deep sedation or conversion into general anaesthesia.

3.2. Secondary Outcomes

In one case the surgeon complained of operative discomfort due to incomplete motor block; however, no conversion to general anaesthesia or deep sedation was required (TKA). Half of the patients received light sedation with propofol (target-controlled infusion, Schnider model for site-effect concentration [17]). Five (4 with THA and 1 with TKA) patients received remifentanil perfusion in the middle of the surgery for painful discomfort beyond the surgical site (spine or shoulder pain due to positioning on the surgical table). Data are reported in Table 2.

Regarding postoperative findings, the time for complete regression of the motor block (charted as Bromage score 0—full flexion of the knee and feet) after 50 mg of chloroprocaine was about 90 min. Up to thirty percent of patients developed pain in the surgical site, requiring morphine titration. One patient (THA) had breakthrough pain requiring postoperative fascia iliaca block. Median PACU LOS was 1 h; however, in patients with THA this time was higher. The incidence of PONV was 4%, and one patient developed urinary retention. All patients were able to start physical therapy on the same day of surgery (Table 3). No transient neurological symptoms related to spinal anaesthesia, LIA, or regional anaesthesia were captured from the electronic health records.

Table 2. Perioperative secondary outcomes.

	Total	THA	TKA	UKA	*p*
	n = 65	*n* = 31	*n* = 25	*n* = 9	
Surgical discomfort	1 (1.5%)	0 (0%)	1 (4%)	0 (0%)	n/a
Hypotension	5 (7.7%)	3 (10%)	2 (8%)	0 (0%)	0.629
No sedation	26 (40%)	11 (35%)	11 (44%)	4 (44%)	0.617
VR	2 (3%)	0 (0%)	1 (4%)	1 (12%)	0.223
Propofol (light sedation)	33 (51%)	17 (55%)	12 (48%)	4 (44%)	0.808
Remifentanil	5 (7%)	4 (13%)	1 (4%)	0 (0%)	0.299

THA—total hip arthroplasty; TKA—total knee arthroplasty; UKA—unicompartmental knee arthroplasty. RA—regional anaesthesia, LP—lumbar puncture; IO—intraoperative, VR—virtual reality glasses. Data are presented as median [IQR] and frequency (percentage).

Table 3. Postoperative secondary outcomes.

	Total	THA	TKA	UKA	*p*
	n = 65	*n* = 31	*n* = 25	*n* = 9	
Time to complete regression of the motor block, min	87 [78 to 97.5]	84 [76 to 96]	94 [79 to 101]	88 [82 to 93]	0.466
Patients having pain ≥4/10 in PACU	20 (30%)	14 (45%)	5 (20%)	1 (11%)	0.0260
with preoperative RA	5 (8%)	1 (3%)	3 (12%)	1 (11%)	0.759
without preoperative RA	14 (22%)	13 (42%)	1 (4%)	0 (0%)	0.130
Pain level in PACU (out of 10) *	5 [4 to 7]	5 [4 to 7.5]	4 [3.5 to 8.5]	7 [7 to 7]	0.705
Morphine use *, mg	6.5 [5.25–10]	7.5 [4.75 to 7.75]	6 [6 to 10.5]	6 [6 to 6]	0.933
PACU LOS, min	61.4 [52 to 115]	97 [60 to 141]	61.5 [42 to 93]	61 [29.6 to 66]	0.0008
PONV	3 (4%)	1 (3%)	2 (8%)	0 (0%)	0.543
UR	1 (1.5%)	1 (3%)	0 (0%)	0 (0%)	0.573
Fail to initiate PT	0	0	0	0	

THA—total hip arthroplasty; TKA—total knee arthroplasty; UKA—unicompartmental knee arthroplasty. MB—motor block; PACU—post-anaesthesia care unit; RA—regional anaesthesia; PONV—postoperative nausea and vomiting; LOS—length of stay; PONV—postoperative nausea and vomiting; UR—urinary retention. PT—physical therapy. *—data reported for patients with pain >4/10. Data are presented as median [IQR] and frequency (percentage).

We illustrate the timing of anaesthesia, surgery, and PACU stay in Figure 1.

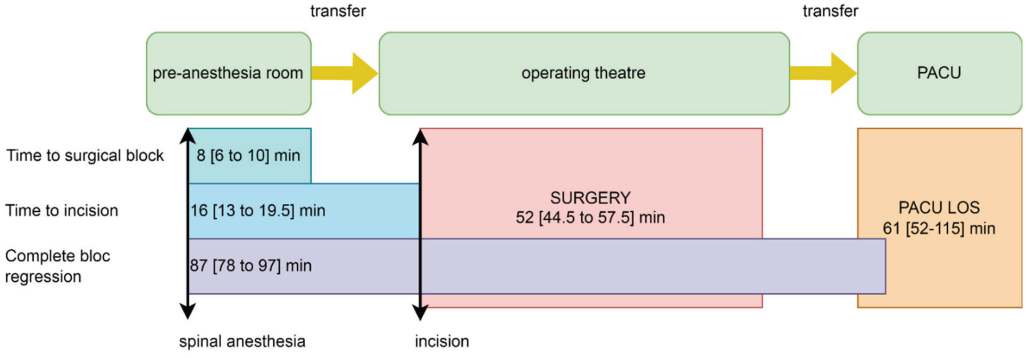

Figure 1. The sequence of anaesthesia, surgery, and PACU in the overall studied population. PACU—post-anaesthesia care unit; LOS—length of stay.

4. Discussion

We report our experience of spinal anaesthesia with a fixed 50 mg dose of chloroprocaine in selected patients, who benefited from non-complicated primary knee or hip arthroplasty with a fast-track protocol. In all patients, the duration of spinal anaesthesia allowed them to accomplish surgery with success and with no need for deep sedation or general anaesthesia. Although plain chloroprocaine for spinal anaesthesia is recommended for procedures not exceeding 40 min [18], several studies have reported its safe use for procedures lasting up to 100 min [19], including hip arthroplasty [10].

Other analysed data are in line with already published outcomes regarding PK/PD-related effects of chloroprocaine (surgical bloc onset, duration, and regression), surgical timing, PACU LOS, PONV, and voiding [9,19,20].

The constant increase in the volume of fast-track and outpatient orthopaedic surgery will predictably lead to the highly controlled optimisation of the anaesthesia care, surgery, and discharge process. For instance, short-acting spinal local anaesthetics were tested and demonstrated a more consistent return of lower-extremity motor function compared to bupivacaine, without a concomitant increase in complications potentially associated with spinal anaesthetics [21,22].

However, we would like to emphasize two points observed in our real-life study.

First, we noticed a significant number of patients who developed pain in the PACU and required morphine titration. The proportion of such patients was two times higher in those who benefited from THA compared to TKA. Moreover, one patient with THA needed an advanced regional analgesia technique for breakthrough pain in PACU. Indeed, chloroprocaine provides a fast onset and relatively short duration, but also the abrupt cessation of a sensitive block because of its high dissociation constant, low partition coefficient, and protein binding and degradation by plasma cholinesterase [23]. As such, a pre-emptive relay analgesia technique should be systematically implemented in patients who benefit from chloroprocaine spinal anaesthesia for short but painful procedures.

All our patients had local infiltration analgesia performed by a surgeon at the end of the procedure. In the case of THA, such a technique probably does not provide 100% relay analgesia. We are not able to conclude if there were some technical flaws while performing LIA; however, the place of systematic preoperative regional analgesia is apparent, with the best technique yet to be defined in both THA and TKA patients.

Another option may be the addition of a spinal short-acting opioid adjuvant to chloroprocaine, such as fentanyl or sufentanyl to extend the time of the analgesic effect [24], but the potential of spinal opioids to produce urinary retention may alter fast-track protocol adherence.

The second point is the changes in the established workflow when chloroprocaine is used for arthroplasty patients (Figure 1). We have a two-bed pre-anaesthesia room adjunct to three orthopaedic operating theatres. In this room, patients are prepared—venous line, standard monitoring, surgical site skin preparation—and receive all types of regional anaesthesia including spinal. Patients are transferred to the operating theatre when the sensitive block is established at least at Th10 level and in-theatre anaesthetic and surgical devices and consumables are ready.

The quick onset of motor block and limited surgical block duration may put pressure on and increase the workload of paramedical staff. Therefore, managing nurses and clinicians should probably be informed about such particularities, as well as PACU nurses to organize fast discharge.

Regarding the eventual breakthrough pain in PACU, following quick chloroprocaine sensitive block regression, patients should receive additional information about relay analgesia and treatment options available (opioids titration or advanced regional analgesia techniques) in PACU to prevent dissatisfaction.

Our study has several limitations. It is an observational study with a convenience sample size, with the strength of case series design (high external validity and no interference in the treatment decision process), and well-known limitations (lack of comparison group, susceptible to selection bias). However, the sample size of 60 patients per group yielded 80% power in a randomized trial comparing spinal chloroprocaine and bupivacaine in terms of time-effect [19]. Therefore, our observations may be valid for the duration of the surgical block. For the analysis of secondary outcomes in PACU (PONV, urinary retention, and opioid needs), the number of patients with chloroprocaine is too low to allow a propensity-matched retrospective design, and a prospective randomized controlled study would be methodologically more appropriate. We were not able to analyse the exact causes of breakthrough pain in our patients; however, this study allowed us to improve our local practice and to implement systematic complementary regional analgesia in addition to LIA in all patients operated under chloroprocaine spinal anaesthesia. Transient neurological symptoms associated with anaesthesia techniques were not captured from the electronic health records, and therefore were not evaluated. The workload of clinicians might be in-

teresting to study when comparing the implementation of different anaesthesia techniques. Patients' opinions and satisfaction were not measured.

5. Conclusions

In conclusion, in selected patients undergoing primary knee or hip arthroplasty, the use of spinal anaesthesia with 50 mg of chloroprocaine was successful and safe for the surgery lasting ≤60 min. Up to 45% of patients may experience breakthrough pain in PACU if relay analgesia is not anticipated. These data may be useful for designing controlled studies.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, reviewed by the Institutional Ethics Committee of the Hospices Civils de Lyon, CSE-HCL-IRB 00013204, with the reference number 22-729, 25 January 2022, communicated to the French National Commission on Informatics and Liberty (CNIL), report N 22-5729, and registered with ClinicalTrials.gov (NCT05365074).

Informed Consent Statement: All patients included in this study received informed consent for their medical data use. Following French legislation, a written patient's agreement was not required for any part of the study.

Data Availability Statement: All data generated in this study are the property of the Hospices Civils de Lyon and not will be shared.

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References

1. Baratta, J.L.; Schwenk, E.S. Regional versus general anesthesia for ambulatory total hip and knee arthroplasty. *Curr. Opin. Anaesthesiol.* **2022**, *5*, 621–625. [CrossRef] [PubMed]
2. Kehlet, H.; Aasvang, E.K. Regional or general anesthesia for fast-track hip and knee replacement—What is the evidence? *F1000Research* **2015**, *4*, 1–6. [CrossRef] [PubMed]
3. van Egmond, J.C.; Verburg, H.; Derks, E.A.; Langendijk, P.N.J.; Icli, C.; van Dasselaar, N.T.; Mathijssen, N.M.C. Optimal dose of intrathecal isobaric bupivacaine in total knee arthroplasty. *Can. J. Anaesth. = J. Can. D'anesthesie* **2018**, *65*, 1004–1011. [CrossRef] [PubMed]
4. Lemoine, A.; Mazoit, J.X.; Bonnet, F. Modelling of the optimal bupivacaine dose for spinal anaesthesia in ambulatory surgery based on data from systematic review. *Eur. J. Anaesthesiol.* **2016**, *33*, 846–852. [CrossRef]
5. Herndon, C.L.; Levitsky, M.M.; Ezuma, C.; Sarpong, N.O.; Shah, R.P.; Cooper, H.J. Lower dosing of bupivacaine spinal anesthesia is not associated with improved perioperative outcomes after total joint arthroplasty. *Arthroplast Today* **2021**, *11*, 6–9. [CrossRef]
6. Batailler, C.; Swan, J.; Sappey Marinier, E.; Servien, E.; Lustig, S. New technologies in knee arthroplasty: Current concepts. *J. Clin. Med.* **2020**, *10*, 47. [CrossRef]
7. Petis, S.; Howard, J.L.; Lanting, B.L.; Vasarhelyi, E.M. Surgical approach in primary total hip arthroplasty: Anatomy, technique and clinical outcomes. *Can. J. Surg. J. Can. Chir.* **2015**, *58*, 128–139. [CrossRef]
8. Smith, K.N.; Kopacz, D.J.; McDonald, S.B. Spinal 2-chloroprocaine: A dose-ranging study and the effect of added epinephrine. *Anesth. Analg.* **2004**, *98*, 81–88. [CrossRef]
9. Ghisi, D.; Boschetto, G.; Spinelli, A.M.; Giannone, S.; Frugiuele, J.; Ciccarello, M.; Bonarelli, S. Spinal anaesthesia with chloroprocaine hcl 1% for elective lower limb procedures of short duration: A prospective, randomised, observer-blind study in adult patients. *BMC Anesth.* **2021**, *21*, 58. [CrossRef]
10. Herndon, C.L.; Martinez, R.; Sarpong, N.O.; Geller, J.A.; Shah, R.P.; Cooper, H.J. Spinal anesthesia using chloroprocaine is safe, effective, and facilitates earlier discharge in selected fast-track total hip arthroplasty. *Arthroplast. Today* **2020**, *6*, 305–308. [CrossRef]

11. Frattinger, C.; Grange, I.; Line Cavalie, M.; Rouhana, K.; Dziadzko, M. Pose de pommade analgésique pour rachianesthésie en chirurgie orthopédique programmée. *Soins* **2018**, *63*, 14–17. [CrossRef]
12. Dziadzko, M.; Mazard, T.; Bonhomme, M.; Raffin, M.; Pradat, P.; Forcione, J.-M.; Minjard, R.; Aubrun, F. Preoperative anxiety in the surgical transfer and waiting area: A cross-sectional mixed method study. *J. Clin. Med.* **2022**, *11*, 2668. [CrossRef]
13. Moerman, N.; van Dam, F.S.A.M.; Muller, M.J.; Oosting, H. The amsterdam preoperative anxiety and information scale (apais). *Anesth. Analg.* **1996**, *82*, 445–451. [PubMed]
14. Aldrete, J.A. The post-anesthesia recovery score revisited. *J. Clin. Anesth.* **1995**, *7*, 89–91. [CrossRef]
15. Bromage, P.R. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiol. Scandinavica. Suppl.* **1965**, *16*, 55–69. [CrossRef] [PubMed]
16. Kerr, D.R.; Kohan, L. Local infiltration analgesia: A technique for the control of acute postoperative pain following knee and hip surgery: A case study of 325 patients. *Acta Orthop.* **2008**, *79*, 174–183. [CrossRef]
17. Schnider, T.W.; Minto, C.F.; Shafer, S.L.; Gambus, P.L.; Andresen, C.; Goodale, D.B.; Youngs, E.J. The influence of age on propofol pharmacodynamics. *Anesthesiology* **1999**, *90*, 1502–1516. [CrossRef]
18. *Clorotekal 10 mg/mL, Solution for Injection, Transparency Committee Opinion ct12667*; HAS: Saint-Denis, France, 2013.
19. Camponovo, C.; Wulf, H.; Ghisi, D.; Fanelli, A.; Riva, T.; Cristina, D.; Vassiliou, T.; Leschka, K.; Fanelli, G. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: A prospective, observer-blinded, randomised, controlled trial. *Acta Anaesthesiol. Scand.* **2014**, *58*, 560–566. [CrossRef]
20. Teunkens, A.; Vermeulen, K.; Van Gerven, E.; Fieuws, S.; Van de Velde, M.; Rex, S. Comparison of 2-chloroprocaine, bupivacaine, and lidocaine for spinal anesthesia in patients undergoing knee arthroscopy in an outpatient setting: A double-blind randomized controlled trial. *Reg. Anesth. Pain Med.* **2016**, *41*, 576–583. [CrossRef]
21. Schwenk, E.S.; Kasper, V.P.; Smoker, J.D.; Mendelson, A.M.; Austin, M.S.; Brown, S.A.; Hozack, W.J.; Cohen, A.J.; Li, J.J.; Wahal, C.S.; et al. Mepivacaine versus bupivacaine spinal anesthesia for early postoperative ambulation. *Anesthesiology* **2020**, *133*, 801–811. [CrossRef]
22. Wyles, C.C.; Pagnano, M.W.; Trousdale, R.T.; Sierra, R.J.; Taunton, M.J.; Perry, K.I.; Larson, D.R.; Amundson, A.W.; Smith, H.M.; Duncan, C.M.; et al. More predictable return of motor function with mepivacaine versus bupivacaine spinal anesthetic in total hip and total knee arthroplasty: A double-blinded, randomized clinical trial. *J. Bone Jt. Surg.* **2020**, *102*, 1609–1615. [CrossRef] [PubMed]
23. Taylor, A.; McLeod, G. Basic pharmacology of local anaesthetics. *BJA Educ.* **2020**, *20*, 34–41. [CrossRef] [PubMed]
24. Singariya, G.; Choudhary, K.; Kamal, M.; Bihani, P.; Pahuja, H.; Saini, P. Comparison of analgesic efficacy of intrathecal 1% 2-chloroprocaine with or without fentanyl in elective caesarean section: A prospective, double-blind, randomised study. *Indian J. Anaesth.* **2021**, *65*, 102–107. [CrossRef] [PubMed]

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Article

Midazolam versus Dexmedetomidine in Patients at Risk of Obstructive Sleep Apnea during Urology Procedures: A Randomized Controlled Trial

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Abstract: Benzodiazepines are the most commonly used sedatives for the reduction of patient anxiety. However, they have adverse intraoperative effects, especially in obstructive sleep apnea (OSA) patients. This study aimed to compare dexmedetomidine (DEX) and midazolam (MDZ) sedation considering intraoperative complications during transurethral resections of the bladder and prostate regarding the risk for OSA. This study was a blinded randomized clinical trial, which included 115 adult patients with a mean age of 65 undergoing urological procedures. Patients were divided into four groups regarding OSA risk (low to medium and high) and choice of either MDZ or DEX. The doses were titrated to reach a Ramsay sedation scale score of 4/5. The intraoperative complications were recorded. Incidence rates of desaturations (44% vs. 12.7%, $p = 0.0001$), snoring (76% vs. 49%, $p = 0.0008$), restlessness (26.7% vs. 1.8%, $p = 0.0044$), and coughing (42.1% vs. 14.5%, $p = 0.0001$) were higher in the MDZ group compared with DEX, independently of OSA risk. Having a high risk for OSA increased the incidence rates of desaturation (51.2% vs. 15.7%, $p < 0.0001$) and snoring (90% vs. 47.1%, $p < 0.0001$), regardless of the sedative choice. DEX produced fewer intraoperative complications over MDZ during sedation in both low to medium risk and high-risk OSA patients.

Keywords: dexmedetomidine; midazolam; STOP BANG questionnaire; intraoperative complications; spinal anesthesia; sedation; obstructive sleep apnea; transurethral resection of bladder; transurethral resection of prostate

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1. Introduction

Obstructive sleep apnea (OSA) is the most common sleep breathing disorder, characterized by repetitive episodes of complete (apnea) or partial airway obstruction (hypopnea) during sleep, often resulting in a reduction in blood oxygen saturation and usually terminated by brief arousals [1,2]. Depending on the diagnostic and sample criteria, the prevalence in the general population is estimated to vary between 3 and 24%. Still, it is generally much higher in patients undergoing surgery (24 to 41%) and in the obese and ageing populations [1,2]. OSA is considered to be a chronic disease associated with cardiovascular and metabolic consequences [3]. Therefore, patients with OSA are exposed to a higher risk for perioperative complications and represent a challenge to anesthesiologists during the entire perioperative period [4–6].

Today, in preoperative screening, some questionnaires are recommended, among which the STOP-BANG questionnaire is the most commonly used [4,7,8]. High-risk patients had a five times greater chance of developing unexpected perioperative complications [9].

Spinal anesthesia offers many advantages over general anesthesia, and, as such, is the technique of choice for transurethral resections of the prostate and bladder (TURB/TURP) [10], and is preferable in OSA patients [11]. In addition, sedation has increased patient satisfaction during regional anesthesia [12,13]. Still, when sedation is induced, close attention is

required for potential adverse events, such as upper airway obstruction, hypoventilation, desaturation, and any cardiovascular complications [14]. Midazolam (MDZ) is one of the oldest and most familiar drugs for sedation. However, relatively stable hemodynamics can cause hypoxia, even in healthy individuals, by reducing hypoxic ventilator responses and inducing upper airway obstruction [15]. Dexmedetomidine (DEX) acts as a selective α2 adrenergic receptor agonist with sedative and analgesic effects [16]. Moreover, DEX has been less associated with the severity of OSA and respiratory depression [17]. Patients with OSA may be at increased risk for adverse respiratory events from intravenous benzodiazepine sedation. At the same time, there is a lack of evidence to assess the adverse effects of α-2 agonists in the OSA population [11].

So far, MDZ and DEX have been compared in various studies and types of surgery under regional anesthesia, showing fewer intraoperative complications in patients sedated with DEX than those with MDZ [18–20]. The majority of patients who underwent TURB and TURP are older and are at increased risk for OSA [7]. Therefore, the primary objective of the current study was to investigate the effects of benzodiazepine and alfa-2 agonists under spinal anesthesia on intraoperative complications such as desaturation, snoring, coughing, and restlessness in patients with TURB and TURP regarding the risk for OSA.

2. Materials and Methods

In this prospective, randomized, blinded clinical study, 115 adult patients aged between 18 and 80, who were scheduled to undergo elective TURB and TURP under spinal anesthesia between April 2021 and February 2022, were enrolled. The study was approved by the Ethics Committee of the University Hospital of Split (Class: 500-03/21-01/12; Registration number: 2181-147-01/06/M.S.-20-02) and was conducted under all of the ethical principles of the Seventh Revision of the Helsinki Declaration from 2013. All subjects gave their informed and individually signed consent for inclusion before participating in the study. The clinical trial registry number is NCT04817033 and can be found at Clinical-trials.gov, 20 August 2022. The exclusion criteria were as follows: regional anesthesia contraindications, American Society of Anesthesiologists (ASA) physical status classification system >III, atrioventricular cardiac block II and III degree, psychotic disorders, dementia, and participants with tracheostomy and allergy on DEX or MDZ.

The STOP-BANG questionnaire includes eight dichotomous (yes/no) questions related to the clinical features of sleep apnea (snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference, and male gender) [7,9]. For each question, answering "yes" scores 1, a "no" response score 0, and the total score ranges from 0 to 8. It classifies participants into three groups based on the STOP-BANG score, as follows: low (0–2), intermediate (3–4), and high risk (5–8). Those with STOP-BANG scores of 3 or 4 can be further classified as having an increased risk for moderate to severe OSA if they have both a STOP (snoring, tiredness, observed apnea, and high blood pressure) score of $\geq$2 and one of the following conditions: (1) BMI > 35 kg/m^2; (2) neck circumference > 40 cm; or (3) are of the male gender.

Before surgery, patients were given the STOP BANG questionnaire. Patients were stratified into two groups according to the STOP-BANG questionnaire results: high (h)-risk OSA, and low- to medium (l-m)-risk OSA. Then, patients in each OSA risk group were allocated by computer-generated permuted block randomization (block size was 10 patients) into the MDZ or DEX group. Thus, in this factorial design, four groups were created: h-risk OSA MDZ, h-risk OSA DEX, l-m risk OSA MDZ, and l-m risk OSA DEX (Figure 1). The group allocations were contained in a closed envelope that was opened before surgery after the completed enrolment procedure.

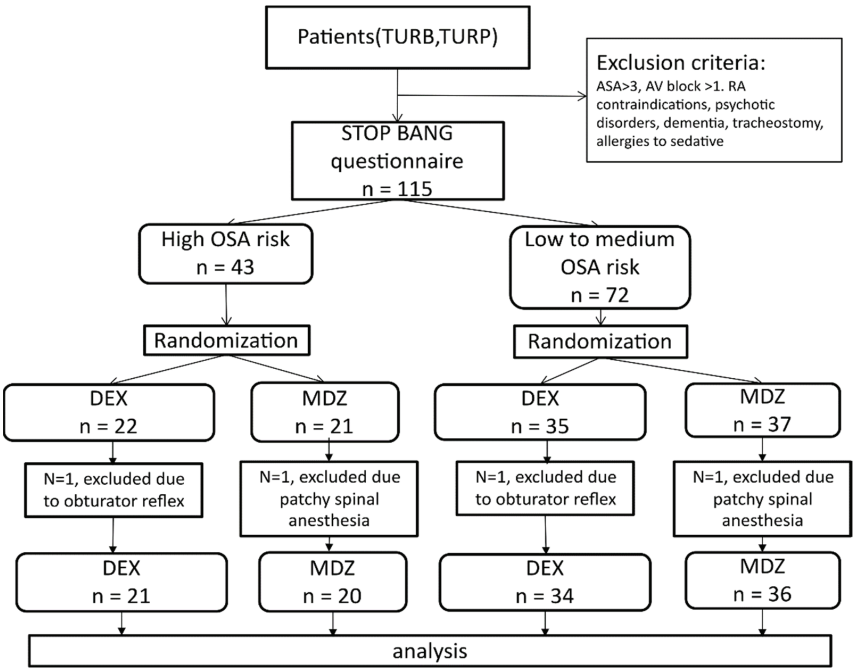

Figure 1. Patient flowchart. OSA—obstructive sleep apnea; TURB—transurethral resection of bladder; TURP—transurethral resection of prostate; RA—regional anesthesia; ASA—American Society of Anesthesiologist; DEX—dexmedetomidine; MDZ—midazolam.

All participants were premedicated with 5 mg of diazepam (Alkaloid, Skopje, N. Macedonia) for 12 h and 1 h before surgery. Thromboprophylaxis (enoxaparin 4000–6000 IU, Sanofi – Aventis Groupe, Paris, France) was given at least 12 h before surgery, depending on the body weight. Patients received an IV cannula with a switch for perfusor in the operating theatre. Non-invasive monitoring (electrodes for ECG, blood pressure cuff, and pulse oximeter) was placed before the induction of spinal anesthesia. The skin was disinfected, and 40 mg of 2% Lidocaine (Belupo, Koprivnica, Croatia) was given subcutaneously at the lumbar vertebrae 3/4 level. A 25 G spinal needle was used, and after the dura and arachnoid were pierced, 12.5–15 mg of 0.5% Levobupivacaine (Fresenius Kabi, Bad Homburg von der Höhe, Germany) was applied. Patients were then positioned in a uniform lithotomy position and a 9 cm high pillow was inserted. Time after a subarachnoid block was T0, and sedation with MDZ or DEX was initiated via continuous intravenous infusion. Drugs were prepared in the following manner: 50 mL of MDZ 0.3 mg/mL (midazolam, B. Braun, Melsungen, Germany) in saline for the MDZ group and 50 mL of DEX 4 μg/mL (Dexdor, Orion Corporation, Espoo, Finland) in saline for the DEX group. MDZ was initiated with a loading dose of 0.25 mg/kg/h (equivalent to 0.04 mg/kg) of ideal body mass, and DEX with loading dose of 0.5 μg/kg for 10 min. Every 10 min, the sedation level was observed with the Ramsay sedation scale (RSS) [21]. We used standard drug dosing [15] similar to other studies [18–20,22]. After the same loading dose, both drugs were titrated individually, that is, the reasons maintenance doses were given in intervals. Equipotency was established by titrating the drugs to achieve an RSS score of 4 or 5 (closed eyes and patient exhibited brisk or sluggish response to a light glabellar tap or loud auditory stimulus). The maintenance dose of MDZ was 0.03 to 0.06 mg/kg/h and 0.2 to 0.7 μg/kg/h for DEX. The independent blinded doctor assessed the RSS level and vital parameters every 10 min, and the primary outcomes. Patients were also blinded. Systolic, diastolic, and mean blood pressure (MAP) were noticed, along with heart rate (HR), oxygen

saturation, RSS level, and adverse intraoperative events: desaturation, snoring as a sign of airway obstruction, cough, and restlessness as factors affecting the surgeon. If peripheral oxygen saturation fell below 90% for longer than 30 s, supplemental oxygen was delivered by facemask with a reservoir bag at a flow of 10 L/min. After approximately 1 min, if oxygenation was still inadequate, chin lift and jaw thrust maneuvers were performed, and an oropharyngeal airway was inserted. If the heart rate fell below 50 bpm, atropine 0.1 mg/kg (Sopharma AD, Sofia, Bulgaria) was given, and if the systolic blood pressure dropped below 100 mmHg (or MAP < 65 mmHg), ephedrine 5 mg (Sintetica, Münster, Germany) bolus was given. The total crystalloid infusion volume was noticed at the end of the surgery. All of the measurements were performed every 10 min and 1 h after surgery in the recovery room.

The sample size was estimated based on the overall rate of intraoperative complications by Silva et al. (18). α was set to 5% and power to 80%. Thus, the required sample size was 27 in both OSA risk groups. The sample size estimate was computed in G*Power software (University of Kiel, Germany).

Statistical Analysis

The dependences of main outcome measures on the studied factors were analyzed by logistical regression. The model included OSA risk and hypnotic treatment as the only variables ($logit[p(outcome)] = \beta_0 + \beta_1 \cdot OSArisk + \beta_2 \cdot drug$). Data are presented as odds ratios or proportions for categorical variables, medians, and IQRs for continuous variables. Furthermore, Mood's test for medians and Fisher's exact test were used to analyze the secondary outcome measures. To aid inference, 95% CI, Akaike informational criteria, and p values were used. p values were interpreted according to the ASA statement on p values. Graphpad Prism 9 was used as software for the statistical analysis (GraphPad Software, San Diego, CA, USA).

Primary outcome measures were as follows: (1) desaturation below 90% and (2) snoring detection regardless of duration or intensity, and (3) coughing and (4) restlessness as factors affecting surgeons because during TURB and TURP, patients have to be relaxed and calm, as their movement could result in a punctured bladder/prostate by surgical resectoscope. So, when the surgeon complained about the participant's movement, investigators checked that on the list. Secondary outcome measures included: hemodynamic changes during sedation (heart rate and arterial blood pressure) and tobacco smoking in anamnesis.

3. Results

A total of 115 patients were enrolled in the present study. Four patients dropped out due to conversion of the anesthesia method from spinal to general, two of them due to patchy spinal, and two due to the obturator reflex that disrupted the surgeon (Figure 1).

The demographic and clinical characteristics in all groups were balanced and in accordance with the patient underlying conditions (Table 1). More specifically, patients with high-risk OSA were more likely to be male; high-risk OSA patients receiving DEX had a greater BMI than the same patients from the low- to medium-risk OSA group ($p = 0.0002$). In both MDZ ($p = 0.0075$) and DEX ($p = 0.0001$) subgroups, the neck circumference was also greater in high-risk OSA patients when compared with the low- to medium-risk OSA patients. DEX patients in the low- to medium-risk OSA group had smaller ASA scores than the same patients in the high-risk OSA group. Finally, in the low- to medium-risk OSA groups, patients receiving DEX needed two additional minutes to close their eyes when compared with the MDZ patients ($p = 0.0052$) (Table 1).

Table 1. Demographic and clinical data.

OSA Risk	Low to Medium				High				*p* Value *
hypnotic	DEX		MDZ		DEX		MDZ		
age (years, median, IQR)	65	61 to 68.25	69.5	61.25 to 69.5	68	63 to 68	69	67 to 71.75	0.1207
sex (male, %)	67.65		80.56		90.48		100		0.0169
BMI (kg/m^2, median, IQR)	25.75 [a]	23.4 to 29.56	28.5	24.59 to 30.03	30.79 [a]	27 to 33.93	28.72	27.44 to 33.29	0.0009
neck circumference (cm, median, IQR)	39 [b]	36.5 to 44	41 [c]	37.5 to 45	46 [b]	42.5 to 48	45 [c]	42.25 to 47	<0.0001
ASA score (median, IQR)	2 [d]	2 to 2	2	2 to 2	2 [d]	2 to 3	2	2 to 2	0.0097
duration of surgical procedure (min., median, IQR)	50	30 to 70	50	30 to 70	40	30 to 70	60	40 to 70	0.3332
time for eyes closing (min., median, IQR)	10 [e]	9 to 11.5	8 [e]	7 to 9	9	7 to 11	9.5	8 to 10.75	0.0389
baseline SpO_2 (%, median, IQR)	97 [f]	96.75 to 99	98 [g]	97 to 98	96 [f,g]	95 to 97	97	96 to 99	0.0053
STOP BANG (point, median, IQR)	3 [h]	2 to 3	3 [i]	2 to 4	5 [h,i]	5 to 6	5 [h,i]	5 to 6	<0.0001

* Kruskal–Wallis test for continuous data and chi square test for categorical data, omnibus *p* value. DEX—dexmedetomidine; MDZ—midazolam; BMI—body mass index; ASA—American Society of Anesthesiologists; OSA—obstructive sleep apnea; [a,b,c,d,e,f,g,h,i]—Dunn's post hoc test, $p < 0.05$.

3.1. Effects of OSA Risk on Primary Outcomes

Having a high risk for OSA increased the incidence of desaturation events from 51.2% to 15.7% (OR = 8.9, 95%CI 3.25 to 28.4, $p < 0.0001$) in comparison with low- to medium-risk for OSA, regardless of sedative choice. Likewise, when snoring events were observed intraoperatively, it was found that high-risk OSA increased the frequency of snoring from 90% to 47.1% (OR = 14.26, 95% CI 4.67 to 55.58, $p < 0.0001$) when compared with low- to medium-risk OSA. Intraoperative coughing or restlessness were not influenced by OSA risk (Table 2).

Table 2. Intraoperative complications.

Outcome	OSA Low to Medium Risk				OSA High Risk				OR (OSA High)	95% CI		OR (Dex)	95% CI	
	DEX (Total *n* = 34)		MDZ (Total *n* = 36)		DEX (Total *n* = 21)		MDZ (Total *n* = 20)			Lower	Upper		Upper	Lower
	n	%	*n*	%	*n*	%	*n*	%						
desaturation	2	5.88%	9	25.00%	5	23.81%	16	80.00%	8.981	3.257	28.4	0.112	0.032	0.323
snoring	10	29.41%	23	63.89%	17	80.95%	20	100.00%	14.26	4.67	55.58	0.195	0.072	0.491
coughing	4	11.76%	14	38.89%	4	19.05%	10	50.00%	1.62	0.66	3.98	0.225	0.084	0.548
restlessness	0	0.00%	9	25.00%	1	4.76%	6	30.00%	1.56	0.48	5.01	0.049	0.002	0.261

OSA—obstructive sleep apnea, DEX—dexmedetomidine, MDZ—midazolam, OR—odds ratio.

3.2. Effects of Hypnotic on Primary Outcomes

Here, 25 out of 56 (44%) MDZ patients had desaturation events compared with 7 out of 55 (12.7%) DEX patients (OR = 0.11, 95%CI 0.28 to 0.03, $p = 0.0001$). Desaturations were resolved by only applying supplemental oxygen in the DEX group, but in MDZ group, seven patients (28% of desaturated MDZ patients) needed additional support ($p = 0.3002$). A chin lift was performed six times and the jaw thrust maneuver once in MDZ patients (three of them were high-risk OSA and four were low- to medium-risk OSA). In addition, 43 out of 56 (76%) MDZ patients snored in contrast with 27 out of 55 (49%) DEX patients (OR = 0.19, 95% CI 0.78 to 0.08, $p = 0.0008$).

DEX decreased the probability of coughing by approximately 4.5 times, as coughing was noticed in 8 out of 55 (14.5%) DEX patients vs. 24 out of 56 (42.1%) MDZ patients (OR = 0.22 95%CI 0.55 to 0.08, $p = 0.0018$). Smoking did not seem to be a risk factor for

intraoperative coughing (OR = 0.82, 95%CI 0.31 to 2.11, $p = 0.6973$). The restlessness, which on its own may disrupt the surgeon, was noted in 1 out of 55 (1.8%) DEX patients as opposed to 15 out of 56 (26.7%) MDZ patients (OR = 0.049, 95%CI 0.26 to 0.002, $p = 0.0044$) (Table 2). In the MDZ group, two deliriums (2/56, 2.56%,) were observed, whereas none were observed in the DEX group.

3.3. Effects of Hypnotics on Hemodynamics

When it comes to hemodynamics, the maximal decreases from baseline in MAP and HR were analyzed. OSA risk did not show any significant effects on MAP or HR decrease when compared with the baseline (i.e., pre-anesthesia measurement) (Figure 2a,b). The DEX group median decrease in MAP from baseline was 26.07 mmHg (IQR 17.8 to 33 mmHg), whereas MDZ caused a median decrease of 21.45 mmHg (IQR 16.33 to 31.26 mmHg) ($p = 0.07$, Figure 2a,c). However, 15 (27%) patients in the DEX group needed ephedrine, whereas 5 (9%) MDZ patients were given the same treatment ($p = 0.0141$).

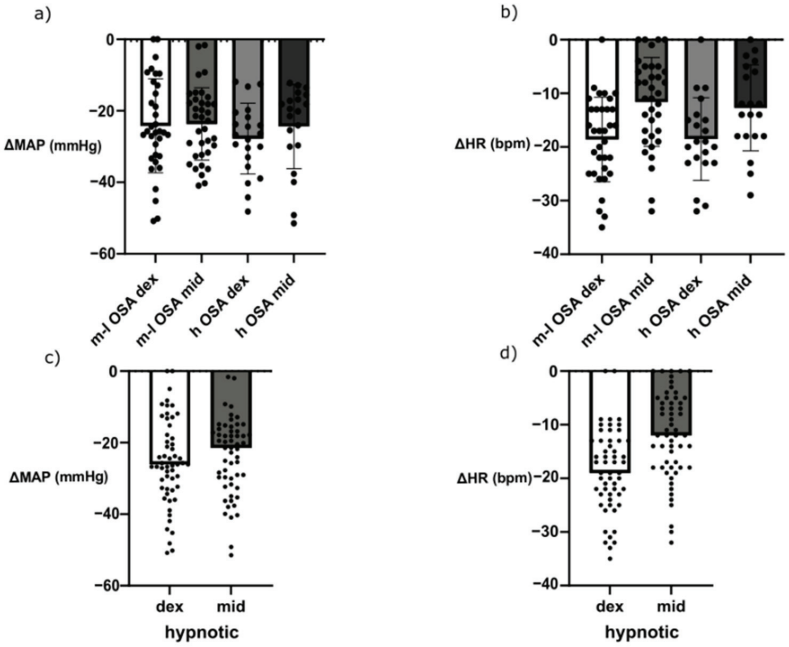

Figure 2. Hemodynamic outcomes. Maximal decrease from the baseline (i.e., pre-anesthesia measurement) of the mean arterial pressure (MAP) and heart rate (HR) in patients stratified by OSA risk and hypnotic; mean and SD are also presented (**a**,**b**). Maximal decrease from baseline of MAP and HR in patients stratified by hypnotic only; median is also presented (**c**,**d**).

When it comes to heart rate, DEX patients experienced a median decrease of 19 bmp (IQR 13 to 23 bpm) compared with MDZ patients who had a median decrease of 12 bpm (IQR 5.2 to 18 bpm) ($p = 0.0002$, Figure 2b,d). Atropine was given to nine (16%) patients in the DEX group and only once (2%) in MDZ group ($p = 0.0082$).

4. Discussion

In this prospective, randomized, controlled trial, we explored if DEX or MDZ is a better sedative for TURB and TURP under spinal anesthesia regarding OSA risk. The results of our study indicate that DEX was superior to MDZ in both anesthesiologic and surgical parts, as it had fewer airway complications and patients were calmer during surgery, regardless of the OSA risk severity.

Most recent guidelines for the management of patients with OSA recommend the use of regional anesthesia when applicable [11]. During spinal anesthesia, sedation is needed as it reduces patient anxiety and may be considered as a means to increase the patient's acceptance of regional anesthetic techniques [23]. DEX has been suggested to cause minimal respiratory depression. Many studies have shown its stable respiratory profile during spinal anesthesia [18,20,24]. On the other hand, Lodenius et al. measured upper airway collapsibility during DEX and propofol sedation in healthy volunteers and showed that DEX sedation does not inherently protect against upper airway obstruction [25]. Maybe these different effects of DEX are because of distinct loading and maintenance dose regimens. There are few studies regarding the administration of DEX in OSA patients and sedation [26–29]. Most of them compared it with propofol and showed better or similar results in respiratory effects. However, all of these sedations were in invasive procedures such as drug-induced sleep endoscopy. For sedation under spinal anesthesia, Shin et al. reported that DEX sedation was shown to be associated with a reduced incidence of obstructive airway events in patients with mild OSA compared with propofol sedation [22]. In addition, a recent study provided evidence of a positive correlation of the STOP-BANG questionnaire with oxygen saturation in patients undergoing DEX sedation, suggesting the use of the STOP-BANG score for preoperative evaluation and DEX sedation management during spinal anesthesia [30].

We found fewer desaturation episodes (i.e., airway complications) in patients treated with DEX when compared with MDZ, regardless of OSA risk, and also noticed a similar effect regarding snoring. In addition, our findings showed that high-risk OSA patients had a four times greater incidence of adverse respiratory events (23.8% vs. 5.8%) than low- to medium-risk of OSA patients treated with DEX. No eligible studies compared patients' risk of adverse events under α2 agonists sedation with regards to confirmed OSA diagnosis [11].

During surgery, patients had to be calm and there should not have been any movement as there was a risk of perforation by the surgical resectoscope. We achieved it with moderate sedation (closed eyes, RSS 4/5), because the pain stimulus was already blocked by spinal anesthesia. It was reported that MDZ could have paradoxical reactions such as confusion, violent behavior, and restlessness [18,31,32], which is in accordance with our findings, where MDZ caused significantly more incidents of restlessness and coughing compared with DEX, which disturbed surgeons, while OSA risk had no effect on such events.

DEX acts as a selective α2 adrenergic receptor agonist and is known to cause hypotension and bradycardia due to decreased centrally mediated sympathetic tone [33]. Spinal anesthesia has a similar effect, although the lithotomy position preserves some drop in blood pressure. Although it did not reach the level of statistical significance, we did find a difference in MAP changes from baseline between DEX and MDZ groups. Furthermore, much more ephedrine was given in DEX group, and DEX showed a significantly decreased median heart rate compared with MDZ. Atropine was given more frequently to DEX patients, which corresponds with previous findings [25,34].

Similar to our results, Silva et al. showed the benefits of DEX over MDZ among older patients, but in different types of surgeries with various body positions within different regional anesthesia methods [18]. Our study was the first to investigate the advantages of different sedative choices in the context of OSA risk, in spinal anesthesia in TURB and TURP surgeries under a uniform lithotomy position (with a 9 cm high pillow) with both sedatives administered via continuous intravenous infusion without the use of opioids. This study proposes the use of the DEX over MDZ in sedation management for TURB and TURP surgeries.

This study has some limitations. It is well known that polysomnography remains the gold standard in sleep investigation and the diagnosis of OSA. Because of the limitations for performing polysomnography in our Split Sleep Center during the COVID pandemic, we could evaluate the risk of OSA for patients using the STOP-BANG questionnaire. Snoring was observed as an indication of upper airway obstruction in our study. However, it is

very difficult to precisely define the presence of snoring due to the different intensities, durations, and level of obstructions, which indicates the need for standardization in clinical trials. In addition, one of limitations is that this study was done in one center and the results could be different in centers not premedicating before such procedures. We only followed up patients during the intraoperative period, hence it would be interesting to prolong that follow up in future studies, so that outcomes such as risk of dysuria due to atropine administration, delirium, and time spent in hospital can be observed.

In conclusion, DEX sedation was shown to be associated with a reduced incidence of airway complications and patients were calmer with less surgery-disturbing factors of restlessness and coughing in comparison with MDZ sedation, for both the low- to medium-risk and high-risk OSA patients. Although DEX-treated patients showed more hemodynamic instability, this was easily resolved by medications and thus we recommend DEX as the sedative of choice for TURB and TURP under spinal anesthesia.

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Institutional Review Board Statement: The study was approved by the Ethics Committee of the University Hospital of Split (Class: 500-03/21-01/12; Registration number: 2181-147-01/06/M.S.-20-02), and was conducted under all of the ethical principles of the Seventh Revision of the Helsinki Declaration from 2013.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets are available upon reasonable request to the corresponding author.

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References

1. Roesslein, M.; Chung, F. Obstructive sleep apnoea in adults: Peri-operative considerations: A narrative review. *Eur. J. Anaesthesiol.* **2018**, *35*, 245–255. [CrossRef] [PubMed]
2. Madhusudan, P.; Wong, J.; Prasad, A.; Sadeghian, E.; Chung, F.F. An update on preoperative assessment and preparation of surgical patients with obstructive sleep apnea. *Curr. Opin. Anaesthesiol.* **2018**, *31*, 89–95. [CrossRef] [PubMed]
3. Goyal, S.K.; Sharma, A. Atrial fibrillation in obstructive sleep apnea. *World J. Cardiol.* **2013**, *5*, 157–163. [CrossRef] [PubMed]
4. Corso, R.; Russotto, V.; Gregoretti, C.; Cattano, D. Perioperative management of obstructive sleep apnea: A systematic review. *Minerva Anestesiol.* **2018**, *84*, 81–93. [CrossRef] [PubMed]
5. Ng, K.T.; Lee, Z.X.; Ang, E.; Teoh, W.Y.; Wang, C.Y. Association of obstructive sleep apnea and postoperative cardiac complications: A systematic review and meta-analysis with trial sequential analysis. *J. Clin. Anesth.* **2020**, *62*, 109731. [CrossRef]
6. Pivetta, B.; Sun, Y.; Nagappa, M.; Chan, M.; Englesakis, M.; Chung, F. Postoperative outcomes in surgical patients with obstructive sleep apnoea diagnosed by sleep studies: A meta-analysis and trial sequential analysis. *Anaesthesia* **2022**, *77*, 818–828. [CrossRef]
7. Chung, F.; Yegneswaran, B.; Liao, P.; Chung, S.A.; Vairavanathan, S.; Islam, S.; Khajehdehi, A.; Shapiro, C.M. STOP Questionnaire. A Tool to Screen Patients for Obstructive Sleep Apnea. *Anesthesiology* **2008**, *108*, 812–821. [CrossRef]
8. Wang, S.; Li, S.; Zhao, Y.; Zhao, X.; Zhou, Z.; Hao, Q.; Luo, A.; Sun, R. Preoperative screening of patients at high risk of obstructive sleep apnea and postoperative complications: A systematic review and meta-analysis. *J. Clin. Anesth.* **2022**, *79*, 110692. [CrossRef]
9. Seet, E.; Chua, M.; Liaw, C.M. High STOP-BANG questionnaire scores predict intraoperative and early postoperative adverse events. *Singap. Med. J.* **2015**, *56*, 212–216. [CrossRef]
10. Bhattacharyya, S.; Bisai, S.; Biswas, H.; Tiwary, M.K.; Mallik, S.; Saha, S.M. Regional anesthesia in transurethral resection of prostate (TURP) surgery: A comparative study between saddle block and subarachnoid block. *Saudi J. Anaesth.* **2015**, *9*, 268–271. [CrossRef]

11. Memtsoudis, S.G.; Cozowicz, C.; Nagappa, M.; Wong, J.; Joshi, G.P.; Wong, D.T.; Doufas, A.G.; Yilmaz, M.; Stein, M.H.; Krajewski, M.L.; et al. Society of Anesthesia and Sleep Medicine Guideline on Intraoperative Management of Adult Patients With Obstructive Sleep Apnea. *Anesth. Analg.* **2018**, *127*, 967–987. [CrossRef] [PubMed]
12. Pollock, J.E.; Neal, J.M.; Liu, S.S.; Burkhead, D.; Polissar, N. Sedation during spinal anesthesia. *Anesthesiology* **2000**, *93*, 728–734. [CrossRef] [PubMed]
13. De Andrés, J.; Valía, J.C.; Gil, A.; Bolinches, R. Predictors of patient satisfaction with regional anesthesia. *Reg. Anesth.* **1995**, *20*, 498–505. [PubMed]
14. Becker, D.E.; Haas, D.A. Management of complications during moderate and deep sedation: Respiratory and cardiovascular considerations. *Anesth. Prog.* **2007**, *54*, 59–68. [CrossRef]
15. Miller, R.D. *Miller's Anesthesia*; Elsevier Saunders: Philadelphia, PA, USA, 2009.
16. Hall, J.E.; Uhrich, T.D.; Barney, J.A.; Arain, S.R.; Ebert, T.J. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth. Analg.* **2000**, *90*, 699–705. [CrossRef]
17. Hsu, Y.W.; Cortinez, L.I.; Robertson, K.M.; Keifer, J.C.; Sum-Ping, S.T.; Moretti, E.W.; Young, C.C.; Wright, D.R.; Macleod, D.B.; Somma, J. Dexmedetomidine pharmacodynamics: Part I: Crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. *Anesthesiology* **2004**, *101*, 1066–1076. [CrossRef]
18. Silva, J.M., Jr.; Katayama, H.T.; Nogueira, F.A.M.; Moura, T.B.; Alves, T.L.; de Oliveira, B.W. Comparison of dexmedetomidine and benzodiazepine for intraoperative sedation in elderly patients: A randomized clinical trial. *Reg. Anesth. Pain Med.* **2019**, *44*, 319–324. [CrossRef]
19. Jo, Y.Y.; Lee, D.; Jung, W.S.; Cho, N.R.; Kwak, H.J. Comparison of Intravenous Dexmedetomidine and Midazolam for Bispectral Index-Guided Sedation During Spinal Anesthesia. *Med. Sci. Monit.* **2016**, *22*, 3544–3551. [CrossRef]
20. Choi, Y.M.; Choi, E.J.; Ri, H.S.; Park, J.Y.; You, J.A.; Byeon, G.J. The effect of dexmedetomidine and midazolam on combined spinal-epidural anesthesia in patients undergoing total knee arthroplasty. *Anesth. Pain Med.* **2020**, *15*, 111–119. [CrossRef]
21. Kress, J.P.; Hall, J.B. Sedation in the mechanically ventilated patient. *Crit. Care Med.* **2006**, *34*, 2541–2546. [CrossRef]
22. Shin, H.J.; Kim, E.Y.; Hwang, J.W.; Do, S.H.; Na, H.S. Comparison of upper airway patency in patients with mild obstructive sleep apnea during dexmedetomidine or propofol sedation: A prospective, randomized, controlled trial. *BMC Anesthesiol.* **2018**, *18*, 120. [CrossRef] [PubMed]
23. Höhener, D.; Blumenthal, S.; Borgeat, A. Sedation and regional anaesthesia in the adult patient. *Br. J. Anaesth.* **2008**, *100*, 8–16. [CrossRef] [PubMed]
24. Shah, P.J.; Dubey, K.P.; Sahare, K.K.; Agrawal, A. Intravenous dexmedetomidine versus propofol for intraoperative moderate sedation during spinal anesthesia: A comparative study. *J. Anaesthesiol. Clin. Pharmacol.* **2016**, *32*, 245–249. [CrossRef] [PubMed]
25. Lodenius, Å.; Maddison, K.J.; Lawther, B.K.; Scheinin, M.; Eriksson, L.I.; Eastwood, P.R.; Hillman, D.R.; Fagerlund, M.J.; Walsh, J.H. Upper Airway Collapsibility during Dexmedetomidine and Propofol Sedation in Healthy Volunteers: A Nonblinded Randomized Crossover Study. *Anesthesiology* **2019**, *131*, 962–973. [CrossRef] [PubMed]
26. Capasso, R.; Rosa, T.; Tsou, D.Y.-A.; Nekhendzy, V.; Drover, D.; Collins, J.; Zaghi, S.; Camacho, M. Variable Findings for Drug-Induced Sleep Endoscopy in Obstructive Sleep Apnea with Propofol versus Dexmedetomidine. *Otolaryngol. Head Neck Surg.* **2016**, *154*, 765–770. [CrossRef]
27. Yoon, B.W.; Hong, J.M.; Hong, S.L.; Koo, S.K.; Roh, H.J.; Cho, K.S. A comparison of dexmedetomidine versus propofol during drug-induced sleep endoscopy in sleep apnea patients. *Laryngoscope* **2016**, *126*, 763–767. [CrossRef]
28. Ma, X.X.; Fang, X.M.; Hou, T.N. Comparison of the effectiveness of dexmedetomidine versus propofol target-controlled infusion for sedation during coblation-assisted upper airway procedure. *Chin. Med. J.* **2012**, *125*, 869–873.
29. Chen, Y.-T.; Sun, C.-K.; Wu, K.-Y.; Chang, Y.-J.; Chiang, M.-H.; Chen, I.-W.; Liao, S.-W.; Hung, K.-C. The Use of Propofol versus Dexmedetomidine for Patients Receiving Drug-Induced Sleep Endoscopy: A Meta-Analysis of Randomized Controlled Trials. *J. Clin. Med.* **2021**, *10*, 1585. [CrossRef]
30. Yun, M.; Kim, J.; Ryu, S.; Han, S.; Shin, Y. The correlation between the STOP-Bang score and oxygen saturation during spinal anesthesia with dexmedetomidine sedation. *Anesth. Pain Med.* **2021**, *16*, 305–311. [CrossRef]
31. Weinbroum, A.A.; Szold, O.; Ogorek, D.; Flaishon, R. The midazolam-induced paradox phenomenon is reversible by flumazenil. Epidemiology, patient characteristics and review of the literature. *Eur. J. Anaesthesiol.* **2001**, *18*, 789–797. [CrossRef]
32. Robin, C.; Trieger, N. Paradoxical reactions to benzodiazepines in intravenous sedation: A report of 2 cases and review of the literature. *Anesth. Prog.* **2002**, *49*, 128–132. [PubMed]
33. Bloor, B.C.; Ward, D.S.; Belleville, J.P.; Maze, M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* **1992**, *77*, 1134–1142. [CrossRef] [PubMed]
34. Riker, R.R.; Shehabi, Y.; Bokesch, P.M.; Ceraso, D.; Wisemandle, W.; Koura, F.; Whitten, P.; Margolis, B.D.; Byrne, D.W.; Ely, E.W.; et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* **2009**, *301*, 489–499. [CrossRef] [PubMed]

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Continuous Ropivacaine Peroneal Nerve Infiltration for Fibula Free Flap in Cervicofacial Cancer Surgery: A Randomized Controlled Study

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Abstract: Introduction: Pain after cervicofacial cancer surgery with free flap reconstruction is both underestimated and undertreated. There is a rational for regional anesthesia at the flap harvest site, but few studies describe it. We assessed the influence of common peroneal nerve infiltration on pain and opioid consumption in patients having oropharyngeal cancer surgery with fibular free flap mandibular reconstruction. **Methods:** After institutional review board (IRB) approval and written informed consent, fifty-six patients were randomly allocated to perineural catheter with ropivacaine infiltration (ROPI) or systemic analgesia (CONTROL). In the ROPI group, an epidural catheter was placed by the surgeon before closure, and ropivacaine 0.2% 15 mL, followed by 4 mL/h during 48 h, was administered. The primary outcomes were pain scores and morphine consumption during the 48 h postoperative period. We also measured ropivacaine concentration at the end of infusion. Finally, we retrospectively assessed long-term pain up to 10 years using electronic medical charts. **Results:** Perineural infiltration of ropivacaine significantly reduced pain scores at the harvest site only at day 1, and did not influence overall postoperative opioid consumption. Ropivacaine assay showed a potentially toxic concentration in 50% of patients. Chronic pain was detected at the harvest site in only one patient (ROPI group), and was located in the cervical area in the case of disease progression. **Discussion:** Although the catheter was visually positioned by the surgeon, continuous ropivacaine infiltration of the common peroneal nerve did not significantly reduce postoperative pain, but induced a blood concentration close to the toxic threshold at day 2. Further studies considering other infiltration locations or other dosing schemes should be tested in this context, both to improve efficacy and reduce potential toxicity.

Keywords: postoperative pain; fibula free flap; ropivacaine infiltration; local anesthetic toxicity

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1. Introduction

Controlling postoperative pain after major cancer surgery is a daily goal for anesthesia teams and a major expectation for the patients.

Efficient postoperative analgesia is reported to positively affect not only the patient's comfort, but many outcomes including mortality, surgical outcomes, hospital stays and costs [1]. It is also a key condition to prevent chronic pain.

Despite the combination of several classes of drugs, constant improved knowledge over years and anticipation, pain is still insufficiently relieved, especially in major cervicofacial cancer patients, both because it is underestimated by communication impairment after tracheotomy and because the needs for analgesia differ enormously between patients [2,3].

Moreover, after oropharyngeal cancer surgery, reconstruction is often necessary, and harvesting a disease-free bone or muscle flap might induce a second location of severe

postoperative pain [4]. Traditional postoperative management of major cervicofacial surgery with free flap reconstruction is a combination of systemic drugs including opioids, non-steroidal anti-inflammatory drugs and other systemic analgesics such as nefopam and paracetamol.

When the flap is taken from a limb such as the fibula flap, additional regional analgesia can be proposed for the common peroneal nerve to provide a postoperative sensory block. This is expected to decrease pain at the harvest site and improve rehabilitation, although the benefit on opioid consumption is unpredictable, since regional analgesia on the limb has no influence on the pain at the cervical site.

Few studies have looked at regional analgesia after free flap reconstructive cervicofacial surgery. Zhang, using a double block bolus [5], and Ferri et al., giving repeated boluses every 8 h through a perineural catheter [6], found a significant benefit on pain after fibula free flap. Conversely, Roof et al. observed no benefit of a constant infusion (ropivacaine 0.2% 6 mL/h, but on a very small group of patients (n = 8) [7].

However, as the pain at the harvest site is expected to last several days [4], there is a rational for continuous perineural infusion that should be further studied.

The purpose of this randomized controlled open study was first to describe the influence of a continuous local anesthetic perineural infiltration at the harvest site (common peroneal nerve) on early postoperative pain and opioid consumption after fibula free flap for mandibular reconstruction.

Subsequently, we assessed the risk of systemic ropivacaine toxicity by collecting blood samples for ropivacaine assay at the end of infusion on postoperative day 2, i.e., at the supposed maximal value of blood concentration. Finally, we retrospectively assessed possible long-term postoperative pain at the cervical and harvest site.

2. Methods

The protocol was approved by the ethical committee of Henri Mondor Hospital, Créteil France (CPPRBP # 04-006), and by our local hospital institutional review board (CSET # 03-1042) in April 2004. Patients scheduled for oropharyngeal cancer or post-cancer (radionecrosis) surgery with fibula free flap reconstruction were eligible. Written informed consent was obtained for each patient during anesthesia preoperative consultation.

Patients were then allocated by a computerized list of random numbers in a 1:1 ratio between ropivacaine regional analgesia of the harvest site associated with systemic analgesia (ROPI group) and systemic analgesia alone (CONTROL group).

Premedication was at the discretion of anesthesiologists. The medical team was aware of randomization, while the patients were not.

Anesthesia was started with remifentanil effect-site target-controlled infusion (Base Primea TCI pump, Minto pharmacokinetic model), propofol and atracurium for tracheal intubation, and maintained with remifentanil, inhalational anesthesia (desflurane or sevoflurane in a mixture of O_2/N_2O 50% each) and bolus injections of atracurium if needed.

Before skin closure, an epidural catheter with end-tip holes only was placed in the ROPI group next to the proximal end of the common peroneal nerve by the plastic surgeon and was fixed by a suture in the skin. After skin closure, 15 mL of ropivacaine 0.2% was injected through the catheter. No further control of the tip of the catheter was performed. This was followed by continuous infusion of ropivacaine 0.2% 4 mL/h initiated in a post-anesthesia care unit (PACU) and administered during 48 h (Ambi T^{TM} PCA pump).

Multimodal postoperative analgesia with other intravenous analgesics (paracetamol, tramadol, nefopam) and morphine 0.15–0.2 mg/kg was administered to all patients.

All patients had planned tracheotomy performed during surgery: postoperative pain assessment took into account this communication difficult, which was explained to the patients preoperatively (day-1).

In the PACU, intravenous (IV) morphine titration was started until visual analog scale < 30/100, and continued with patient-controlled analgesia (PCA) of morphine (no continuous infusion, bolus of 1 mg allowed every 5 min).

The following parameters were recorded: demographic characteristics, duration of anesthesia, remifentanil consumption, intraoperative morphine doses, PACU titration doses and postoperative morphine consumption.

Pain was assessed regularly using a 100 mm visual analog scale (from 0 to 100) both at the fibula site (harvest site) and cervical site.

One blood sample for ropivacaine assay was collected at postoperative hour 48 or at the time of catheter removal (if removed earlier) in 16 of the patients who were allocated to receive ropivacaine. Venous blood was sampled in heparinized tubes. The plasma separated by centrifugation was stored at −18 °C until assayed. Ropivacaine was measured using gas chromatography with a limit of quantification of less than 0.01 $\mu g \cdot mL^{-1}$. The intra- and inter-day coefficients of variation were 6 and 8% at 0.2 $\mu g \cdot mL^{-1}$ [8].

For late postoperative assessment, which was not part of the initial study, a second IRB approval was obtained to extract additional information on possible late postoperative pain (harvest and cervical site) from the electronic chart of patients in September 2020. Retrospective electronic medical chart review up to 10 years was performed. The presence of pain at the cervical and harvesting site and requirement of analgesic treatment was recorded 1, 3, 5 and 10 years after the reconstructive surgery.

3. Statistical Analysis

The sample size was chosen in order to decrease postop VAS at rest from 40 (usual value) to 30 mm in the ROPI group with a common standard deviation of 13 mm, with a bilateral risk error alpha = 0.05 and a power > 90%. For this purpose, 29 patients were necessary in each group.

We checked the normality of distribution of variables using the Shapiro–Wilk test. Continuous variables were compared with a Student's *t*-test or a Mann–Whitney U test and expressed as the mean ± standard deviation or median (interquartile range, IQR), as appropriate. For categorical data, a chi-square test or Fisher's exact test was used. $p < 0.05$ was considered as statistically significant. Statistical analysis was performed with Medcalc v15.4 statistical software (Ostend, Belgium).

4. Results

The study was conducted from June 2004 to November 2007.

The flowchart is displayed in Figure 1. In each group, 29 patients were randomized. Then, 2 were excluded in the ROPI group because surgery was aborted for surgical concerns. Thus, 27 patients in the ROPI group and 29 patients in the CONTROL group were included in this modified post-randomization intention-to-treat analysis.

No difference was noticed in demographic and intraoperative characteristics (Table 1) except for remifentanil consumption, which was significantly higher in the ROPI group.

Postoperative pain score at the harvest site was significantly less at post-op day 1 (H 28, Figure 2) only.

No significant difference was observed between groups in pain score at the cervical site (Figure 3).

Opioid consumption, which is a global consequence of pain at both sites, did not differ significantly between groups (Figure 4).

No adverse events related to the postoperative analgesic catheter and no complications at the harvest site were observed in any group.

Time to discharge from the hospital was not different between groups (Table 1).

The catheter was removed 48 after ropivacaine infusion initiation in 25 patients and earlier in the remaining two. In these patients, removal occurred at 12 and 20 after infusion initiation. Analgesic data were analyzed until the time of removal.

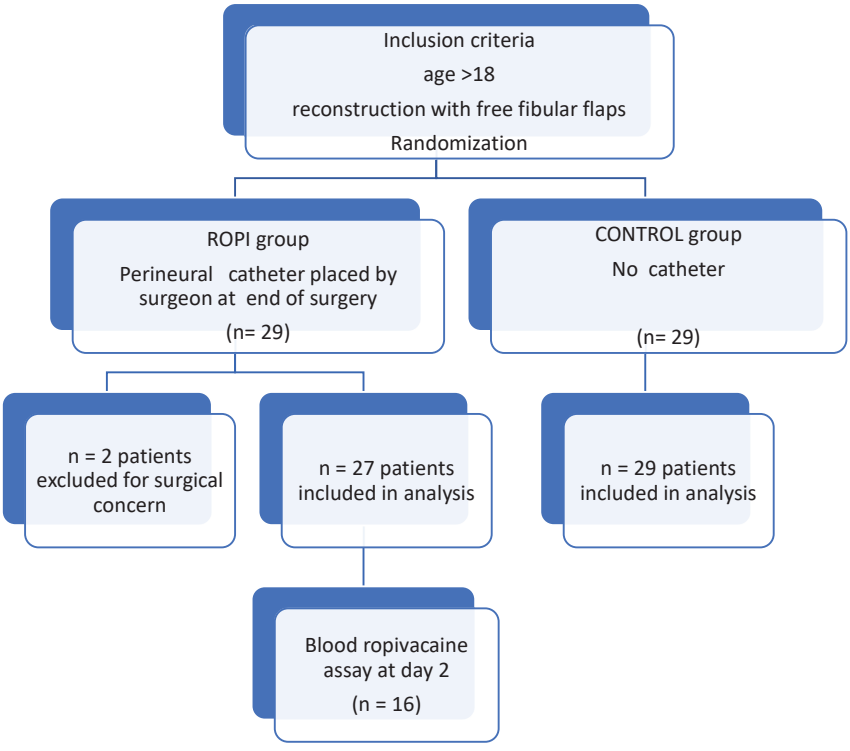

Figure 1. Study flow chart.

Table 1. Demographic and perioperative data (M ± SD).

	ROPI (*n* = 27)	CONTROL (*n*= 29)	*p* Value
Age (y)	53 ± 15	53 ± 15	NS
Weight (kg)	69 ± 16	64 ± 13	NS
Height (cm)	169 ± 7	169 ± 8	NS
Gender male/female (*n*)	21/6	19/10	NS
Preoperative analgesics (number of patients) Opioid Non-opioid	6/27 3 3	8/29 8 0	NS
Remifentanil average rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.092 ± 0.033	0.074 ± 0.031	0.048 *
Duration of anesthesia (min)	557 ± 58	570 ± 58	NS
Morphine cumulative consumption D0-D2 (mg)	51 ± 32	61 ± 38	NS
Length of stay (day)	22 ± 12	23 ± 10	NS

* $p < 0.05$.

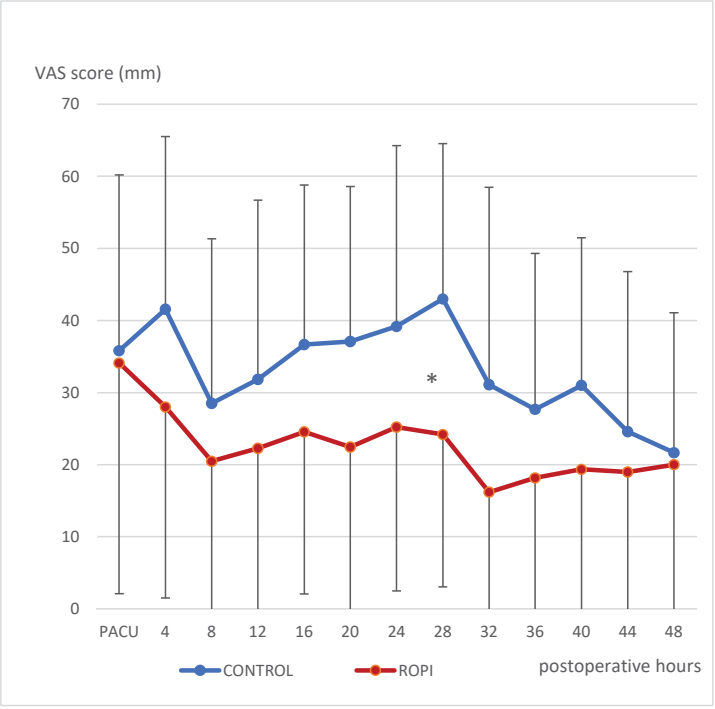

Figure 2. Pain scores at rest (VAS mm) at fibula harvest site. Mean and SD vs. postoperative time (hours) starting in PACU. * $p < 0.05$.

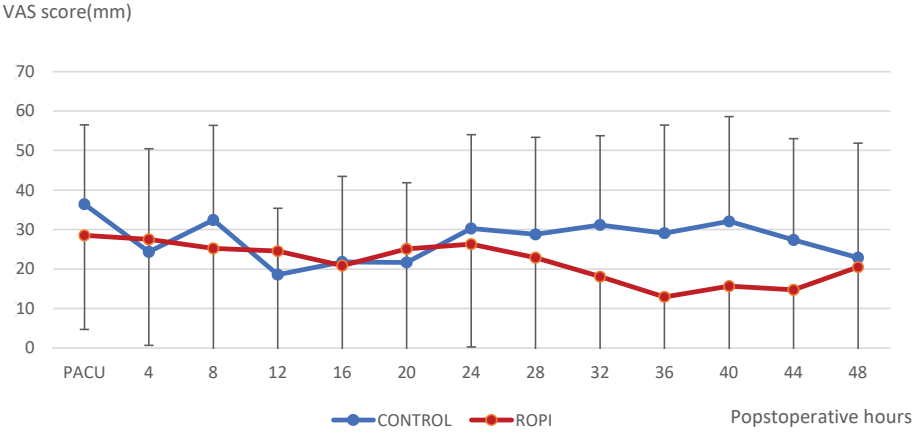

Figure 3. Pain scores at the cervical site at rest; mean and SD vs. postoperative time (hours) starting in PACU.

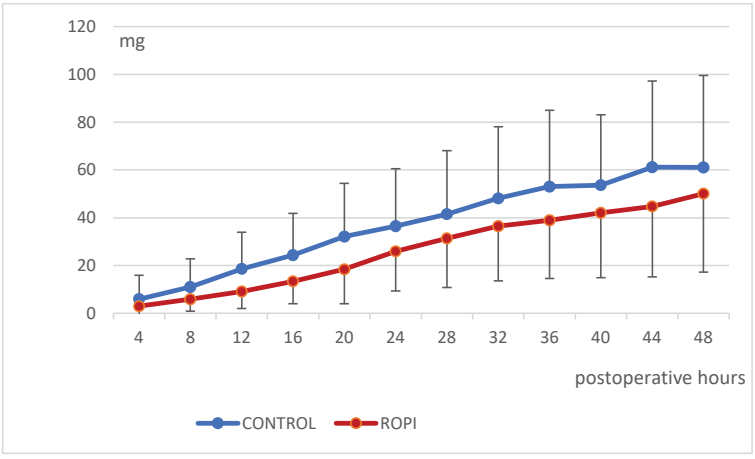

Figure 4. Cumulative morphine consumption (Mean and SD) until 48 h postoperative.

Ropivacaine blood concentration in 16 patients in the catheter group was 2.1 ± 1.1 µg/mL with a minimum 0.36 of and maximum of 3.96 µg/mL (Figure 5). Although 8 patients (50%) had a blood concentration above the threshold of 2.2 µg/mL, classically considered as high risk for systemic toxicity [9], no symptoms were observed in any patient in the ROPI group. Unbound ropivacaine concentration was not assayed. Postoperative protidemia (Day 1) was 49 ± 5 g/L, i.e., a mean loss of 20 g/L in comparison to preoperative values of (69 ± 5 g/L).

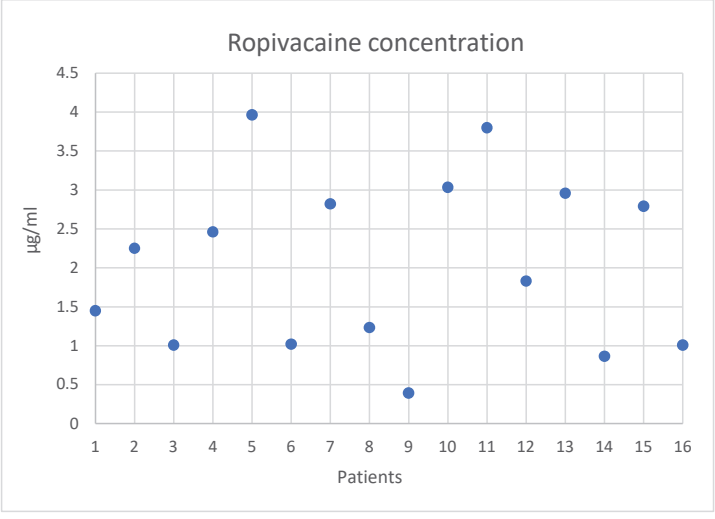

Figure 5. Individual values of ropivacaine blood concentration at the end of infusion.

All patients had at least 1-year follow-up and one third of them had retrospective electronic assessment up to 10 years. In this long-term retrospective analysis, only one patient, in the ROPI group had moderate chronic pain sequelae in the fibula harvest site, which lasted up for 6 years. No other pain in the harvest site was reported.

Few patients developed chronic pain at the cervicofacial site due to initial surgery. However, some of them declared new cervicofacial pain developed later in relation to cancer evolution, new cervicofacial cancer or infection (Table 2).

Table 2. Chronic pain patients requiring medication (number of patients/number of patients assessed).

Delay from Surgery	ROPI (*n* = 27)	CONTROL (*n*= 29)	*p* Value
1 year	3/27	5/29	0.7
3 years	4/17	5/20	1
5 years	3/15	4/14	0.6
10 years	1/10	1/9	1

This long-term follow-up was not planned in the initial randomized study; therefore, these data cannot be considered as the result of the initial study, but rather as retrospective observational results with an important percentage of lost follow-ups.

5. Discussion

This study shows that a continuous infiltration of ropivacaine 0.2%, administered next to the upper extremity of the common peroneal nerve for 48 h, only significantly reduced pain scores at the harvest site of a fibular free flap at day 1, without significant influence on pain scores at other time points, nor on cumulative morphine consumption. Ropivacaine assay performed in 16 patients revealed a high concentration of local anesthetic in 8 patients.

Among numerous free flap reconstructive options available after major cervicofacial surgery, we focused on the fibula because it is considered as the most efficient flap regarding aesthetic and functional rehabilitation (swallowing, eating and speaking) for mandibular reconstruction. It is often proposed in cancer surgery, may gather an homogeneous population and is eligible for limb regional analgesia. In addition, it is known for delayed healing and chronic pain, estimated between 2% and 60% of the patients [10–12], which both may be improved by optimal postoperative pain management.

Therefore, there was a strong rational for regional infiltration at the harvest site. It should last at least for 24 h, but may not be necessary later than day 2, since pain markedly decreased after 48 h [5,7].

Among the few studies available, a double block (femoral + common fibular nerve with ropivacaine 0, 33%) decreased pain score until the 12th postoperative hour at rest and the 8th hour in movement [5]. Repeated chirocaine boluses every 8 h decreased pain score on average from 4 before reinjection to less than 1 after reinjection [6]. Conversely, ropivacaine continuous infiltration through a catheter placed by the surgeon was unable to significantly improve pain scores [7], even with a similar drug delivery protocol as in our study [13].

Several explanations may be proposed to explain the discrepancy between these results and ours.

First, infusing in front of the peroneal nerve may be too distal to cover the whole surgical harvest zone. Combining a femoral block or placing the catheter more proximal in the poplitea fossa in front of the sciatic nerve may improve the efficacy on postop pain. Additionally, in our study, the catheter was placed by the surgeon resident and its placement may have been imperfect. Preoperative block performed with ultrasound control by the anesthesiologist may cover a wider zone and be more reproducible.

Moreover, placing a catheter for postoperative reinjections induces a risk of catheter displacement after only a few hours, as observed by Marhofer [14], which may have happened to some of our patients. This does not contraindicate placing a catheter; the more distant from the surgical zone and articulation, the lesser would be the risk.

On the other hand, the doses given might have been inappropriate to achieve pain relief. Firstly, an initial 15 mL bolus, which we used in this study, is reported to be the most adapted dose before reaching a ceiling effect [13], while An infusion rate of 4 to 6 mL/h of ropivacaine 0.2% is the classically recommended dose for perineural block of limb or chest, and as a balance between underdosage and potentially toxic doses.

However, in this special localization, a more important diffusion volume or systemic absorption and increased local inflammation might explain the high blood concentrations observed.

Ferri et al. gave boluses of 20 mL every 8 h [6]; by doing so, they may have achieved a better local diffusion at higher injection pressure with less systemic resorption, as suspected in a recent meta-analysis [15]. This issue should be studied for every location of perineural block, since the balance between local efficacy and systemic absorption differs with the diffusion space of each block and the inflammatory state around it.

Besides its disappointing efficacy, the ropivacaine infiltration, as administered in our study, induced, at the end of infusion, venous blood concentration above the maximal usually tolerated threshold of 2.2 µg/mL in 50% of patients [9]. In 2 of them, it induced concentrations higher than 3.7 µg/mL, which have been described inducing seizures [16].

Another study infusing ropivacaine in the extra-pleural space after thoracotomy observed lower concentrations than in our study, despite higher doses (6 or 9 mL/h) [17]. Fortunately, no sign of toxicity was observed in our study, similar to a previous work with a similar range of concentrations [18].

Toxicity is correlated not to the total, but to the unbound fraction, which was not recorded in our study. Hypoprotidemia due to preoperative denutrition or to intraoperative hemodilution may worsen the risk. However, usually this hypoprotidemia involves mainly albumin, whereas Ropivacaine binds mainly to alpha-1-acid glycoprotein (AAG), which increases after trauma or inflammation [19], Consequently, the major inflammation state observed in cervicofacial cancer surgery may have protected the patients from unbound ropivacaine toxicity by decreasing the unbound fraction, especially after prolonged infusion, as shown by Blumenthal [20].

In recent studies on cervicofacial surgery, pain is maximum in the first postoperative hours or day, but 50% of patients already have no pain at discharge [2]. This result is consistent with ours, with only one patient complaining of chronic pain at the harvest site, which resolved after several years.

Finally, the influence on chronic pain did not appear as relevant as expected from the literature [10,21]. Some reviews are based on old original papers where multimodal analgesia including anti-NMDA agents such as N_2O, nefopam or ketamine were not used, whereas they were used in our study.

Our study had a few shortcomings; firstly the sample size has a statistical power insufficient to detect differences in postoperative pain scores, morphine requirements or potential chronic pain at the harvest site. Average values were similar to the assumption used for the number of subjects calculation, but interindividual variability was underestimated. In other words, some patients have very high levels of pain and analgesic requirements, and risk factors for these outliers are not easy to establish [2].

This result supports the recommendation to regularly assess the pain scores of patients after this surgery, and to adapt analgesia protocol to the individual needs of outliers [5].

The higher remifentanil rate of infusion may be due to stronger pain in the ROPI group, which may have offset a potential benefit of regional anesthesia. However, it may also be due to a random effect in this rather small groups of patients.

In this study, the epidural catheter placed by the surgeon near the proximal side of the common peroneal nerve can partly be assimilated to wound infiltration, despite the fact that the epidural catheter has holes only in its terminal end. Nevertheless, the complexity of this type of surgery may yield heterogeneous pain results as in our study; we reference regional techniques such as popliteal ultrasound guided block with intermittent reinjection, which might be more effective and more reproducible [22].

Other shortcomings were that allocation to one or the other group was unblinded to professionals, which could have yielded bias in harvest site pain-score assessment, but not in morphine PCA consumption. Finally, long-term assessment was retrospectively performed through electronic chart database consultation, which could provide some bias or missing data.

6. Conclusions

Ropivacaine continuous infiltration of 4 mL/h for 48 h in front of the common peroneal nerve cannot be recommended for analgesia after fibular free flap because of both insufficient analgesic efficacy and high, potentially toxic, blood concentrations.

Future research and clinical practice should consider more proximal blocks and/or different drugs delivery schemes including repeated boluses and continuous search of the lower dilution efficient for each type of block, and drug assay on a few patients for every new block or scheme tested.

A huge variability in pain and analgesic requirements between patients supports the recommendation of repeated pain assessment and individualized analgesic drug adjustments, especially in the first days after surgery.

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Institutional Review Board Statement: The protocol was approved by the ethical committee of Henri Mondor Hospital, 94010 Créteil France (CPPRBP # 04-006), and by our local hospital institutional review board (CSET # 03-1042) in April 2004. At the time of the study (2004), registration as a randomized controlled trial was not mandatory.

Informed Consent Statement: Written Informed consent was obtained from all patients involved in the study to publish the paper.

Data Availability Statement: Data are available on demand to corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Wu, C.L.; Raja, S.N. Treatment of acute postoperative pain. *Lancet* **2011**, *377*, 2215–2225. [CrossRef]
2. Bianchini, C.; Malago, M.; Crema, L.; Aimoni, C.; Matarazzo, T.; Bortolazzi, S.; Pastore, A. Post-operative pain management in head and neck cancer patients: Predictive factors and efficacy of therapy. *Acta Otorhinolaryngol. Ital.* **2016**, *36*, 91–96. [CrossRef]
3. Inhestern, J.; Schuerer, J.; Illge, C.; Thanos, I.; Meissner, W.; Volk, G.F.; Guntinas-Lichius, O. Pain on the first postoperative day after head and neck cancer surgery. *Eur. Arch. Otorhinolaryngol.* **2014**, *272*, 3401–3409. [CrossRef]
4. Hinther, A.; Nakoneshny, S.C.; Chandarana, S.P.; Matthews, T.W.; Dort, J.C. Efficacy of postoperative pain management in head and neck cancer patients. *J. Otolaryngol.-Head Neck Surg.* **2018**, *47*, 29. [CrossRef]
5. Zhang, X.; Sun, C.; Bai, X.; Zhang, Q. Efficacy and safety of lower extremity nerve blocks for postoperative analgesia at free fibular flap donor sites. *Head Neck* **2018**, *40*, 2670–2676. [CrossRef]
6. Ferri, A.; Varazzani, A.; Valente, A.; Pedrazzi, G.; Bianchi, B.; Ferrari, S.; Sesenna, E. Perioperative pain management after fibular free flap harvesting for head-and-neck reconstruction using mini-catheters to inject local anesthetic: A pilot study. *Microsurgery* **2018**, *38*, 295–299. [CrossRef]
7. Roof, S.; Ferrandino, R.; Eden, C.; Khelemsky, Y.; Teng, M.; Genden, E.; Jr, S.D.; Miles, B.A. Local infusion of ropivacaine for pain control after osseous free flaps: Randomized controlled trial. *Head Neck* **2021**, *43*, 1063–1072. [CrossRef]
8. Dureau, P.; Charbit, B.; Nicolas, N.; Benhamou, D.; Mazoit, J.X. Effect of Intralipid(R) on the Dose of Ropivacaine or Levobupivacaine Tolerated by Volunteers: A Clinical and Pharmacokinetic Study. *Anesthesiology* **2016**, *125*, 474–483. [CrossRef]
9. Knudsen, K.; Suurküla, M.B.; Blomberg, S.; Sjövall, J.; Edvardsson, N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br. J. Anaesth.* **1997**, *78*, 507–514. [CrossRef]
10. Kearns, M.; Ermogenous, P.; Myers, S.; Ghanem, A.M. Osteocutaneous flaps for head and neck reconstruction: A focused evaluation of donor site morbidity and patient reported outcome measures in different reconstruction options. *Arch. Plast. Surg.* **2018**, *45*, 495–503. [CrossRef]
11. Ling, X.F.; Peng, X. What Is the Price to Pay for a Free Fibula Flap? A Systematic Review of Donor-Site Morbidity following Free Fibula Flap Surgery. *Plast. Reconstr. Surg.* **2012**, *129*, 657–674. [CrossRef] [PubMed]
12. Shpitzer, T.; Neligan, P.; Boyd, B.; Gullane, P.; Gur, E.; Freeman, J. Leg Morbidity and Function Following Fibular Free Flap Harvest. *Ann. Plast. Surg.* **1997**, *38*, 460–464. [CrossRef] [PubMed]

13. Christiansen, C.B.; Madsen, M.H.; Rothe, C.; Andreasen, A.M.; Lundstrøm, L.; Lange, K.H.W. Volume of ropivacaine 0.2% and common peroneal nerve block duration: A randomised, double-blind cohort trial in healthy volunteers. *Anaesthesia* **2018**, *73*, 1361–1367. [CrossRef] [PubMed]
14. Marhofer, D.; Triffterer, L.; Leonhardt, M.; Weber, M.; Zeitlinger, M. Dislocation rates of perineural catheters: A volunteer study. *Br. J. Anaesth.* **2013**, *111*, 800–806. [CrossRef]
15. Jagannathan, R.; Niesen, A.D.; D'Souza, R.S.; Johnson, R.L. Intermittent bolus versus continuous infusion techniques for local anesthetic delivery in peripheral and truncal nerve analgesia: The current state of evidence. *Reg. Anesth. Pain Med.* **2019**, *44*, 447–451. [CrossRef]
16. Dhir, S.; Ganapathy, S.; Lindsay, P.; Athwal, G.S. Case report: Ropivacaine neurotoxicity at clinical doses in interscalene brachial plexus block. *Can. J. Anaesth.* **2007**, *54*, 912–916. [CrossRef]
17. Maurer, K.; Blumenthal, S.; Rentsch, K.M.; Schmid, E.R. Continuous extrapleural infusion of ropivacaine 0.2% after cardiovascular surgery via the lateral thoracotomy approach. *J. Cardiothorac. Vasc. Anesth.* **2008**, *22*, 249–254. [CrossRef]
18. Behnke, H.; Worthmann, F.; Cornelissen, J.; Kahl, M.; Wulf, H. Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery. *Br. J. Anaesth.* **2002**, *89*, 251–253. [CrossRef]
19. El-Boghdadly, K.; Pawa, A.; Chin, K.J. Local anesthetic systemic toxicity: Current perspectives. *Local Reg. Anesth.* **2018**, *11*, 35–44. [CrossRef]
20. Blumenthal, S.; Dullenkopf, A.; Rentsch, K.; Borgeat, A. Continuous Infusion of Ropivacaine for Pain Relief after Iliac Crest Bone Grafting for Shoulder Surgery. *Anesthesiology* **2005**, *102*, 392–397. [CrossRef]
21. Macrae, W.A. Chronic post-surgical pain: 10 years on. *Br. J. Anaesth.* **2008**, *101*, 77–86. [CrossRef] [PubMed]
22. Paladini, G.; Di Carlo, S.; Musella, G.; Petrucci, E.; Scimia, P.; Ambrosoli, A.; Fusco, P. Continuous Wound Infiltration of Local Anesthetics in Postoperative Pain Management: Safety, Efficacy and Current Perspectives. *J. Pain Res.* **2020**, *13*, 285–294. [CrossRef] [PubMed]

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Review

The Effect of Propofol versus Inhalation Anesthetics on Survival after Oncological Surgery

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Abstract: Every year, 19.3 million patients worldwide are diagnosed with cancer. Surgical resection represents a major therapeutical option and the vast majority of these patients receive anesthesia. However, despite surgical resection, almost one third of these patients develop local recurrence or distant metastases. Perioperative factors, such as surgical stress and anesthesia technique, have been suggested to play a role to a greater or lesser extent in the development of recurrences, but oncology encompasses a complicated tumor biology of which much is still unknown. The effect of total intravenous anesthesia (TIVA) or volatile anesthesia (VA) on survival after oncological surgery has become a popular topic in recent years. Multiple studies conclude in favor of propofol. Despite the a priori probability that relevant differences in postoperative outcomes are due to the anesthesia technique employed, TIVA or VA, is extremely small. The existing literature includes mainly hypothesis-forming retrospective studies and small randomized trials with many methodological limitations. To date, it is unlikely that use of TIVA or VA affect cancer-free survival days to a clinically relevant extent. This review addresses all relevant studies in the field and provides a substantiated different view on this deeply controversial research topic.

Keywords: sevoflurane; cancer-free survival; oncology; anesthesia; TIVA; volatile anesthetics

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1. Introduction

Every year, 19.3 million patients worldwide are diagnosed with cancer [1]. Of these patients, more than half undergo surgical resection. This makes surgical resection of the primary tumor not only one of the most widely used treatments, but also one of the most important therapeutic options for most patients with solid tumors. Of the patients undergoing surgical resection, the vast majority receive anesthesia at least once [2]. Despite resection, approximately one third of these patients develop local recurrence or metastasis. Recurrent or metastatic disease has a dismal prognosis and is associated with the vast majority of cancer-related deaths [3]. In addition to various cancer cell intrinsic properties, environmental factors also play an important role in cancer initiation and progression. Perioperative factors, including surgical stress, pain, and anxiety, as well as the anesthesia technique used during surgery, was supposed to influence the course and progression of cancer directly or indirectly through their impact on tumor-associated environmental factors. In the following paragraphs, we discuss the perioperative vulnerability to the development of tumor recurrences, the plausibility that anesthesia technique affects the likelihood of the development of these recurrences, and the pathophysiology regarding the hypothesized association between the use of some anesthetics and progression of cancer. Finally, we present a summary of the most relevant literature on this issue.

2. Perioperative Factors

Several physiological responses occur in the body around surgery: inflammation, increase in circulating catecholamines, immune suppression, and platelet activation. Perioperative triggers might provoke these reactions. One important trigger is stress due to

tissue damage from surgical resection. In response to tissue damage, various physiological responses—amongst others, wound healing—occur. This response bears great similarity to pathological responses between tumor cells and the surrounding, nonmalignant cells and non-cellular matrix [4]. Through the interaction of a wound-healing response, existing interactions between cancer cells and their immediate environment can be influenced, with potential consequences on the course (i.e., inhibition or stimulation) of the disease. In addition, pro- and anti-inflammatory responses are induced in an attempt to properly and specifically harness the immune system response in the service of the host. For example, in response to surgical trauma, secretion of various growth factors occurs perioperatively, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EDF) [5–7]. These growth factors stimulate wound healing by activating cellular programs aimed at proliferation and migration of epithelial and endothelial cells, thereby repopulating a tissue and restoring supportive vascular supply. These programs are therefore essential for adequate wound healing. In the context of cancer, however, these programs affect not only the perioperative emergent wound bed, but also the local and systemic context of the tumor [8]. The intrinsically beneficial physiological properties of wound healing are also hijacked by the tumor and harnessed for the benefit of tumor progression. Protective responses can therefore lead to an undesirable, tumor-stimulating effect. This dynamic between cancer cells and their environment is described by the so-called seed-and-soil hypothesis. The hypothesis describes the interaction of malignant cells with their specific context, which can be both stimulating and inhibitory. The formation of metastases through the dissemination and colonization of cancer cells in fertile soil is an important part of this hypothesis [9]. During surgery, dissemination hypothetically occurs through the destruction of not only the tumor, but also the supply and drainage vessels through which tumor cells may enter the circulation [10]. This hypothesis becomes less likely if one takes into account the tumor- doubling time: the time it takes to double the number of tumor cells. When one calculates backwards, in many cases the tumor/metastasis will have existed, undetected, before surgery. The destruction of the vasculature does cause hypoperfusion, resulting in hypoxia and ischemia. This stimulates the expression of hypoxia-induced factors (HIFs), which promote cancer metabolism and tumor growth [11]. Entering the circulation, HIFs interacts with activated platelets, neutrophils, and endothelial cells, as well as transient pro-angiogenic signals. These signals are most likely induced by the surgical inflammatory response and would potentially positively influence formation of metastases [12]. The seed-and-soil hypothesis therefore illustrates the vulnerability to colonization in fertile soil arising from modulation of the immune system and activation or inhibition of neural and/or pro-inflammatory signaling pathways, which in turn prime both the local and systemic environment of the tumor to create a favorable environment for a new metastatic niche [13–15]. However, the influence of pro- and/or anti-inflammatory signaling pathways on cancer cell growth is highly heterogeneous and varies by malignancy [14,15]. As a result of the systemic modulation of the immune system, the risk of recurrent and/or metastatic disease is relatively high. The wound-healing response and seed-and-soil hypothesis are important factors in recurrences, but more deserves to be discussed.

Surgical stress from tissue trauma activates more than just a wound-healing response. The stress response (and also anxiety, hypothermia, metabolic disturbances and fasting) activates the sympathetic nervous system, also affecting tumor cells and the microenvironment with possible development of recurrences [16–18]. Activation yields increases in circulating catecholamine levels, causing β-adrenoceptor activation. Specifically, the signaling pathway in tumor cells via cyclic adenosine monophosphate (cAMP) is activated, providing upregulation of transcription factors encoding VEGF, MMPs and HIFs, among others [19].

Finally, tissue injury initiates the activation of platelets and tissue factors to promote coagulation. Activation of the coagulation cascade is supposed to influence the formation of metastases because, among other things, platelets contain many cellular growth factors

(PDGF, VEGF) as well as matrix proteins and inflammatory mediators [20]. In short, many triggers that activate physiological responses and potentially increase the risk of recurrence exist perioperatively.

Based on previous theory, in 1980, a link between perioperative stress, anesthesia and cancer progression was suggested [21]. In the following years, several retrospective studies were conducted to investigate the association between the type of anesthesia during oncological interventions and cancer-related survival after the surgical procedure. Several retrospective studies suggested that inhalational anesthetics might increase the risk of recurrence and thus negatively affect survival after surgery [22].

3. The Hypothesis

In 2016, Wigmore et al. were the first to publish a retrospective study comparing the effect of total intravenous anesthesia (TIVA) versus inhalational anesthetics (IA) on mortality after oncological surgery [22]. The study was conducted in England among more than 7000 patients undergoing resection of the primary tumor. Patients exposed to IA were found to be 1.5 times more likely to die compared with patients who received TIVA (propofol). In the same year, Lee et al. reported that IA compared to TIVA resulted in a significantly higher risk ($p = 0.037$) of developing a recurrence in 300 patients undergoing radical mastectomy for breast cancer [23]. However, no difference was found in mortality. The above studies led to more retrospective reviews, which were finally analyzed in a meta-analysis. As with Wigmore, this meta-analysis showed a difference in mortality to the detriment of IA (Sevoflurane) [24]. Based on the above results, two questions arise: (1) To what extent is the association between the perioperative use of specific anesthetics and the postoperative progression of disease postulated in these retrospective studies biologically plausible? (2) To what extent is the effect reported in these retrospective studies reproducible in methodologically well-conducted randomized trials?

As discussed earlier, tumor biology is highly complex and a subject with much to explore, as well as discuss. Metastasis occurs when cells undergo somatic changes that cause them to spread by infiltrating the lymphatic or vascular network, survive there, and then have the ability to grow at distance [12]. In other words, cancer is complex, with the ultimate course being the result of hundreds of interacting factors. On the other hand, TIVA (e.g., propofol) and IA are agents that are largely similar pharmacodynamically. Both bind to the $GABA_A$ receptor and both stimulate the release of neurotransmitters that inhibit the conduction of action potentials in the central nervous system. Despite their similarity, they have been reported to make a fundamental difference (hazard ratio of 1.46 (1.29 to 1.66)) in cancer survival when applied in an oncological context [22]. In addition, it is important to realize that in the development of specific chemo- or immunotherapeutics, an effective agent is said to be present if the therapy gives a 2% to 2.3% reduction in the recurrence rate [25]. Given the hundreds of oncologic factors, the high similarity between the two anesthetics, and the relatively short duration of exposure, a relationship between the two does not seem, a priori, very plausible. Therefore, the a priori probability that the above, short-term variations will have a substantial impact on the course of the disease in an individual patient seems extremely small.

As far as the above is not convincing, it is further supported by a critical review of the static basis of the reported studies. In 2005, Ioannidis published an article in which he emphasizes the importance of a critical review of scientific research [26]. Ioannidis calls attention to the importance of the *p*-value and points out that it is mostly overvalued in the existing literature and the dependence of the a priori probability and the *p*-value receives far too little attention. Ioannidis argues that a study design should take into account three factors: (a) the power of a study; (b) the probability of bias; and (c) the prior probability that a relationship found is real (a priori probability). From this, the positive predictive value is then calculated. The article shows that for most studies, the probability that the outcome matches reality is less than 0.5. Only a correctly conducted randomized controlled trial (RCT) and a meta-analysis of correctly conducted RCTs have a positive predictive

value of 0.85. For smaller, less transparent studies, the positive predictive value drops to only 0.20. Furthermore, Ioannidis points out that replicates are essential in studies with an a priori low prior probability.

4. Mechanisms of Anesthetic on Cancer

When pathophysiological knowledge substantiates an association found in a study, the likelihood that the association actually exists is greater. The hypothesis underlying the question whether TIVA or IA is superior in the oncologic patient is based on immunosuppressive properties of sevoflurane and protective properties of propofol. Results of studies of these properties are highly variable and, therefore, not a solid basis for the hypothesis.

Although tumor growth, recurrence, and metastasis can be differently affected by the immune status (pro- or anti-inflammatory) at different time points and in different tumor types, the suggested protective properties of propofol could be explained by its anti-inflammatory properties. These properties have been demonstrated in several areas in both animal and in vitro studies. Propofol provides suppression of prostaglandin and cytokine production [27], prevents immunosuppression [28], reduces migration of cancer cells through MMP suppression, and provides increased activity of natural-killer (NK) cells [29]. Furthermore, propofol has been shown to reduce both cancer cell motility and the degree of invasiveness, and lastly gives reduction of HIF-1a [30].

In human studies, it has been shown that more activated T-helper cells circulated and lower concentrations of VEGF-C, TGF-B and IL-6 were found—all markers associated with the formation of angiogenesis and metastases.

IA were reported to have opposite effects which can be traced to known cytoprotective properties in the heart, brain and kidney, as well as reduction in infarct size in models for ischemia-reperfusion injury [31]. The cytoprotective properties are detrimental in oncology, for example, an upregulation of HIF1-α has been demonstrated in vivo [32], also reduced NK cell activity and increased migration of cancer cells [30,33]. In vitro studies support this hypothesis. Thus, based on in vivo and in vitro studies, IA would promote immunosuppression and stimulate a pro-malignant environment. However, contrary to previous findings, sevoflurane has also been shown to reduce cell motility and invasion by reducing MMP2 and MMP9. Given the heterogeneous nature of tumor biology, the in vitro studies should be interpreted with caution. The studies are not directly equivalent to the human cellular environment and therefore cannot be extrapolated one-to-one to clinical outcomes.

5. Existing Literature

Interest in the influence of anesthesia technique on oncological outcome measures has increased significantly in recent years. This is partly due to the previously mentioned study by Wigmore et al. [22]. Based on these results, dozens of retrospective studies followed, focused on basic pathophysiology, and producing heterogenous results. These results are summarized in Table 1. In early 2021, a meta-analysis was published by Chang et al. with 19 studies comparing propofol with volatile anesthetics [24]. The primary outcome was mortality and cancer-free survival in patients undergoing surgery for a malignancy. In terms of overall mortality, a difference was found in favor of propofol. However, no such difference was found in the duration of cancer-free survival. The main limitation of this meta-analysis is that it involves only retrospective studies. At most, such studies generate hypotheses, but do not confirm or reject them. For this reason, it is important to check whether there are randomized studies that confirm the hypothesized effect.

Yan et al. published two randomized studies including 80 patients each with breast cancer who underwent breast-conserving resection or radical mastectomy under propofol/remifentanyl TIVA or IA with sevoflurane. The primary outcomes were the concentrations of VEGF, TGF-B in serum, and the expression of myeloid-deriving suppressor [49,50]. As a secondary outcome, both studies looked at mortality and cancer-free survival after two years of follow-up. Both studies showed no significant difference in cancer-free survival

or mortality. However, since breast cancer has a relatively good two-year survival, these results are difficult to interpret and a real effect can be neither demonstrated nor excluded on the basis of these data. This problem is compounded by the relatively small groups of patients in the two studies. Guerrero Orriach et al. published a randomized study including 100 patients with infiltrating bladder carcinoma, comparing the effect of general anesthesia in combination with locoregional analgesia or systemic opioids on cancer-related survival after radical cystectomy [57]. A subgroup analysis to the effect of propofol versus sevoflurane showed a difference in favor of propofol ($p = 0.02$).

Table 1. Studies investigating the effect of intravenous anesthetics versus inhalation anesthetics on overall survival and cancer-free survival.

Author	Overall Survival	Recurrence-Free Days
Schmoch 2021 [34]		—
Takeyama 2021 [35]		
Koo 2020 [36]	—	
Lai 2020 [37]		
Enlund 2020 [38]		—
Huang 2020 [39]		
Dong 2020 [40]		
Hong 2019 [41]		—
Huang 2019 [42]		—
Lai 2019 [43]		—
Sung 2021 [44]		
Yoo 2019 [45]		
Oh 2019 [46]		—
Lai 2019 [47]		
Sessler 2019 [48]		

Table 1. *Cont.*

Author	Overall Survival	Recurrence-Free Days
Yan 2018 [49]		
Yan 2019 [50]		
Zheng 2018 [51]		—
Wu 2018 [52]		—
Oh 2018 [53]		
Kim 2017 [54]		
Jun 2017 [55]		
Wigmore 2016 [22]		—
Lee 2016 [23]		
Enlund 2014 [56] (Breast cancer)		—
Enlund 2014 [56] (Colon cancer)		—
Enlund 2014 [56] (Rectal cancer)		—

 : no significant difference.  : a significant difference in favor of intravenous anesthestics. —: outcome measurement not described.

Similarly, a second subgroup analysis of the effect of propofol combined with an epidural versus sevoflurane combined with opioids showed a difference in favor of propofol (p = 0.02). However, the study has several important limitations. First, only a limited number of prognostic characteristics were included, which may unfairly consider both patient groups as equal. A sample size calculation was missing, which makes it unclear on which assumptions the number of included patients is based. It also remains unclear how many patients were included in the subgroup analyses. Finally, as discussed earlier, the a priori chance of a real difference in outcome between patients who underwent resection under propofol or sevoflurane is very small. Although a significant difference in survival between the two study groups was reported, given the very low prior probability, no solid conclusion can be drawn from this finding. To reach a more reliable conclusion, the dichotomous way of thinking should be converted to a more nuanced, continuous way of thinking: how likely is the difference assumed in the hypothesis, what is the effect size, and is the expected effect size clinically relevant? However, the a priori probability of an anesthesia-related effect on survival after oncological surgery is extremely small, and if present, may be very limited and clinically irrelevant.

The latest and most important randomized study was carried out by Sessler et al. [48]. This study was the largest (2108 patients) multicenter (13 hospitals around the world) trial employing high-quality methodology, including women with breast cancer. Patients underwent mastectomy or wide local resection. Propofol and a paravertebral block (the expected most tumor-suppressive anesthesia technique) was compared with sevoflurane and the use of opioids (the expected most tumor-promoting anesthesia technique) with the outcome being cancer-recurrence-free days. The follow-up was five to six years.

The main result was that no difference was found between the two groups ($p = 0.84$). Strictly speaking, the calculated sample size was too small for the observed event rate (number of tumor recurrences). Moreover, the trial ended early as the number of inclusions was not achieved and the futility calculation clearly showed that no difference was to be expected even with further inclusions. It remains for the reader to judge whether one considers a difference clinically relevant if one could not have found it in 2100 patients and not even a signal towards benefit for propofol and regional anesthesia was found.

There are currently several large randomized studies (CAN-, GA-CARES-, VAPOR-C TRIALS etc.) in extensive abdominal surgery comparing propofol with sevoflurane. These studies will have to show that even in operations with more surgical stress, more pain, and more opioid need, no significant difference is going to be found.

A limitation of our paper is that it is not a systematic review and we were not able to statistically pool the results into a meta-analysis. We deliberately chose not to write a systematic review, because we want to show precisely how heterogeneous the outcomes are in the research field and how important it is not only to look at the numerical outcomes of the applied statistics, but precisely also to consider the a priori probability and thus the applied statistics (the alpha and beta error margins chosen among others).

A second limitation is that our search strategy was not classically designed as might be expected of a systematic review. It was not searched by two independent researchers from the start, but only after an initial screening. However, we believe that the chance of missed studies is small because two authors did review the references of the initially included studies.

6. Conclusions

Oncology consists of a complex tumor biology of which much is not yet known and not fully understood. In addition to tumor-specific factors, multiple perioperative factors play a role, such as inflammation, pain, stress, and surgical trauma. A popular topic of research came from the question as to whether TIVA or IA is superior in the oncologic patient. The hypothesis is based on immunosuppressive properties of sevoflurane and protective properties of propofol. Important to realize is that the a priori probability that two anesthetics (propofol and inhalational anesthetics) will provide a relevant difference in oncological outcomes is extremely small and that in the context of extraordinary claims requiring extraordinary data, compelling evidence must be put forward to convince the reader that one of the anesthetics can make a significant difference on tumor biology. Therefore, judging the influence of anesthetics on tumor biology is challenging. The existing literature mainly includes many hypothesis-forming retrospective studies; small suboptimal reported randomized trials with many methodological limitations in which the difference found is very unlikely to be existent or clinically relevant. The study by Sessler et al. is leading to date and concludes that no difference is found in the use of propofol or sevoflurane with the outcome measure being cancer-free survival days.

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Abbreviations

cAMP	cyclic Adenosine Monophosphate
EDF	Epidermal Growth Factor
HIF	Hypoxic Induced Factors
MMPs	Matrix Metalloproteinases
NK cells	Naturel Killer cells
PDGF	Platelet-derived Growth Factor
RCT	Randomized Controlled Trial
TGF	Transforming Growth Factor
TIVA	Total Intravenous Anesthesia
VEGF	Vascular Endothelial Growth Factor

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]
2. Hiller, J.G.; Perry, N.J.; Poulogiannis, G.; Riedel, B.; Sloan, E.K. Perioperative events influence cancer recurrence risk after surgery. *Nat. Rev. Clin. Oncol.* **2018**, *15*, 205–218. [CrossRef] [PubMed]
3. Mehlen, P.; Puisieux, A. Metastasis: A question of life or death. *Nat. Rev. Cancer* **2006**, *6*, 449–458. [CrossRef] [PubMed]
4. Chang, H.Y.; Nuyten, D.S.A.; Sneddon, J.B.; Hastie, T.; Tibshirani, R.; Sørlie, T.; Dai, H.; He, Y.D.; Veer, L.J.V.; Bartelink, H.; et al. Robustness, scalability, and integration of a wound-response gene expression signature in predicting breast cancer survival. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 3738–3743. [CrossRef] [PubMed]
5. Murdoch, C.; Muthana, M.; Coffelt, S.B.; Lewis, C.E. The role of myeloid cells in the promotion of tumour angiogenesis. *Nat. Rev. Cancer* **2008**, *8*, 618–631. [CrossRef] [PubMed]
6. Cao, R.; Björndahl, M.A.; Religa, P.; Clasper, S.; Garvin, S.; Galter, D.; Meister, B.; Ikomi, F.; Tritsaris, K.; Dissing, S.; et al. PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. *Cancer Cell* **2004**, *6*, 333–345. [CrossRef]
7. Hirakawa, S.; Kodama, S.; Kunstfeld, R.; Kajiya, K.; Brown, L.F.; Detmar, M. VEGF-A induces tumor and sentinel lymph node lymphangiogenesis and promotes lymphatic metastasis. *J. Exp. Med.* **2005**, *201*, 1089–1099. [CrossRef]
8. Beecher, S.M.; O'Leary, D.P.; McLaughlin, R.; Sweeney, K.J.; Kerin, M.J. Influence of complications following immediate breast reconstruction on breast cancer recurrence rates. *Br. J. Surg.* **2016**, *103*, 391–398. [CrossRef]
9. Paget, S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev.* **1989**, *8*, 98–101.
10. Hashimoto, M.; Tanaka, F.; Yoneda, K.; Takuwa, T.; Matsumoto, S.; Okumura, Y.; Kondo, N.; Tsubota, N.; Tsujimura, T.; Tabata, C.; et al. Significant increase in circulating tumour cells in pulmonary venous blood during surgical manipulation in patients with primary lung cancer. *Interact. Cardiovasc. Thorac. Surg.* **2014**, *18*, 775–783. [CrossRef]
11. Hong, W.X.; Hu, M.S.; Esquivel, M.; Liang, G.Y.; Rennert, R.C.; McArdle, A.; Paik, K.J.; Duscher, D.; Gurtner, G.C.; Lorenz, H.P.; et al. The Role of Hypoxia-Inducible Factor in Wound Healing. *Adv. Wound Care* **2014**, *3*, 390–399. [CrossRef] [PubMed]
12. Lambert, A.W.; Pattabiraman, D.R.; Weinberg, R.A. Emerging Biological Principles of Metastasis. *Cell* **2017**, *168*, 670–691. [CrossRef] [PubMed]
13. Sceneay, J.; Chow, M.T.; Chen, A.; Halse, H.M.; Wong, C.S.; Andrews, D.M.; Sloan, E.K.; Parker, B.S.; Bowtell, D.D.; Smyth, M.J.; et al. Primary tumor hypoxia recruits CD11b+/Ly6Cmed/Ly6G+ immune suppressor cells and compromises NK cell cytotoxicity in the premetastatic niche. *Cancer Res.* **2012**, *72*, 3906–3911. [CrossRef] [PubMed]
14. Rigas, B.; Kashfi, K. Cancer prevention: A new era beyond cyclooxygenase-2. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1–8. [CrossRef] [PubMed]
15. Forget, P.; Bentin, C.; Machiels, J.P.; Berliere, M.; Coulie, P.G.; De Kock, M. Intraoperative use of ketorolac or diclofenac is associated with improved disease-free survival and overall survival in conservative breast cancer surgery. *Br. J. Anaesth.* **2014**, *113*, i82–i87. [CrossRef]
16. Desborough, J.P. The stress response to trauma and surgery. *Br. J. Anaesth.* **2000**, *85*, 109–117. [CrossRef]
17. Sloan, E.K.; Priceman, S.J.; Cox, B.F.; Yu, S.; Pimentel, M.A.; Tangkanangnukul, V.; Arevalo, J.M.G.; Morizono, K.; Karanikolas, B.D.W.; Wu, L.; et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res.* **2010**, *70*, 7042–7052. [CrossRef]

18. Kim-Fuchs, C.; Le, C.P.; Pimentel, M.A.; Shackleford, D.; Ferrari, D.; Angst, E.; Hollande, F.; Sloan, E.K. Chronic stress accelerates pancreatic cancer growth and invasion: A critical role for beta-adrenergic signaling in the pancreatic microenvironment. *Brain Behav. Immun.* **2014**, *40*, 40–47. [CrossRef]
19. Pon, C.K.; Lane, J.R.; Sloan, E.K.; Halls, M.L. The β2-adrenoceptor activates a positive cAMP-calcium feedforward loop to drive breast cancer cell invasion. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2016**, *30*, 1144–1154. [CrossRef]
20. Palumbo, J.S.; Talmage, K.E.; Massari, J.V.; La Jeunesse, C.M.; Flick, M.J.; Kombrinck, K.W.; Jirousková, M.; Degen, J.L. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. *Blood* **2005**, *105*, 178–185. [CrossRef]
21. Shapiro, J.; Jersky, J.; Katzav, S.; Feldman, M.; Segal, S. Anesthetic drugs accelerate the progression of postoperative metastases of mouse tumors. *J. Clin. Investig.* **1981**, *68*, 678–685. [CrossRef] [PubMed]
22. Wigmore, T.J.; Mohammed, K.; Jhanji, S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology* **2016**, *124*, 69–79. [CrossRef] [PubMed]
23. Lee, J.H.; Kang, S.H.; Kim, Y.; Kim, H.A.; Kim, B.S. Effects of propofol-based total intravenous anesthesia on recurrence and overall survival in patients after modified radical mastectomy: A retrospective study. *Korean J. Anesthesiol.* **2016**, *69*, 126–132. [CrossRef] [PubMed]
24. Chang, C.Y.; Wu, M.Y.; Chien, Y.J.; Su, I.M.; Wang, S.C.; Kao, M.C. Anesthesia and Long-term Oncological Outcomes: A Systematic Review and Meta-analysis. *Anesth. Analg.* **2021**, *132*, 623–634. [CrossRef] [PubMed]
25. Morgan, G.; Ward, R.; Barton, M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. *Clin. Oncol.* **2004**, *16*, 549–560. [CrossRef] [PubMed]
26. Ioannidis, J.P.A. Why most published research findings are false. *PLoS Med.* **2005**, *2*, e124. [CrossRef]
27. Inada, T.; Hirota, K.; Shingu, K. Intravenous anesthetic propofol suppresses prostaglandin E2 and cysteinyl leukotriene production and reduces edema formation in arachidonic acid-induced ear inflammation. *J. Immunotoxicol.* **2015**, *12*, 261–265. [CrossRef]
28. Inada, T.; Yamanouchi, Y.; Jomura, S.; Sakamoto, S.; Takahashi, M.; Kambara, T.; Shingu, K. Effect of propofol and isoflurane anaesthesia on the immune response to surgery. *Anaesthesia* **2004**, *59*, 954–959. [CrossRef]
29. Melamed, R.; Bar-Yosef, S.; Shakhar, G.; Shakhar, K.; Ben-Eliyahu, S. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: Mediating mechanisms and prophylactic measures. *Anesth. Analg.* **2003**, *97*, 1331–1339. [CrossRef]
30. Desmond, F.; McCormack, J.; Mulligan, N.; Stokes, M.; Buggy, D.J. Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. *Anticancer Res.* **2015**, *35*, 1311–1319.
31. Wu, L.; Zhao, H.; Wang, T.; Pac-Soo, C.; Ma, D. Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection. *J. Anesth.* **2014**, *28*, 740–758. [CrossRef] [PubMed]
32. Tavare, A.N.; Perry, N.J.S.; Benzonana, L.L.; Takata, M.; Ma, D. Cancer recurrence after surgery: Direct and indirect effects of anesthetic agents. *Int. J. Cancer* **2012**, *130*, 1237–1250. [CrossRef] [PubMed]
33. Zhu, M.; Li, M.; Zhou, Y.; Dangelmajer, S.; Kahlert, U.; Xie, R.; Xi, Q.; Shahveranov, A.; Ye, D.; Lei, T. Isoflurane enhances the malignant potential of glioblastoma stem cells by promoting their viability, mobility in vitro and migratory capacity in vivo. *Br. J. Anaesth.* **2016**, *116*, 870–877. [CrossRef] [PubMed]
34. Schmoch, T.; Jungk, C.; Bruckner, T.; Haag, S.; Zweckberger, K.; von Deimling, A.; Brenner, T.; Unterberg, A.; Weigand, M.A.; Uhle, F.; et al. The anesthetist's choice of inhalational vs. intravenous anesthetics has no impact on survival of glioblastoma patients. *Neurosurg. Rev.* **2021**, *44*, 2707–2715. [CrossRef] [PubMed]
35. Takeyama, E.; Miyo, M.; Matsumoto, H.; Tatsumi, K.; Amano, E.; Hirao, M.; Shibuya, H. Long-term survival differences between sevoflurane and propofol use in general anesthesia for gynecologic cancer surgery. *J. Anesthesia* **2021**, *35*, 495–504. [CrossRef]
36. Koo, B.-W.; Lim, D.-J.; Oh, A.-Y.; Na, H.-S. Retrospective Comparison between the Effects of Propofol and Inhalation Anesthetics on Postoperative Recurrence of Early- and Intermediate-Stage Hepatocellular Carcinoma. *Med. Princ. Pract.* **2020**, *29*, 422–428. [CrossRef]
37. Lai, H.-C.; Lee, M.-S.; Liu, Y.-T.; Lin, K.-T.; Hung, K.-C.; Chen, J.-Y.; Wu, Z.-F. Propofol-based intravenous anesthesia is associated with better survival than desflurane anesthesia in pancreatic cancer surgery. *PLoS ONE* **2020**, *15*, e0233598. [CrossRef]
38. Enlund, M.; Berglund, A.; Ahlstrand, R.; Walldén, J.; Lundberg, J.; Wärnberg, F.; Ekman, A.; Widfeldt, N.S.; Enlund, A.; Bergkvist, L. Survival after primary breast cancer surgery following propofol or sevoflurane general anesthesia—A retrospective, multicenter, database analysis of 6305 Swedish patients. *Acta Anaesthesiol. Scand.* **2020**, *64*, 1048–1054. [CrossRef]
39. Huang, N.-C.; Lee, M.-S.; Lai, H.-C.; Lin, H.-T.; Huang, Y.-H.; Lu, C.-H.; Hsu, C.-H.; Wu, Z.-F. Propofol-based total intravenous anesthesia improves survival compared to desflurane anesthesia in gastric cancer surgery. *Medicine* **2020**, *99*, e20714. [CrossRef]
40. Dong, J.; Zeng, M.; Ji, N.; Hao, S.; Zhou, Y.; Gao, Z.; Gu, H.; Zhang, L.; Ma, D.; Peng, Y.; et al. Impact of Anesthesia on Long-term Outcomes in Patients with Supratentorial High-grade Glioma Undergoing Tumor Resection: A Retrospective Cohort Study. *J. Neurosurg. Anesthesiol.* **2020**, *32*, 227–233. [CrossRef]
41. Hong, B.; Lee, S.; Kim, Y.; Lee, M.; Youn, A.M.; Rhim, H.; Hong, S.H.; Kim, Y.H.; Yoon, S.H.; Lim, C. Anesthetics and long-term survival after cancer surgery-total intravenous versus volatile anes-thesia: A retrospective study. *BMC Anesthesiol.* **2019**, *19*, 233. [CrossRef] [PubMed]

42. Huang, Y.-H.; Lee, M.-S.; Lou, Y.-S.; Lai, H.-C.; Yu, J.-C.; Lu, C.-H.; Wong, C.-S.; Wu, Z.-F. Propofol-based total intravenous anesthesia did not improve survival compared to desflurane anesthesia in breast cancer surgery. *PLoS ONE* **2019**, *14*, e0224728. [CrossRef] [PubMed]
43. Lai, H.-C.; Lee, M.-S.; Lin, K.-T.; Chan, S.-M.; Chen, J.-Y.; Lin, Y.-T.; Wu, Z.-F. Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in intrahepatic cholangiocarcinoma surgery. *Medicine* **2019**, *98*, e18472. [CrossRef] [PubMed]
44. Sung, C.-H.; Tsuang, F.-Y.; Shih, C.-C.; Chang, J.-L.; Liao, M.-H.; Yang, Y.-W.; Lee, T.-S.; Cheng, H.-L.; Wu, C.-Y. Scalp Block Is Associated with Improved Recurrence Profiles in Patients Undergoing Primary Glioma Resection Surgery. *J. Neurosurg. Anesthesiol.* **2021**, *33*, 239–246. [CrossRef]
45. Yoo, S.; Lee, H.-B.; Han, W.; Noh, D.-Y.; Park, S.-K.; Kim, W.H.; Kim, J.-T. Total Intravenous Anesthesia *versus* Inhalation Anesthesia for Breast Cancer Surgery. *Anesthesiology* **2019**, *130*, 31–40. [CrossRef]
46. Oh, T.K.; Kim, H.; Jeon, Y. Retrospective analysis of 1-year mortality after gastric cancer surgery: Total intravenous anesthesia versus volatile anesthesia. *Acta Anaesthesiol. Scand.* **2019**, *63*, 1169–1177. [CrossRef]
47. Lai, H.-C.; Lee, M.-S.; Lin, C.; Lin, K.-T.; Huang, Y.-H.; Wong, C.-S.; Chan, S.-M.; Wu, Z.-F. Propofol-based total intravenous anaesthesia is associated with better survival than desflurane anaesthesia in hepatectomy for hepatocellular carcinoma: A retrospective cohort study. *Br. J. Anaesth.* **2019**, *123*, 151–160. [CrossRef]
48. I Sessler, D.; Pei, L.; Huang, Y.; Fleischmann, E.; Marhofer, P.; Kurz, A.; Mayers, D.B.; A Meyer-Treschan, T.; Grady, M.; Tan, E.Y.; et al. Recurrence of breast cancer after regional or general anaesthesia: A randomised controlled trial. *Lancet* **2019**, *394*, 1807–1815. [CrossRef]
49. Yan, T.; Zhang, G.-H.; Wang, B.-N.; Sun, L.; Zheng, H. Effects of propofol/remifentanil-based total intravenous anesthesia versus sevoflurane-based inhalational anesthesia on the release of VEGF-C and TGF-β and prognosis after breast cancer surgery: A prospective, randomized and controlled study. *BMC Anesthesiol.* **2018**, *18*, 131. [CrossRef]
50. Yan, T.; Zhang, G.-H.; Cheng, Y.-Z.; Wu, L.-X.; Liu, X.-Y.; Sun, Y.-L.; Zheng, H.; Sun, L. Effects of anesthetic technique and surgery on myeloid-derived suppressor cells and prognosis in women who underwent breast cancer surgery: A prospective study. *Cancer Manag. Res.* **2019**, *11*, 5513–5522. [CrossRef]
51. Zheng, X.; Wang, Y.; Dong, L.; Zhao, S.; Wang, L.; Chen, H.; Xu, Y.; Wang, G. Effects of propofol-based total intravenous anesthesia on gastric cancer: A retrospective study. *OncoTargets Ther.* **2018**, *11*, 1141–1148. [CrossRef] [PubMed]
52. Wu, Z.-F.; Lee, M.-S.; Wong, C.-S.; Lu, C.-H.; Huang, Y.-S.; Lin, K.-T.; Lou, Y.-S.; Lin, C.; Chang, Y.-C.; Lai, H.-C. Propofol-based Total Intravenous Anesthesia Is Associated with Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology* **2018**, *129*, 932–941. [CrossRef] [PubMed]
53. Oh, T.K.; Kim, K.; Jheon, S.; Lee, J.; Do, S.H.; Hwang, J.W.; Song, I.A. Long-term oncologic outcomes for patients undergoing volatile versus intravenous anesthesia for non-small cell lung cancer surgery: A retrospective propensity matching analysis. *Cancer Control* **2018**, *25*, 1073274818775360. [CrossRef] [PubMed]
54. Kim, M.H.; Kim, D.W.; Kim, J.H.; Lee, K.Y.; Park, S.; Yoo, Y.C. Does the type of anesthesia really affect the recurrence-free survival after breast cancer surgery? *Oncotarget* **2017**, *8*, 90477–90487. [CrossRef] [PubMed]
55. Jun, I.J.; Jo, J.Y.; Kim, J.I.; Chin, J.H.; Kim, W.J.; Kim, H.R.; Lee, E.H.; Choi, I.C. Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: A retrospective observational study. *Sci. Rep.* **2017**, *7*, 14020. [CrossRef] [PubMed]
56. Enlund, M.; Berglund, A.; Andreasson, K.; Cicek, C.; Enlund, A.; Bergkvist, L. The choice of anaesthetic—Sevoflurane or propofol—And outcome from cancer surgery: A retrospective analysis. *Upsala J. Med. Sci.* **2014**, *119*, 251–261. [CrossRef]
57. Orriach, J.L.G.; Ponferrada, A.R.; Manso, A.M.; Imbroda, B.H.; Belmonte, J.J.E.; Aliaga, M.R.; Fernandez, A.R.; Crespo, J.D.; Perez, A.M.S.; Heredia, A.F.; et al. Anesthesia in Combination with Propofol Increases Disease-Free Survival in Bladder Cancer Patients Who Undergo Radical Tumor Cystectomy as Compared to Inhalational Anesthetics and Opiate-Based Analgesia. *Oncology* **2020**, *98*, 161–167. [CrossRef]

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Intraoperative Cell Savage, Infection and Organ Failure in Infective Endocarditis Patients—A Retrospective Single Center Evaluation

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Abstract: Surgery is indicated in about 50% of infective endocarditis patients, and bleeding or the transfusion of blood a common finding. The intraoperative use of cell salvage may reduce the perioperative transfusion requirement, but its use is limited in the underlying disease. In this retrospective study, we therefore evaluated n = 335 patients fulfilling the modified Duke criteria for infective endocarditis characterized by the use of intraoperative cell salvage with autologous blood retransfusion. Inflammation markers and organ dysfunction, including catecholamine dependency, were evaluated by using linear regression analysis. Between 2015 and 2020, 335 patients underwent surgery for left-sided heart valve endocarditis. Intraoperative cell salvage was used in 40.3% of the cases, especially in complex scenarios and reoperation. Intraoperative cell salvage significantly altered the white blood cell count after surgery. On average, leucocytes were 3.0 Gpt/L higher in patients with intraoperative cell salvage compared to patients without after adjustment for confounders (95% CI: 0.39–5.54). Although the difference in WBC was statistically significant, i.e., higher in the ICS group compared to the no-ICS group, this difference may be clinically unimportant. Organ dysfunction, including hemodynamic instability and lactate values, were comparable between groups. In conclusion, intraoperative cell salvage enhanced the re-transfusion of autologous blood, with minor effects on the postoperative course of inflammatory markers, but was not associated with increased hemodynamic instability or organ dysfunction in general. The restriction of intraoperative cell salvage in surgery for infective endocarditis should be re-evaluated, and more prospective data in this topic are needed.

Keywords: infective endocarditis; organ failure; cell salvage; blood transfusion

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1. Introduction

The use of intraoperative cell salvage (ICS) was shown to reduce perioperative transfusion requirements in multiple clinical scenarios [1]. Cardiac surgical procedures account for a significant amount of allogeneic blood transfusion, and, accordingly, ICS was shown to reduce the transfusion rates of red blood cells without an adverse impact on clinical outcomes [2,3]. Therefore, ICS is an integral part of the patient blood management concept in cardiac surgery [4–6]. However, the use of ICS is not recommended in patients suffering from systemic infection or in circumstances where a wound blood might be contaminated [7].

Infective endocarditis (IE) represents a life threatening disease with in-hospital mortality rates of approximately 40% [8]. Cardiac surgery is necessary in almost half of patients with IE [9] and is frequently more complicated than cardiac surgery for non-endocarditis valve pathologies [10]. For patients undergoing surgery for IE, the most common reasons for the complexity of surgery are previous cardiac surgery, in 48% [11], multiple valve surgery, in 38%, and the presence of a cardiac abscess, in 27%. In addition to endocarditis-related coagulopathy, the complexity of IE surgery may lead to increased perioperative bleeding and consequently higher requirements for transfusion of blood products, especially in patients with prosthetic valve IE [12].

It is therefore reasonable to include ICS in the concept of cardiac surgery for IE, especially in the case of reoperation or prosthetic valve surgery. On the other hand, the perioperative course of IE patients is often accompanied by sepsis or septic shock, leading to multiorgan failure with high mortality rates [13]. In these circumstances, the use of ICS is restricted by guidelines for transfusion [14], although the data supporting these findings are limited.

The debate about using or not using ICS in complex IE surgery is a daily praxis in cardiac surgery centers. This study aims to elucidate the current practice of ICS use in our center and to present data on ICS use among IE patients with a focus on inflammatory parameters and organ failure in the early postoperative period.

2. Materials and Methods

2.1. Patient Recruitment and Study Design

The study was approved by the ethical committee of Friedrich-Schiller University Jena, Germany (registration number: 2021-2502-Daten, Chairperson: Prof. E. Schleussner) on 4 January 2022. Informed consent was waived because of the anonymous and observational character of the study. All charts from patients operated for left-sided infective endocarditis between 2015 and 2020 at our center were reviewed. Patients were divided into two groups according to the intraoperative usage of cell salvage.

Within the study period, n = 335 patients underwent cardiac surgery for left-sided endocarditis and were eligible for evaluation.

2.2. Inclusion Criteria

Only patients fulfilling the modified Duke criteria for the definition of infective endocarditis were included in our evaluation [15]. Patients with possible IE prior to surgery were not included in the analysis.

2.3. Intraoperative Cell Salvage Use

ICS usually consists of three components: (1) the collection of tissue blood into a collection reservoir. In this step, tissue blood is usually mixed with heparinized saline to avoid clotting, and tissue debris is removed through a filter membrane. (2) The separation and washing of eryhtrocytes in a centrifugation process with normal saline solution. In this step, the effluent containing plasma fractions, platelets, WBC, free hemoglobin and anticoagulats (i.e., heparin) is separated and discarded. (3) The collection of the washed erythrocyte solution for re-transfusion. A hematocrite of >50% and protein reduction of >90% represent the quality standard of ICS blood and is recommended. However, washed ICS blood may not be immunologically inert, and contamination with gram-positive bacterial commensals of the skin were described without adverse events in the affected patients. Therefore, recent guidelines do not recommend ICS in the cases of infection or tissue contamination.

In the current setting, ICS was implemented on the discretion of the cardiac surgeon and the anesthesiologist in charge following the flowchart depicted in Figure 1. ICS was performed with the intraoperative autotransfusion system XTRA (LivaNova GmbH, Munich, Germany). The system was built up and used according to the manufacturer's instructions. To avoid clotting, the collection system was primed with normal saline solution and an additional supplementation of 25,000 IE of heparin per liter NaCl, as recommended.

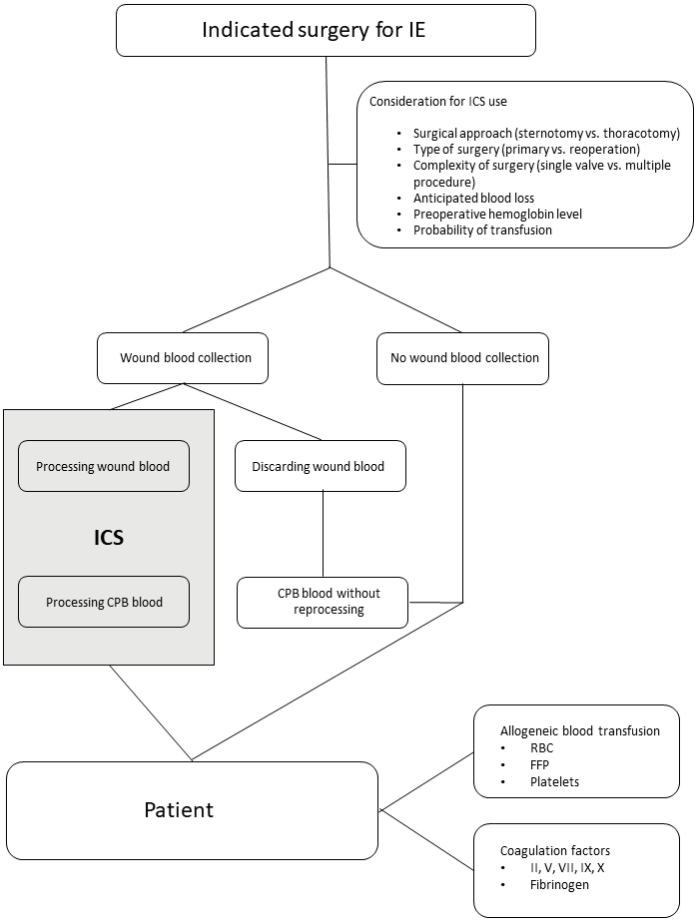

Figure 1. Flowchart highlighting the decision pathway for ICS use and transfusion during IE surgery. IE: infective endocarditis; ICS: intraoperative cell salvage; CPB: cardiopulmonary bypass; RBC: red blood cells; FFP: fresh frozen plasma.

ICS was begun after sternotomy during the preparation process and the prior implementation of the cardiopulmonary bypass circuit. After CPB initiation, tissue blood was preferentially suctioned into the CPB reservoir. Once the infected tissue areas were prepared, blood and tissue debris were discarded via an external suction unit to avoid the re-transfusion of potentially affected and contaminated material. Blood collection via ICS was restarted after CPB separation to minimize blood loss during the restoration of coagulation and chest closure. After weaning from the CPB, residual circuit blood was preferentially processed within the ICS procedure to remove residual heparin and to concentrate hemoglobin content of the machine blood. The ICS-processed blood was administered before transferring the patient to the ICU. Additional blood products or coagulation factors were transfused as needed. The ICS procedure is also depicted in the flowchart of Figure 1.

2.4. Biochemical and Laboratory Markers

Data were obtained from electronic patient charts (COPRA, version 6.78.2.0 and 5.24.974; COPRA System GmbH, Sasbachwalden, Germany) and the clinical database (SAP, version 7300.1.3.1079, Walldorf, Germany). Biochemical values were taken prior to surgery, immediately after surgery and on the first three postoperative days. To describe the use of

vasoactive and inotropic agents, the vasoactive-inotropy score (VIS) [16] was calculated as recommended. Organ dysfunction was defined by calculating the Sequential Organ Failure Assessment [17].

2.5. Statistical Analysis

Whereas continuous data are presented in median [25th–75th percentile] values, categorical data are displayed as number and percentage. Continuous patient characteristics were compared by two-sided non-parametric Mann–Whitney U test, and categorical data were compared by two-sided chi-square test. Independent risk factors associated with the referring laboratory and clinical markers were evaluated by applying binary logistic regression analysis. Regression coefficients with 95% confidence intervals as well as partial eta squared were reported to assess the effect of the risk factors. p values < 0.05 were considered to be statistically significant, all analyses were exploratory and no correction for multiple testing was performed. Statistical analyses were performed using IBM SPSS Statistics, Version 26.0 (IBM Corporation, Armonk, NY, USA), and the graphics were designed with SigmaPlot, Version 14.5 (Systat software, Erkrath, Germany).

3. Results

3.1. Patient Characteristics

In the period between January 2015 and December 2020, we identified n = 335 patients who underwent surgery for left-sided IE at our institution. Patients had a median age of 67 [58.0–75.0] years and the majority were male (76%). The median EuroSCORE II prior to surgery was 6.3 [3.45–10.63]. The median duration of surgery was 200 [154.0–269.0] min, with an intraoperative time on cardiopulmonary bypass of 113 [83.0–156.0] min and a cross clamping time of 70 [59.0–98.0] min. The most common surgical procedures were complex procedures (including multiple valve procedures with or without the resection of an abscess or aortic root) (46.9% of cases), followed by single aortic valve replacement via sternotomy (30.4%), single mitral valve replacement/reconstruction (13.7%) or minimal invasive mitral valve surgery (9%). The rate of reoperation for prosthetic IE was 29.6%. Intraoperative cell salvage was used in n = 135 (40.3%) of the cases. ICS was more common in complex surgical cases as well as reoperations. Duration of surgery, time on CPB as well as cross clamping time were longer in patients with ICS compared to the no-ICS patients.

All patient characteristics are listed in Table 1.

Table 1. Patient characteristics of the total cohort as well as separate values for intraoperative cell salvage (ICS) and no intraoperative cell salvage (no-ICS) use.

	Total	ICS	No-ICS	p-Value
	n = 335	n = 135	n = 200	
Age [years]	67 [58.0–75.0]	67 [58.0–75.0]	66.5 [58.0–75.0]	0.741
Male gender, n (%)	254 (75.8)	105 (77.8)	149 (74.5)	0.492
EUROSCORE II (%)	6.3 [3.45–10.63]	7.7 [5.34–10.99]	4.7 [2.80–9.04]	0.001
Intraoperative data				
Duration of surgery (min)	200 [154.0–269.0]	255 [211.0–341.0]	172 [138.0.–213.0]	0.001
Time on CPB (min)	113 [83.0–156.0]	141 [108.0–189.0]	96.5 [74.0–131.0]	0.001
Cross clamping time (min)	70 [50.0.–98.0]	88 [62.0–126.0]	61 [47.3–82.8]	0.01
Surgical procedure, n (%)				
Complex procedures	157 (46.9)	86 (63.7)	71 (35.5)	0.001
Single aortic, sternotomy	102 (30.4)	35 (25.9)	67 (33.5)	
Single mitral, sternotomy	46 (13.7)	10 (7.4)	36 (18.0)	
Mitral valve, minimal invasive	30 (9.0)	4 (3.0)	30 (9.0)	
Reoperation, n (%)				
yes	99 (29.6)	60 (44.4)	39 (19.5)	0.001
no	236 (70.4)	75 (55.6)	161 (80.5)	

3.2. Course of Inflammatory Markers

Median values of C-reactive protein (CRP) were preoperatively elevated in both patient groups and further increased in the postoperative phase, with peak values on postoperative day two (POD2). In contrast, white blood cell counts (WBCs) were in the normal range prior to surgery and increased in the postoperative phase. Peak values appeared immediately after surgery and declined within the next three days, with values staying above the normal upper value. Linear regression analysis revealed no significant differences in terms of CRP prior to or after surgery between ICS and no-ICS patients. However, the WBC values were significantly higher immediately after surgery in ICS patients compared to no-ICS patients ($p = 0.024$). On average, the WBC values of ICS patients were 3.0 Gpt/l higher compared to no-ICS patients after adjustment for confounders (95% CI: 0.39–5.54). Furthermore, reoperation, former values of inflammation and lactate values, as well as markers of organ dysfunction, were also independent factors associated with differences in terms of CRP and WBC values in the perioperative phase. For details, see Figure 2 and Tables S1 and S2 of the Supplementary Materials.

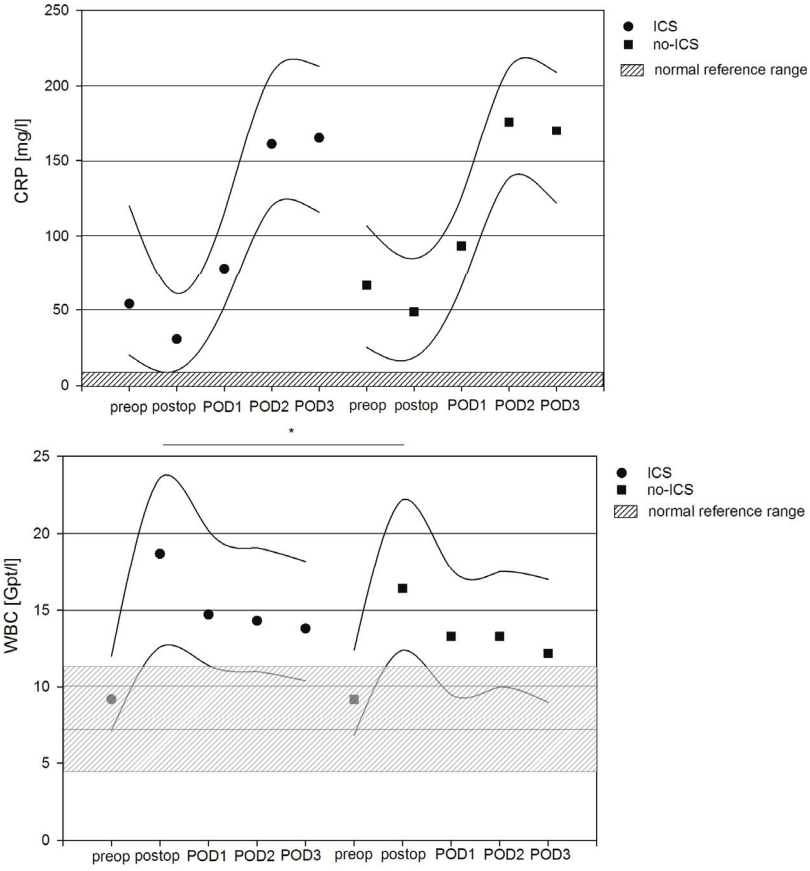

Figure 2. Course of inflammatory markers C-reactive protein and white blood cell count between intraoperative cell salvage (ICS) and no-ICS patients. Circles and squares represent median values, and lines mark 25th and 75th percentiles. * indicates significant difference between the groups resulting from linear regression analysis.

3.3. Course of Hemodynamic Parameters

Median values in terms of the vasoactive inotropy score (VIS) peaked intraoperatively and continuously declined within the first three days after surgery. Linear regression analysis found no significant differences between both patient groups. However, the intraoperative lactate level, perioperative renal dysfunction (defined by elevated creatinine) and the grade of inflammation (defined as elevated CRP values) were factors associated with hemodynamic instability. In detail, VIS in patients with elevated preoperative lactate levels were on average 19.7 points higher compared to patients with low preoperative lactate values after adjustment for confounders (95% CI: 8.3–31.2, $p = 0.001$). Intraoperative VIS in patients with preoperative high creatinine levels were on average 0.3 points higher compared to patients without elevated creatinine levels after adjustment for confounders (95% CI: 0.15–0.45, $p = 0.001$). Finally, intraoperative VIS in patients with elevated CRP values were on average 0.3 points higher compared to patients with lower CRP values after adjustment for confounders (95% CI: 0.08–0.44, $p = 0.005$). Median lactate values peaked immediately after surgery and declined over the following postoperative days. Again, ICS was not associated with increased perioperative lactate values, but linear regression analysis revealed the perioperative use of catecholamines, the duration of the CPB and cross clamping time and former lactate values as factors associated with the course of lactate in the referring patient cohort (Figure 3 and Tables S1 and S2 of the Supplement).

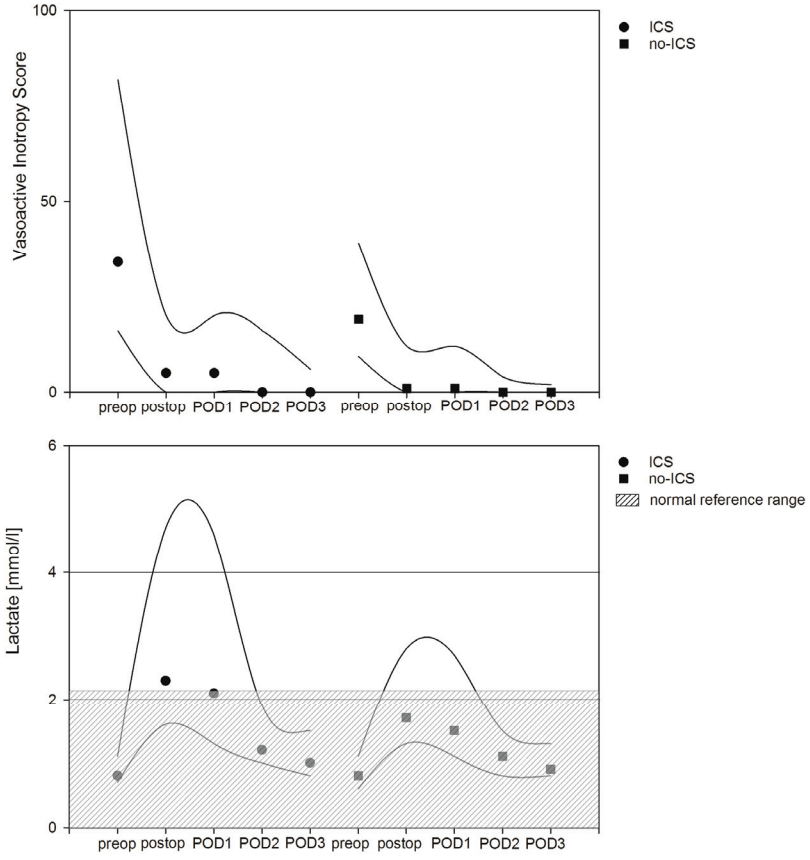

Figure 3. Course of vasoactive inotropy score and lactate levels as surrogate for hemodynamic instability between intraoperative cell salvage (ICS) and no-ICS patients. Circles and squares represent median values, and lines mark 25th and 75th percentiles.

3.4. Perioperative Organ Dysfunction

To describe the course of organ dysfunction, the SOFA score was calculated daily. The median preoperative SOFA was 4 [4.0–6.0], with peak values on the day of surgery. There were no significant differences in terms of the referring SOFA scores. The factors associated with organ dysfunction were the grade of inflammation (postoperative SOFA with elevated WBCs were on average 0.1 point higher (95% CI: 0.02–0.145, $p = 0.010$) after adjustment for confounders), the patient's age (postoperative SOFA increased on average by 0.05 point with every year of age (95% CI: 0.01–0.08, $p = 0.013$) after adjustment for confounders) and preexisting organ failure (postoperative SOFA increased on average by 1 point with every point increase in preexisting SOFA score (95% CI: 0.05–1.14, $p = 0.001$) after adjustment for confounders). A separate evaluation of the underlying laboratory markers predicting organ function showed values above the upper normal range for creatinine and bilirubin as well as values on the lower limit of normal for platelets on POD1 without any differences between ICS and no-ICS patients (see Figure 4 and Tables S1 and S2 of the Supplement).

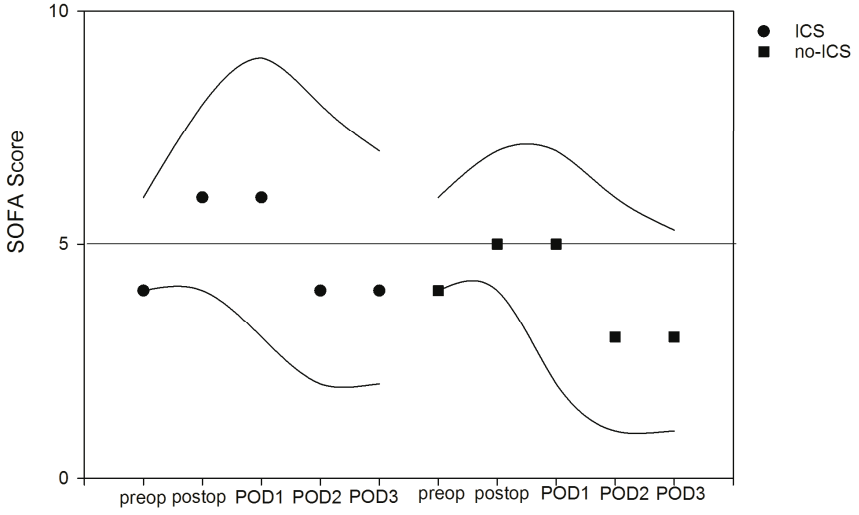

Figure 4. Course of sequential organ failure assessment (SOFA) between intraoperative cell salvage (ICS) and no-ICS patients. Circles and squares represent median values, and lines mark 25th and 75th percentiles.

3.5. Intraoperative Transfusion Requirement

Patients in the ICS group were more likely to receive the transfusion of red cells and coagulation products while undergoing surgery. In detail, patients in the ICS group received more packed red blood cells (3 [2.0–5.0] vs. 2 [0.0–3.0], $p = 0.001$), fresh frozen plasma (0 [0.0–600.0] vs. 0 [0.0–0.0] mL, $p = 0.001$), coagulation factors II, V, VII, and X (2000 [0.0–3000.0] vs. 0 [0.0–2000.0], $p = 0.001$) IU, fibrinogen (2 [2.0–4.0] vs. 0 [0.0–2.0] g, $p = 0.001$) and platelets (1 [0.0–2.0] vs. 0 [0.0–0.0] units, $p = 0.001$) compared to patients in the no-ICS group. Moreover, patients in the ICS group additionally received in median 700 [415.5–1000.0] mL of washed cell salvage blood. Median hemoglobin levels were comparable in the perioperative phase in both patient groups.

3.6. Patient Outcome Data

Patients stayed in hospital for a median 14 [8.0–22.0] days, and a median of 6 [3.0–13.9] days on ICU after surgery. The postoperative ventilation time was a median of 14 [6.1–68.4] h after surgery. The days on hemodialysis or circulatory support after surgery were a median of 0 [0.0–2.0] days or 0 [0.0–0.0] days, respectively. The hospital survival rate was 69.6% in the total patient cohort (see Table 2).

Table 2. Patient outcome data of the total cohort as well as separate values for intraoperative cell salvage (ICS) and no intraoperative cell savage (no-ICS). ICU: intensive care unit.

Postoperative Outcomes	Total	ICS	No-ICS	*p*-Value
Days in hospital	14 [8.0–22.0]	15 [7.0–23.3]	13 [8.0–21.5]	0.712
Days on ICU	6 [3.0–13.0]	7 [3.0 -14.0]	6 [3.0–13.0]	0.350
Duration of ventilation (h)	14 [6.1–68.4]	20 [7.6–109.6]	12 [5.4–54.7]	0.009
Days on hemodialysis	0 [0.0–2.0]	0 [0.0–3.0]	0 [0.0–2.0]	0.08
Days on mechanical circulatory support	0 [0.0–0.0]	0 [0.0–0.0]	0 [0.0–0.0]	0.162
Hospital survival, *n* (%)	233 (69.6)	86 (63.7)	147 (73.5)	0.177

4. Discussion

The aim of this retrospective study was to evaluate the course of parameters associated with the intraoperative use of cell salvage in patients undergoing surgery for infective endocarditis. The results of the study can be summarized as follows:

1. ICS was frequently used in surgery for IE, especially in complex surgical cases and reoperation.
2. ICS did not increase inflammation, except for WBCs immediately after surgery. However, the difference in terms of WBC was statistically significantly higher in the ICS group compared to the no-ICS group, and this difference may be clinically unimportant.
3. ICS did not alter the course of hemodynamic instability, defined by catecholamine dosage and lactate values.
4. Patients with IE usually present with varying degrees of organ dysfunction in the perioperative period. ICS did not alter SOFA-related organ dysfunction (i.e., renal–creatinine, liver–bilirubin or coagulation–platelets).
5. Surgery for IE was associated with a high probability of a transfusion requirement. Due to more complex cases and the resulting surgical approaches, patients in the ICS group were more likely to be transfused with RBC or coagulation products. The use of ICS led to a significant amount of washed tissue blood for re-transfusion.

ICS was designed to collect tissue blood during surgery associated with moderate to high blood loss. During the washing process, tissue debris and other agents are removed, while patient's erythrocytes are collected for re-transfusion [18]. Recent meta-analyses describe a reduction in the transfusion probability of 39% by using ICS, especially during orthopedic and cardiac surgery [19,20]. Therefore, ICS is an integral part of the patient blood management concept [4]. Although there is no absolute contraindication, the use of ICS in infected and contaminated fields remain controversial. Therefore, recent guidelines recommend the application of ICS in these circumstances on a case-to-case basis and to consider its use with caution [21]. However, data regarding the benefits or disadvantages are scarce [22] and are to the best of our knowledge non-existent for IE patients.

In theory, ICS may transfer infective agents and toxins from the surgical field into the patient's circulation with the aggravation of the inflammatory response and sepsis symptoms. In this context, Bland and colleagues determined the bacterial and endotoxin contamination rate of blood collected during elective cardiac surgery. Blood collected in the cell salvage system was culture positive in 96.8% of the samples and 24% had detectable endotoxin levels. Most of the collected blood contained gram-positive bacterial commensals of the skin. However, none of the patients presented with adverse events after surgery [23]. In another study, Luque-Oliveros was able to detect bacterial species in 85% of the red blood cell reinfusion bag of the cell salvage system, with staphylococcus epidermidis (69%) being the most frequent microorganism. Staphylococcus epidermidis was most likely found in patients with a high body mass index and valve surgery [24]. In neither of these studies were adverse events recorded in the patient's clinical course or outcome. Cardiac surgery with the subsequent use of cardiopulmonary bypass and suction and the retransfusion of cardiotomy suction blood significantly elevates profinflammatory

cytokines in the postoperative phase. Avoiding the retransfusion of cardiotomy suction blood reduces the postoperative inflammatory release of TNF-alpha, IL-6 and complement factor 3a [25]. In this respect, ICS was shown to reduce proinflammatory mediators, such as cytokines or complement system components, in comparison to direct cardiotomy suction [3]. Damgaard and colleagues showed reduced plasma IL-6 and IL-8 levels after ICS use in the immediate postoperative phase in elective CABG patients. Moreover, tumor necrosis factor receptor, IL-10 and procalcitonin levels were significantly reduced in ICS blood [26]. Furthermore, even in off-pump coronary artery bypass grafting surgery, proinflammatory cytokines were elevated in the postoperative phase and ICS was able to remove cytokines effectively [27]. Taken together, cardiotomy suction blood and processed ICS blood is frequently contaminated by bacterial commensals. Moreover, the surgical procedure itself and the use of CPB circuits enhances the inflammatory response, leading to elevated levels of cytokines and complement factors in the postoperative phase. ICS is able to reduce the levels of cytokines from cardiotomy suction blood. In a previous study, we demonstrated enhanced proinflammatory markers in IE patients compared to non-IE patients immediately after CPB and within 6h of surgery [28]. Moreover, Träger and colleagues described peak values in terms of IL-6 and IL-8 levels in IE patients during and immediately after surgery [29]. However, data on the inflammatory profile or bacterial contamination of ICS-processed blood in IE patients are missing.

Hemodynamic instability, defined by elevated lactate levels and catecholamine support, is common during the perioperative phase in patients with IE [29–31]. Lactate levels and catecholamine support in our patient cohort peaked in the early postoperative phase and continuously declined in the days after surgery. These data are in line with previous reports [29,31]. Belletti and colleagues defined factors associated with high-dose inotropic support using vasoactive-inotropic scores of >10. In that case, the duration of surgery, a male gender, the preoperative impairment of kidney function, the worsening of heart failure and the preoperative platelet count presented factors associated with postoperative high-dose inotropic support. Similar data were found in our patient cohort. Here, former levels of lactate and catecholamine support as well as creatinine, bilirubin and CRP levels and the duration of CPB were associated with the course of lactate and catecholamine support. However, ICS was not an independent factor of hemodynamic instability in our patients. Moreover, data supporting hemodynamic alterations of ICS in IE or general surgical patients are missing.

IE is often accompanied by major perioperative complications. Recent data suggest the rate of major complications in IE patients is 38%, with cardiovascular and neurological events as well as renal dysfunction being the most prominent affected organ systems [32]. Moreover, liver dysfunction may play a pivotal role in patients with IE and worsen outcomes [13]. In intensive care patients, the SOFA score was established to describe the degree of organ dysfunction [17]. This score is also frequently used in IE patients and was shown to predict mortality in these patients [33,34]. SOFA scores in our patient cohort peaked on POD1 and declined thereafter. The factors associated with higher SOFA scores were age, the type of surgery, the grade of inflammation (defined by CRP and WBC values), hemodynamic instability (defined by the course of lactate and inotropic support) as well as former course of SOFA values. These data are in line with previous reports that addressed age, surgery, CRP levels and diabetes mellitus as independent factors associated with SOFA scores and mortality in IE patients [33–35].

A considerable number of patients undergoing surgery for IE require the transfusion of red packed blood, coagulation products or platelets during the perioperative phase. The probability as well as the amount of the given products increases with the type of surgery and especially in cases of prosthetic valve endocarditis [12]. Patients in the current cohort also received more allogeneic blood transfusions and coagulation products in the context of reoperation. Moreover, ICS was more common in reoperations and complex cases, rather than single valve replacement. With a focus on coagulation, ICS was shown to significantly reduce coagulation factors [36]. Moreover, thrombelastometry fibrinogen levels, measured

in FIBTEM-MCF, significantly decreased in the salvaged blood. The authors concluded that amounts of >18.5% of salvaged blood may impair the coagulation function, especially in patients with lower FIBTEM-MCF before and after cardiac surgery [37]. However, the CPB itself alters the coagulation function and hence reduces certain coagulation factors [38]. In this respect, ICS of the residual CPB blood may reduce the incidence of postoperative blood loss and subsequently the application of coagulation products (i.e., fresh frozen plasma) [39]. Furthermore, a considerable number of patients require emergency surgery while being on anticoagulants prior to surgery. Coagulation disturbances in these circumstances are common and need to be managed intraoperatively [40]. On the other hand, IE itself deeply interacts with the coagulation system by increasing systemic coagulation activation, enhancing platelet activity and impairing fibrinolysis [41]. The role of ICS in these circumstances is therefore complex and needs to be characterized in further studies.

To recap, the use of ICS during IE surgery may have advantages as well as disadvantages. Crucial aspects that might be considered prior to ICS use during IE surgery are therefore listed in Table 3.

Table 3. Probable advantages or disadvantages of intraoperative cell salvage (ICS) during infective endocarditis (IE) surgery. RBC: red blood cells; CPB: cardiopulmonary bypass.

Advantages of ICS in IE Surgery	Disadvantages of ICS in IE Surgery
Reduction in allogeneic RBC transfusion	Enhanced inflammatory reaction by retransfusion of cytokines
Reduction in cristalloid or colloidal fluid administration	Possible retransfusion of bacteria or bacterial commensals from infected tissue
Reduction in postoperative bleeding tendency by eliminating heparin from CPB blood	Reduction in blood coagulation factors during washing process
Reduction in inflammatory reaction by reducing cytokines from ICS blood	
Reduction in immunologic response against allogeneic blood transfusion	

The current study has several limitations. First, we present a monocentric retrospective evaluation with all its benefits and limitations. Second, ICS was more common in sicker patients with a higher EUROSCORE II prior to surgery, with prosthetic valve IE and reoperation. As these patients usually present with a higher probability of transfusion and coagulation disturbances, and therefore our results may be biased. However, as ICS was more common in these patients, a bias towards the positive effects of ICS is unlikely. Third, due to the retrospective design, we were not able to present data for cytokines or other inflammatory markers related to ICS usage in our patients. Moreover, data on the course of coagulation factors are missing. Therefore, our results should be interpreted with caution and in terms of considerations. However, as we present a large cohort of IE patients with and without ICS use, our data hint towards reliable results with respect to our hypothesis.

5. Conclusions

Our results showed that the transfusion of RBC and coagulation factors after surgery for IE was common. The use of ICS enhanced the retransfusion of autologous blood with minor effects on the postoperative course of inflammatory markers. The use of ICS was not associated with increased hemodynamic instability or a worsening of the degree of organ dysfunction, as measured by a SOFA score. The restriction of ICS in IE surgery should be re-evaluated, and more prospective data in this topic are needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12010382/s1, Table S1: Course of laboratory and clinical parameters between intraoperative cell saver usage (ICS) and no-ICS patients. Bold mark significant difference, between the groups resulting from linear regression analysis; Table S2: Dependent variables.

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References

1. Carless, P.A.; Henry, D.A.; Moxey, A.J.; O'Connell, D.; Brown, T.; Fergusson, D.A. Cell Salvage for Minimising Perioperative Allogeneic Blood Transfusion. In *Cochrane Database of Systematic Reviews*; The Cochrane Collaboration, Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2006; p. CD001888.pub2.
2. Wang, G.; Bainbridge, D.; Martin, J.; Cheng, D. The Efficacy of an Intraoperative Cell Saver During Cardiac Surgery: A Meta-Analysis of Randomized Trials. *Anesth. Analg.* **2009**, *109*, 320–330. [CrossRef] [PubMed]
3. Paparella, D.; Whitlock, R. Safety of Salvaged Blood and Risk of Coagulopathy in Cardiac Surgery. *Semin. Thromb. Hemost.* **2016**, *42*, 166–171. [CrossRef] [PubMed]
4. Yousuf, M.S.; Samad, K.; Ahmed, S.S.; Siddiqui, K.M.; Ullah, H. Cardiac Surgery and Blood-Saving Techniques: An Update. *Cureus* **2022**, *14*, e21222. [CrossRef]
5. Sikorski, R.A.; Rizkalla, N.A.; Yang, W.W.; Frank, S.M. Autologous Blood Salvage in the Era of Patient Blood Management. *Vox Sang.* **2017**, *112*, 499–510. [CrossRef]
6. Neef, V.; Vo, L.; Herrmann, E.; Triphaus, C.; Judd, L.; Winter, A.; Zacharowski, K.; Choorapoikayil, S.; Meybohm, P. The Association between Intraoperative Cell Salvage and Red Blood Cell Transfusion in Cardiac Surgery—an Observational Study in a Patient Blood Management Centre. *Anaesthesiol. Intensive Ther.* **2021**, *53*, 1–9. [CrossRef]
7. Waters, J.H. Indications and Contraindications of Cell Salvage. *Transfusion* **2004**, *44*, 40S–44S. [CrossRef] [PubMed]
8. Murdoch, D.R.; Corey, G.R.; Hoen, B.; Miró, J.M.; Fowler, V.G.; Bayer, A.S.; Karchmer, A.W.; Olaison, L.; Pappas, P.A.; Moreillon, P.; et al. Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch. Intern. Med.* **2009**, *169*, 463–473. [CrossRef] [PubMed]
9. Prendergast, B.D.; Tornos, P. Surgery for Infective Endocarditis: Who and When? *Circulation* **2010**, *121*, 1141–1152. [CrossRef]
10. Diab, M.; Lehmann, T.; Bothe, W.; Akhyari, P.; Platzer, S.; Wendt, D.; Deppe, A.-C.; Strauch, J.; Hagel, S.; Günther, A.; et al. Cytokine Hemoadsorption During Cardiac Surgery versus Standard Surgical Care for Infective Endocarditis (REMOVE): Results from a Multicenter, Randomized, Controlled Trial. *Circulation* **2022**, *145*, 959–968. [CrossRef]
11. Manne, M.B.; Shrestha, N.K.; Lytle, B.W.; Nowicki, E.R.; Blackstone, E.; Gordon, S.M.; Pettersson, G.; Fraser, T.G. Outcomes after Surgical Treatment of Native and Prosthetic Valve Infective Endocarditis. *Ann. Thorac. Surg.* **2012**, *93*, 489–493. [CrossRef]
12. Salem, M.; Friedrich, C.; Saad, M.; Frank, D.; Salem, M.; Puehler, T.; Schoettler, J.; Schoeneich, F.; Cremer, J.; Haneya, A. Active Infective Native and Prosthetic Valve Endocarditis: Short- and Long-Term Outcomes of Patients after Surgical Treatment. *J. Clin. Med.* **2021**, *10*, 1868. [CrossRef] [PubMed]
13. Diab, M.; Sponholz, C.; von Loeffelholz, C.; Scheffel, P.; Bauer, M.; Kortgen, A.; Lehmann, T.; Färber, G.; Pletz, M.W.; Doenst, T. Impact of Perioperative Liver Dysfunction on In-Hospital Mortality and Long-Term Survival in Infective Endocarditis Patients. *Infection* **2017**, *45*, 857–866. [CrossRef] [PubMed]

14. Richtlinie Zur Gewinnung von Blut Und Blutbestandteilen Und Zur Anwendung von Blutprodukten (Richtlinie Hämotherapie), Aufgestellt Gemäß §§ 12a Und 18 Transfusionsgesetz von Der Bundesärztekammer Im Einvernehmen Mit Dem Paul-Ehrlich-Institut. Bundesärztekammer. 2017. Available online: https://www.bundesaerztekammer.de/fileadmin/user_upload/_old-files/downloads/pdf-Ordner/RL/RiliH_Lese.pdf (accessed on 17 May 2022).
15. Li, J.S.; Sexton, D.J.; Mick, N.; Nettles, R.; Fowler, V.G.; Ryan, T.; Bashore, T.; Corey, G.R. Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2000**, *30*, 633–638. [CrossRef]
16. Gaies, M.G.; Gurney, J.G.; Yen, A.H.; Napoli, M.L.; Gajarski, R.J.; Ohye, R.G.; Charpie, J.R.; Hirsch, J.C. Vasoactive-Inotropic Score as a Predictor of Morbidity and Mortality in Infants after Cardiopulmonary Bypass. *Pediatr. Crit. Care Med. J. Soc. Crit. Care Med. World Fed. Pediatr. Intensive Crit. Care Soc.* **2010**, *11*, 234–238. [CrossRef] [PubMed]
17. Vincent, J.L.; Moreno, R.; Takala, J.; Willatts, S.; De Mendonça, A.; Bruining, H.; Reinhart, C.K.; Suter, P.M.; Thijs, L.G. The SOFA (Sepsis-Related Organ Failure Assessment) Score to Describe Organ Dysfunction/Failure. On Behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* **1996**, *22*, 707–710. [CrossRef] [PubMed]
18. Konig, G.; Waters, J.H. Washing and Filtering of Cell-Salvaged Blood—Does It Make Autotransfusion Safer? *Transfus. Altern. Transfus. Med. TATM* **2012**, *12*, 78–87. [CrossRef]
19. Huët, C.; Salmi, L.R.; Fergusson, D.; Koopman-van Gemert, A.W.; Rubens, F.; Laupacis, A. A Meta-Analysis of the Effectiveness of Cell Salvage to Minimize Perioperative Allogeneic Blood Transfusion in Cardiac and Orthopedic Surgery. International Study of Perioperative Transfusion (ISPOT) Investigators. *Anesth. Analg.* **1999**, *89*, 861–869. [CrossRef]
20. Meybohm, P.; Choorapoikayil, S.; Wessels, A.; Herrmann, E.; Zacharowski, K.; Spahn, D.R. Washed Cell Salvage in Surgical Patients: A Review and Meta-Analysis of Prospective Randomized Trials under PRISMA. *Medicine (Baltimore)* **2016**, *95*, e4490. [CrossRef]
21. Klein, A.A.; Bailey, C.R.; Charlton, A.J.; Evans, E.; Guckian-Fisher, M.; McCrossan, R.; Nimmo, A.F.; Payne, S.; Shreeve, K.; Smith, J.; et al. Association of Anaesthetists Guidelines: Cell Salvage for Peri-Operative Blood Conservation 2018. *Anaesthesia* **2018**, *73*, 1141–1150. [CrossRef]
22. Liu, Z.; Yang, X.; Zhao, E.-Z.; Wan, X.; Cao, G.; Zhou, Z. The Use of Cell Salvage during Second-Stage Reimplantation for the Treatment of Chronic Hip Periprosthetic Joint Infection: A Retrospective Cohort Study. *J. Orthop. Surg.* **2022**, *17*, 85. [CrossRef]
23. Bland, L.A.; Villarino, M.E.; Arduino, M.J.; McAllister, S.K.; Gordon, S.M.; Uyeda, C.T.; Valdon, C.; Potts, D.; Jarvis, W.R.; Favero, M.S. Bacteriologic and Endotoxin Analysis of Salvaged Blood Used in Autologous Transfusions during Cardiac Operations. *J. Thorac. Cardiovasc. Surg.* **1992**, *103*, 582–588. [CrossRef] [PubMed]
24. Luque-Oliveros, M. Bacteremia in the Red Blood Cells Obtained from the Cell Saver in Patients Submitted to Heart Surgery. *Rev. Lat. Am. Enferm.* **2020**, *28*, e3337. [CrossRef] [PubMed]
25. Westerberg, M.; Bengtsson, A.; Jeppsson, A. Coronary Surgery without Cardiotomy Suction and Autotransfusion Reduces the Postoperative Systemic Inflammatory Response. *Ann. Thorac. Surg.* **2004**, *78*, 54–59. [CrossRef] [PubMed]
26. Damgaard, S.; Nielsen, C.H.; Andersen, L.W.; Bendtzen, K.; Tvede, M.; Steinbrüchel, D.A. Cell Saver for On-Pump Coronary Operations Reduces Systemic Inflammatory Markers: A Randomized Trial. *Ann. Thorac. Surg.* **2010**, *89*, 1511–1517. [CrossRef]
27. Allen, S.J.; McBride, W.T.; McMurray, T.J.; Phillips, A.S.; Penugonda, S.P.; Campalani, G.; Young, I.S.; Armstrong, M.A. Cell Salvage Alters the Systemic Inflammatory Response After Off-Pump Coronary Artery Bypass Grafting Surgery. *Ann. Thorac. Surg.* **2007**, *83*, 578–585. [CrossRef]
28. Diab, M.; Tasar, R.; Sponholz, C.; Lehmann, T.; Pletz, M.W.; Bauer, M.; Brunkhorst, F.M.; Doenst, T. Changes in Inflammatory and Vasoactive Mediator Profiles during Valvular Surgery with or without Infective Endocarditis: A Case Control Pilot Study. *PloS ONE* **2020**, *15*, e0228286. [CrossRef]
29. Träger, K.; Skrabal, C.; Fischer, G.; Datzmann, T.; Schroeder, J.; Fritzler, D.; Hartmann, J.; Liebold, A.; Reinelt, H. Hemoadsorption Treatment of Patients with Acute Infective Endocarditis during Surgery with Cardiopulmonary Bypass—A Case Series. *Int. J. Artif. Organs* **2017**, *40*, 240–249. [CrossRef]
30. Belletti, A.; Jacobs, S.; Affronti, G.; Mladenow, A.; Landoni, G.; Falk, V.; Schoenrath, F. Incidence and Predictors of Postoperative Need for High-Dose Inotropic Support in Patients Undergoing Cardiac Surgery for Infective Endocarditis. *J. Cardiothorac. Vasc. Anesth.* **2018**, *32*, 2528–2536. [CrossRef]
31. Kühne, L.-U.; Binczyk, R.; Rieß, F.-C. Comparison of Intraoperative versus Intraoperative plus Postoperative Hemoadsorption Therapy in Cardiac Surgery Patients with Endocarditis. *Int. J. Artif. Organs* **2019**, *42*, 194–200. [CrossRef]
32. Mir, T.; Uddin, M.; Qureshi, W.T.; Regmi, N.; Tleyjeh, I.M.; Saydain, G. Predictors of Complications Secondary to Infective Endocarditis and Their Associated Outcomes: A Large Cohort Study from the National Emergency Database (2016–2018). *Infect. Dis. Ther.* **2022**, *11*, 305–321. [CrossRef]
33. Lin, Y.; Dong, S.; Yuan, J.; Yu, D.; Bei, W.; Chen, R.; Qin, H. Accuracy and Prognosis Value of the Sequential Organ Failure Assessment Score Combined With C-Reactive Protein in Patients with Complicated Infective Endocarditis. *Front. Med.* **2021**, *8*, 576970. [CrossRef]
34. Lin, Y.; Liu, F.; Gong, S.; Liao, B.; Liu, H.; Yuan, J.; Yu, D.; Qin, H.; Wu, M.; Dong, S. Validity of SOFA Score as a Prognostic Tool for Critically Ill Elderly Patients with Acute Infective Endocarditis. *Rev. Cardiovasc. Med.* **2021**, *22*, 967–973. [CrossRef] [PubMed]
35. Asai, N.; Shiota, A.; Ohashi, W.; Watanabe, H.; Shibata, Y.; Kato, H.; Sakanashi, D.; Hagihara, M.; Koizumi, Y.; Yamagishi, Y.; et al. The SOFA Score Could Predict the Severity and Prognosis of Infective Endocarditis. *J. Infect. Chemother. Off. J. Jpn. Soc. Chemother.* **2019**, *25*, 965–971. [CrossRef] [PubMed]

36. Adam, E.H.; Funke, M.; Zacharowski, K.; Meybohm, P.; Keller, H.; Weber, C.F. Impact of Intraoperative Cell Salvage on Blood Coagulation Factor Concentrations in Patients Undergoing Cardiac Surgery. *Anesth. Analg.* **2020**, *130*, 1389–1395. [CrossRef] [PubMed]
37. Son, K.; Yamada, T.; Tarao, K.; Kitamura, Y.; Okazaki, J.; Sato, Y.; Isono, S. Effects of Cardiac Surgery and Salvaged Blood Transfusion on Coagulation Function Assessed by Thromboelastometry. *J. Cardiothorac. Vasc. Anesth.* **2020**, *34*, 2375–2382. [CrossRef]
38. Yavari, M.; Becker, R.C. Coagulation and Fibrinolytic Protein Kinetics in Cardiopulmonary Bypass. *J. Thromb. Thrombolysis* **2009**, *27*, 95–104. [CrossRef]
39. Muraki, R.; Totsugawa, T.; Nagata, K.; Nakajima, K.; Oshita, T.; Arimichi, M.; Yoshitaka, H.; Sakaguchi, T. Cell Salvage Processing of Residual Cardiopulmonary Bypass Volume in Minimally Invasive Cardiac Surgery. *Heart Vessel.* **2019**, *34*, 1280–1286. [CrossRef]
40. Fang, Z.A.; Navaei, A.H.; Hensch, L.; Hui, S.-K.R.; Teruya, J. Hemostatic Management of Extracorporeal Circuits Including Cardiopulmonary Bypass and Extracorporeal Membrane Oxygenation. *Semin. Thromb. Hemost.* **2020**, *46*, 062–072. [CrossRef]
41. Buyukasýk, N.S.; Ileri, M.; Alper, A.; Senen, K.; Atak, R.; Hisar, I.; Yetkin, E.; Turhan, H.; Demirkan, D. Increased Blood Coagulation and Platelet Activation in Patients with Infective Endocarditis and Embolic Events. *Clin. Cardiol.* **2004**, *27*, 154–158. [CrossRef]

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Opioid Reduced Anesthesia in Major Oncologic Cervicofacial Surgery: A Retrospective Study

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Abstract: Opioid sparing is one of the new challenges in anesthesia and perioperative medicine. Opioid reduced anesthesia (ORA) is part of this approach, and it consists of a multimodal analgesia-associating non-opioid analgesic regional anesthesia to reduce intraoperative opioid requirements. Major cervicofacial oncologic surgery could specifically benefit from ORA, since it is known to generate intense and prolonged postoperative pain, with a high risk of pulmonary complications. Methods: This is a retrospective case-controlled study of 172 patients with major cervicofacial oncologic surgery. Group ORA (dexmedetomidine and lidocaine), $n = 86$, was compared to patients treated with standard opioid based anesthesia, Group control, $n = 86$. The main endpoint was to study perioperative opioid consumption and postoperative pain scores, and the secondary endpoint was to observe opioid related side effects. Results: The ORA group received 6.2 ± 3.1 mg morphine titration at the end of surgery, while the control group received 10.1 ± 3.7 mg $p < 0.0001$; there was no significant difference in post-operative analgesia requirements and pain scores between the groups. Intraoperatively, the ORA protocol yielded bradycardia in 4 persons, while in the control group, only 2 persons had bradycardia necessitating intervention, $p < 0.05$. Postoperatively, episodes of hypoxemia (50%) and the need for additional pressure-assisted ventilation (6%), was significantly different in the ORA group than in the control group (70% and 19%), $p < 0.05$. There was no difference between the two groups for the incidence of nausea and vomiting, ileus, or postoperative delirium. Discussion: ORA was not associated with a decrease in postoperative pain and opioid requirement, but possibly reduced the incidence of hypoxemia and the use of additional pressure-assisted ventilation, although we cannot rule out confounding factors. The possible benefits of ORA remain to be demonstrated by prospective studies.

Keywords: opioid free anesthesia; opioid reduced anesthesia; dexmedetomidine; cervicofacial oncologic surgery

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1. Introduction

Opioids are historically part of the fundamental tripod of anesthesia, in association with hypnotics and neuromuscular blockers. In France, 1.1% of the population received a prescription for strong opioids in 2017, with an increase of +104% between 2004 and 2017. According to pharmacovigilance reports, this increase in consumption was also accompanied by episodes of overdoses, which increased by 98% between 2004 and 2016 [1].

Opioids are frequently administered during the perioperative period; it is estimated that 50% of patients are discharged with a prescription for strong opioids for the management of postoperative pain, and more than 3% still use them 3 months later [2].

Opioids have multiple side effects, including a dose-dependent respiratory depressant effect, sedation, chest rigidity, cough depression, and bronchoconstriction at high doses. A total of 46% percent of patients treated with intravenous opioids experience respiratory depression [3]. Postoperative nausea and vomiting (PONV) is the most frequent and feared

side effect of opioids, with a mean incidence of 25% for vomiting and 52% for nausea [4]. Finally, opioids may induce hyperalgesia, tolerance, and dependence. Hyperalgesia refers to an increased sensitivity to feeling pain from a stimulus that usually provokes it. In a meta-analysis by Fletcher et al., high-dose vs. low-dose intraoperative remifentanil was responsible for a significant increase in early postoperative pain scores and was associated with increased morphine consumption [5]. Tolerance refers to the decrease in a pharmacologic effect and the need' to increase the dose required to achieve the same effect; it can occur during both occasional and chronic pain, which can subsequently complicate pain management and increase the risk of opioid-related adverse events [6].

New anesthetic strategies seek to rationalize the administration of opioids by considering new drug synergies. One alternative is opioid free anesthesia (OFA) or, more moderately, opioid reduced anesthesia (ORA). Under general anesthesia, the patient will not experience pain, but rather nociception, which is the propagation of a painful stimulus by the sensory system and the reflex activation of the sympathetic system. Therefore, the management of intraoperative analgesia corresponds to the control of the hemodynamic response to nociception [7]. The activation of opioid receptors is one pathway of blocking the transmission of nociceptive information, but it is not the only one. OFA considers the plurality of mechanisms of action involved in nociception and is based on a balanced and multimodal analgesia by combining regional anesthesia (RA), NMDA receptor antagonists (ketamine, magnesium sulfate), anti-inflammatory drugs (NSAIDs, dexamethasone, and intravenous lidocaine), and α-2 agonists (dexmedetomidine or clonidine). The concept of OFA/ORA uses this synergy of action on different receptors to counter the nociceptive response to minimize the use of opioids. To date, OFA is a controversial strategy, despite a recent meta-analysis describing postoperative outcome improvements in several surgical settings [8]. Nevertheless, its clinical value is still being evaluated, as there are only few robust studies in this field. In the worrying context of the opioid crisis, it remains a hot topic: 74 ongoing studies on OFA are listed on clinicaltrials.gov. Another recent meta-analysis of 23 randomized controlled trials and more than 1000 patients observed equivalent analgesia between patients who received opioids and those in the OFA group at 2 h postoperatively, with a 20% reduction in PONV in favor of OFA [9]. However, it did not observe a significant difference in postoperative morphine consumption [9]. Another recent meta-analysis by Salomé did not find any clinically relevant benefit to OFA in terms of analgesia or postoperative opioid consumption [10]. Less radical, ORA aims only to reduce the use of intraoperative opioids, without eradicating them completely.

Pain is the most frequent symptom related to cervicofacial oncologic surgery: 86% of patients describe pain at the time of diagnosis [11]. This pain is exacerbated postoperatively and uncontrolled in 50% of patients [12]. Cervicofacial cancer surgery is often a major, long, and decaying surgery. In the case of extended tumor resection, the need for a reconstruction flap to fill in the loss of substance makes it a double or even triple site surgery. While the flap harvest site is often accessible to regional anesthesia to limit postoperative pain, facial blocks to cover the tumor resection area are rarely performed in routine practice. The accumulation of these multiple sites is responsible for complex pain mechanisms in the postoperative period, which are difficult to relieve despite a quality multimodal systemic analgesia [13]. Moreover, cervicofacial cancer patients often present several risk factors for postoperative complications: alcohol and tobacco addictions, respiratory and cardiovascular comorbidities, malnutrition, and chronic pain [14]. A total of 41% percent of cervicofacial cancer surgery patients use opioids preoperatively [15]. All these vulnerabilities lead to a very high postoperative morbidity and mortality: 43% of patients present a respiratory complication after this type of surgery with free flap reconstruction, and 10% acquire a pulmonary infection after laryngectomy. Finally, postoperative hospital mortality is 4% in these patients vs. 1% in the general population [16]. To date, there is no study evaluating the use of OFA or ORA in cervicofacial oncologic surgery. In this retrospective study, we investigated whether intraoperative morphine sparing with ORA was associated

with a better intra- and postoperative analgesia and a reduction in opioid-related side effects compared to traditional opioid-based anesthesia.

Our main endpoint was the intra- and postoperative opioid requirements and postoperative pain scores in major cervicofacial cancer surgery by using an ORA protocol.

2. Materials and Methods

This single center retrospective study was performed between January 2019 and March 2020. Patients data were collected and processed in agreement with Gustave Roussy institutional review board approval on 11 September 2020, which did not identify any element contrary to medical ethics. In accordance with the recommendations of the Commission Nationale de l'Informatique et des Libertés and the new European GRPD regulations, patients were informed of the collection of their data by an information letter and could object if they wished. The control group consisted of scheduled major cervicofacial surgery lasting more than 4 h, with or without reconstruction. The indications of these major surgeries were decided by a multidisciplinary committee; patients with cardiovascular conditions, respiratory instability, or cognitive disability, along with other vital emergency situations, were excluded until improvement and stabilization were achieved.

All patients of the ORA group exhibited the same indications and counter indications as the control group; however, patients were included if they had no counter indications to ORA medications, which were dexmedetomidine and IV lidocaine. These exclusion criteria were: patients with cardiac conduction disorders, such as atrioventricular block or sinoatrial block, patients treated with beta-blockers and calcium channel blockers, those with a heart rate lower than 50/min during the anesthesia consultation, and patients with severe malnutrition.

2.1. Anesthesia Protocol and Postoperative Management

Protocol

In all patients, general anesthesia included propofol titration, ketamine, dexamethasone, and a non-depolarizing neuromuscular blockade. Anesthesia was maintained with sevoflurane, desflurane, or total intravenous target-controlled anesthesia (TIVA) with propofol, depending on the patient's medical history, and IV bolus (0.3 mg/kg) followed by 0.15 mg/kg/h of ketamine. A peripheral block with a bolus of ropivacaine 2% was performed before induction at the harvest site in case of reconstruction, when possible, to improve intra- and postoperative analgesia [17].

In the control group, remifentanil was administered by target-controlled infusion (TCI), whereas in the ORA group, intraoperative analgesia was provided by a mean IV bolus of dexmedetomidine 0.4µg/kg at induction, followed by a continuous infusion at the discretion of the anesthetist in charge. Lidocaine IV was started with a bolus of 1.5 mg/kg for patients not treated with regional anesthesia, followed by a continuous infusion of 1 mg/kg/h for all patients, which was stopped at the start of skin closure. In the ORA Group, TCI remifentanil was still connected as a back-up, but administered only if the hemodynamic response to nociception, defined as tachycardia or hypertension, did not appear to be controlled by the ORA protocol alone. In both groups, intraoperative changes in remifentanil targets and dexmedetomidine doses were at the discretion of the anesthesiologist in charge. All patients were administered an infusion of magnesium sulfate (2 g) intraoperatively.

In both groups, multimodal postoperative analgesia at the end of the procedure included paracetamol, nonsteroidal anti-inflammatory drugs, nefopam, and a morphine titration (0.5–0.15 mg/kg) before awakening, followed by intravenous morphine in patient controlled analgesia mode (PCA) for 24 to 72 h. A continuous perineural infusion of ropivacaine was prescribed in patients who benefited from a regional block with peri-neural catheterization. Intraoperative monitoring of the patients included invasive measurement of blood pressure by arterial catheter associated with a pulse wave contour analysis system (EV1000®) Edwards Lifesciences Corp., Irvine, CA, USA, monitoring of the depth of

anesthesia by the bispectral index, and monitoring of the neuromuscular blockade using an NMT Philips Intellivue accelerometer module (Royal Philips Electronics, Amsterdam, The Netherlands).

Postoperatively, patients were transferred to the post-anesthesia care unit (PACU) and then to the surgical continuous care unit (SCCU) for 24 to 72 h, depending on the surgery and the evolution. Patients with hypoxemia or desaturation less than 95% necessitating more than 3L of oxygen, or other type of mild respiratory complications, such as atelectasis, could benefit from high-flow nasal oxygen therapy or intermittent pressure-assisted ventilation support. The intensivist in charge could also decide the need for continuous invasive ventilation at any time, and transfer the patient to a medical intensive care unit for more respiratory support if needed.

In addition, from November 2019, patients with tracheostomy at the end of surgery were also included in a preemptive respiratory optimization protocol, with pressure-assisted ventilation (PAV) as part of a quality assurance program. This protocol consisted of 1 session of 30 min of PAV 6 times a day for 24 h, starting in the PACU, and continued in the SICU. In this protocol, FiO_2 was adapted to have a saturation above 95%, and pressure ventilation was adjusted to obtain a tidal volume of 6–8 mL/min.

The following main endpoint parameters were recorded; intraoperative remifentanil dose and morphine titration dose at the end of the operation, as well as at Day 1 and Day 3, and the occurrence of uncontrolled pain (defined by a numeric pain rating verbal scale (NVS) > 3) and clinically acceptable pain (defined by a NVS $\leq$ 3) during the first 72 postoperative hours, as well as the site of origin of the pain.

The secondary parameters were: episodes of postoperative hypoxemia defined as SpO_2 < 95%, or the need of oxygen higher than 3 L/min. The necessity of additional pressure-assisted ventilation or high-flow nasal oxygen postoperatively, in the case of hypoxemia or hypoventilation, the occurrence of postoperative nausea and vomiting (PONV) until Day3, postoperative ileus defined by the absence of stool at D3, urinary retention defined by the necessity of a new bladder catheterization after removal of the urinary catheter, and post-operative delirium defined by an equivalent score on the Nursing Delirium Screening Scale (Nu-DESC) > 2.

Hemodynamic tolerance of the anesthetic protocol was assessed by episodes of bradycardia requiring a bolus of atropine and intraoperative hypotension evaluated by the average noradrenaline flow in mg/h.

2.2. Statistical Analysis

Patient data were anonymized and recorded in the REDCap® database (Vanderbilt University, Nashville, TN, USA) of our institution. Qualitative variables were described using numbers and percentages. Quantitative variables were presented by their mean and standard deviation, when the distribution was normal, and by their median and interquartile range (25th and 75th percentile of the distribution) otherwise.

To test the association between anesthesia technique and the different qualitative variables of interest, we used the Chi-squared test, if validity conditions were met, and the Fisher exact test otherwise. For quantitative variables, we used the nonparametric Wilcoxon test.

Linear regression was employed to adjust the effect of ORA on opioid consumption (intraoperative remifentanil dose, morphine titration dose at the end of the operation, and morphine consumption at Day 1 and Day 3). The following variables were used in the adjusted models: sex, age (years), and ASA score groups (ASA score I and II, ASA score III and IV).

All statistical analyses were performed with SAS© 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient Characteristics

Data from 172 patients were collected in the analysis, with 86 patients in each group. The main demographic characteristics were comparable: 39.6% were women, with a mean age of 58 years. A total of 19.2% of patients were in chronic pain and were receiving an opioid treatment preoperatively. However, the two groups were not comparable regarding all characteristics (Table 1).

Table 1. Baseline characteristics of patients.

Characteristics	Total	Control *n* = 86	ORA *n* = 86	*p* Value
Female sex, *n* (%)	68 (39.6)	33 (38.4)	35 (40.7)	0.87
Age (years), mean (min-max)	57.5 (19–91)	59.2 (19–91)	55.8 (20–77)	0.08
ASA score I and II, *n* (%)	131 (76.2)	58 (67.4)	73 (84.9)	0.01
Comorbidities				
High blood pressure, *n* (%)	51 (29.7)	31 (36)	20 (23.3)	0.09
Diabetes, *n* (%)	16 (9.3)	12 (14)	4 (4.7)	0.06
Cardiovascular disease *, *n* (%)	9 (5.2)	8 (9.3)	1 (1.2)	0.04
COPD, *n* (%)	76 (44.2)	45 (52.3)	31 (36)	0.04
Sleep apnea syndrome, *n* (%)	8 (4.7)	2 (2.3)	6 (7)	0.27
Obesity, *n* (%)	18 (10.5)	9 (10.5)	9 (10.5)	0.99
Malnutrition, *n* (%)	25 (14.5)	18 (20.9)	7 (8.1)	0.029
Chronic pain treated by opioids, *n* (%)	33 (19.2)	18 (20.9)	15 (17.4)	0.71
Previous cancer, *n* (%)	52 (30.2)	36 (41.9)	16 (18.6)	0.002
Surgery				
Median duration, hours [min-max]	10 [4–16]	10 [4–14]	10 [5–16]	0.58
Free flap reconstruction, *n* (%)	158 (91.9)	84 (97.7)	74 (86)	0.01
Tracheostomy, *n* (%)	153 (89)	82 (95.3)	71 (82.5)	0.4
Mandibulectomy, *n* (%)	62 (36)	35 (40.7)	27 (31.4)	0.26
Glossectomy, *n* (%)	35 (20.3)	15 (17.4)	20 (23.3)	0.44
Maxillectomy, *n* (%)	31 (18)	13 (15.1)	18 (20.9)	0.67
Pharyngectomy, *n* (%)	41 (23.8)	26 (30.2	15 (17.4)	0.07
Laryngectomy, *n* (%)	18 (10.4)	6 (7)	12 (14)	0.21
Other **, *n* (%)	27 (15.7)	11 (12.7)	16 (18.6)	0.81

* Cardiovascular disease, including coronary artery disease, peripheral arterial disease, and carotid atherosclerosis. ** Other surgery, including parotidectomy, ventriculoplasty, and ethmoidectomy crico-hyoido-ethmoido-pexy. ASA: American Society of Anesthesiology; COPD: chronic obstructive pulmonary disease; ORA: opioid reduced anesthesia.

Surgeries lasted a median of 10 h (minimum = 4; maximum = 16) and consisted mainly of mandibulectomy and pharyngectomy with flap reconstruction. Tracheotomized patients in the ORA group (71 out of 86) received postoperative preemptive pressure support ventilation as part of a quality assurance program. In the control group, 82 out of 86 benefited from this protocol.

Main endpoint: opioid consumption and pain scores.

The ORA group received significantly less remifentanil intraoperatively 0.01 μg/kg/min vs. 0.07 μg/kg/min in the historical cohort ($p < 0.0001$). The morphine titration dose at the end of the procedure was also significantly lower in the ORA group: 6.2 ± 3.1 vs. 10.1 ± 3.7 mg in the control group ($p < 0.0001$).

Postoperatively, the cumulative consumption of morphine by PCA at D1 and D3 was similar between the 2 groups, respectively, with 18mg in median at D1(min = 4; max = 20) in the control group vs. 17 (min = 6; max = 30) mg in the ORA group ($p = 0.639$) and 34 (18–63) vs. 38 (16–73) mg at D3 ($p = 0.799$).

Pain scores: At Day1, the incidence of clinically acceptable pain relief at rest (NVS < 3) was significantly higher in the OFA group, with 48.8% vs. 29.4% in the control group, ($p = 0.009$). No significant difference was observed for uncontrolled pain.

No difference was noticed at Day 2 and Day3.

Intraoperative events and drugs used are displayed in Table 2.

Table 2. Intraoperative events.

	Total *n* = 172	Control *n* = 86	ORA 86	*p* Value
Propofol (mg/kg), median [IQ 25; 75]	2.46 [2.03; 2.86]	2.42 [2.01; 2.85]	2.5 [2.06; 2.86]	0.263
Remifentanil for intubation, *n* (%)	135 (78.5)	85 (98.8)	50 (58.1)	<0.001
Dexmedetomidine bolus (µg/kg), median [IQ 25; 75]	-	-	0.4 [0.3; 0.5]	-
Maintenance				
Sevoflurane, *n* (%)	162 (94.2)	80 (93)	82 (95.4)	0.746
Desflurane, *n* (%)	8 (4.7)	5 (5.8)	3 (3.5)	0.720
TIVA Propofol, *n* (%)	2 (1.2)	1 (1.2)	1 (1.2)	0.999
Minimal infusion rate of dexmedetomidine (µg/kg/h), median [IQ 25; 75]	-	-	0.2 [0.2; 0.4]	-
Maximal infusion rate of dexmedetomidine (µg/kg/h), median [IQ 25; 75]	-	-	0.8 [0.7; 1]	-
Regional anesthesia, *n* (%)	111 (64.5)	48 (55.8)	63 (73.3)	0.025
Perineural catheterization, *n* (%)	93 (54.1)	56 (65.1)	37 (43)	0.006
Fluid infusion (mL/kg/h), median [IQ 25;75]	10 [8; 12]	10 [8;12]	10 [8;12]	0.987
Intraoperative transfusion, *n* (%)	88 (51.2)	58 (67.4)	30 (34.9)	<0.001
Urine output (mL/kg/h), median [IQ 25; 75]	1.6 [0.8;3]	1.3 [0.8; 3]	2.1 [1.2; 3.3]	0.042

ORA: opioid reduced anesthesia; IQ: interquartile; D: postoperative day.

The pain score assessment was equivalent between the two groups over the 72 h (Figure 1).

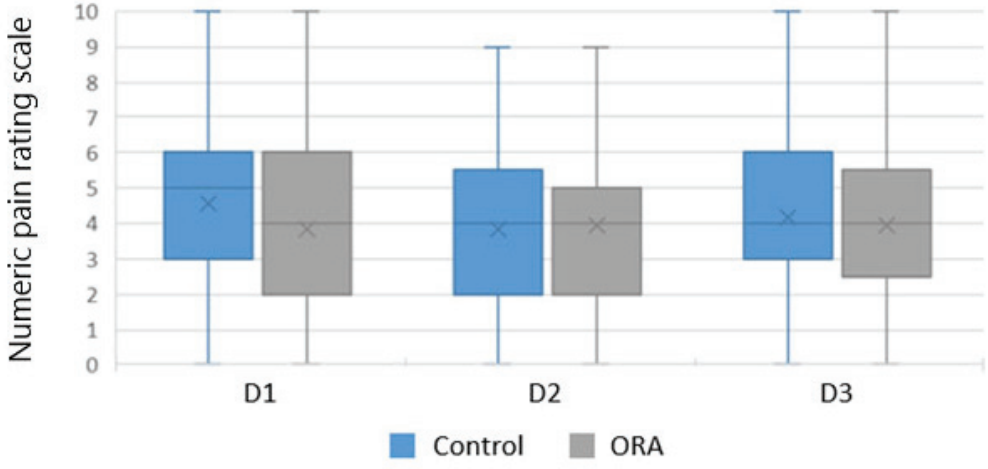

Figure 1. Pain assessment over the first 72 h. ORA: opioid reduced anesthesia; D: postoperative day.

Pain was mainly localized at the cervical and facial area (81%), followed by the flap harvest site (43%), and then the tracheostomy (26%) (Figure 2).

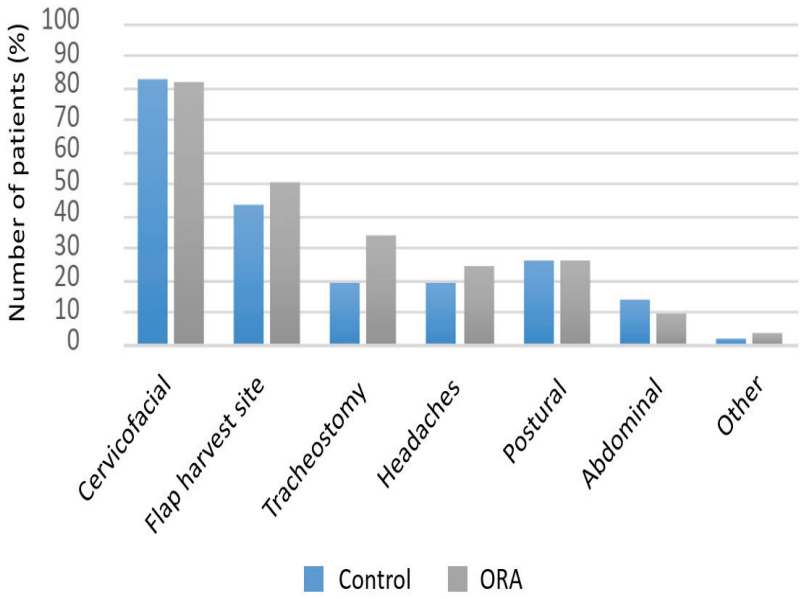

Figure 2. Pain location; ORA: opioid reduced anesthesia.

3.2. Secondary Endpoints

Opioids Adverse Effects Endpoints

The ORA group experienced 43 (50%) episodes of hypoxemia, while the control group exhibited 60 (70%) ($p = 0.013$). The necessity of using additional PAV or HFO was lower in the ORA group, with 5 (6%) vs. 16 (19%) in the control group ($p = 0.018$).

The incidence of PONV at Day2 was similar in both groups, with 17 (20%) in the ORA group vs. 16 (19%) in the control group ($p = 0.999$).

Hemodynamic tolerance of the anesthetic protocol: the rate of infusion of vasopressor support by norepinephrine was significantly more important in the ORA group in comparison to the control group, with a mean of 0.2mg/hour vs. 0.1mg/hour ($p = 0.044$). Other secondary endpoints are displayed in Table 3.

Table 3. Secondary endpoints: opioids side effects and intraoperative hemodynamic tolerance.

Secondary Endpoints	Total *n* = 172	Control *n* = 86	ORA *n* = 86	*p* Value
Postoperative opioid side effects				
Hypoxemia, *n* (%)	103 (59.9)	60 (69.8)	43 (50.0)	0.013
Additional PAV or HFO, *n* (%)	21 (12.2)	16 (18.6)	5 (5.8)	0.018
PONV, *n* (%)	33 (19.2)	16 (18.6)	17 (19.8)	1.000
Ileus, *n* (%)	43 (25)	20 (23.3)	23 (26.7)	0.723
Acute urinary retention, *n* (%)	20 (11.6)	9 (10.5)	11 (12.8)	0.813
Delirium, *n* (%)	11 (6.5)	6 (7.1)	5 (5.8)	0.764
Intraoperative hemodynamic tolerance				
Bradycardia, *n* (%)	6 (3.5)	2 (2.3)	4 (4.7)	0.682
Norepinephrine infusion, mean ± SD (mg/h)	0.2 ±0.2	0.1 ±0.2	0.2 ±0.2	0.044

HFO: high-flow oxygen; PAV = pressure-adjusted ventilation; ORA: opioid reduced anesthesia; SD: standard deviation. PONV= postoperative nausea and vomiting.

4. Discussion

In this retrospective study, ORA protocol did not have a significant impact on pain scores or postoperative morphine consumption, despite a reduction in intraoperative opioid doses. Pain was not optimized in more than 50% of the patients, underlining the

difficulty of postoperative analgesic management in major cervicofacial cancer surgery patients [17]. Indeed, this is a surgery involving a highly innervated anatomical region. The pain trajectory of cervicofacial cancer patients is complex and might be characterized by paroxysmal attacks of pain with a continuous pain background, associating neuropathic, bone, joint, and cutaneous-mucosal and multi-site pain with a significant inflammatory component [13,18]. The resection surgery most often requires a flap covering, adding another pain site. Although the flap harvest site pain can be mostly relieved by regional anesthesia, cervicofacial blocks, such as those involving the V2 and V3 (trigeminal) nerves, are practiced by only a few teams in routine clinical practice; these procedures should be developed and their effect on acute and possible chronic pain studied. ORA is a multimodal anti-nociceptive strategy with an anti-inflammatory component, achieved by intravenous lidocaine; however, it seems difficult to prejudge its effectiveness in such a painful surgery where patients are often pre-exposed to opioids.

Concerning the adverse effects of opioids, ORA patients showed a statistically significant reduction in hypoxemic events, as well as postoperative PAV or HFO; we do not believe this is attributable to the lesser opioid use in the ORA group at Day 1, since there is not enough data in this retrospective study to speculate further on this result, as our respiratory PAV protocol might also have been a confounding factor in this small-sized heterogeneous population.

There was no reduction in other opioids side effects, such as PONV, in the ORA group. In addition, we noticed a particularly smooth awakening in the ORA group that persisted for 24 h after surgery. However, this observation was subjective, since there was no standardized planned evaluation to compare the two groups in this respect. Alpha-2 agonists are recognized and used daily in intensive care for their sedative and analgesic virtues in assisted ventilation weaning and in the prevention of delirium [19].

The cardiac rhythm tolerance of the ORA protocol was acceptable, with the occurrence of 4 episodes of bradycardia requiring atropine. There was also some intraoperative hypotension requiring vasopressor support in the ORA group, probably related to the vasoplegia induced by dexmedetomidine and intravenous lidocaine.

Major cervicofacial oncologic surgery is characterized by a high intraoperative blood pressure lability. It includes an initial period of tumor debulking, marked by a major nociceptive stimulation associated with a hemodynamic response, which decreases as soon as the tumor is resected. Subsequently, the blood pressure maintenance objectives shift to focus on the perfusion of the free flap. This blood pressure lability is also related to the vasculopathy of cervicofacial cancer patients, some of whom have lost the carotid baroreflex following previous cervical radiotherapy and have sequential post-radiation dysautonomia.

To develop perioperative medicine, the introduction of the ORA protocol in our department was part of a global approach to improve recovery after major surgery. The concomitant implementation of a protocol of respiratory rehabilitation by preemptive PAV and the surge in practice of regional anesthesia at the harvest site may have been confounding factors.

Data in the literature on OFA and ORA are discordant. Mulier's randomized controlled trial described a decrease in postoperative pain, opioid consumption, desaturations, and PONV in the OFA group vs. anesthesia with opioids in laparoscopic bariatric surgery, with no difference in intraoperative hemodynamics [20]. Similarly, the randomized controlled trial of 80 bariatric laparoscopic urological surgery patients by Bhardwaj et al. revealed fewer respiratory depressions and better analgesia in the OFA group [21]. No episodes of bradycardia were described in this study.

On the other hand, the recent randomized controlled trial POFA of 303 patients, led by Beloeil et al., was discontinued prematurely because of episodes of severe bradycardia attributed to dexmedetomidine [22]. Unexpectedly, more respiratory events were found in the OFA group. There was no difference in postoperative pain, but there was a decrease in opioid consumption. The OFA group exhibited less PONV, but there was no difference in

postoperative ileus. The primary endpoint in this latter study was a composite including hypoxemia, nausea-vomiting, and postoperative cognitive dysfunction as adverse effects of opioids, possibly losing specificity upon statistical evaluation.

The hemodynamic adverse effects of alpha 2 agonists in anesthesia were confirmed by the meta-analysis conducted by Demiri et al., which included more than 56 studies and 4800 patients. Indeed, they were significantly associated with more hypotensive episodes and bradycardia, both pre- and postoperatively [23]. In Frauenknecht's meta-analysis including 23 randomized studies and 1300 patients, with a high level of evidence, OFA decreased the rate of postoperative nausea and vomiting, but had no effect on postoperative pain. The study did not evaluate the rate of respiratory complications [9]. In the recent meta-analysis by Salomé et al., conducted on 2209 patients in 33 randomized controlled trials, the OFA technique showed a reduction in PONV and pain in PACU, but had no effect on postoperative pain or opioid consumption at 48 h. This study did not find more hemodynamic complications in the OFA group [10]; finally, in another recent meta-analysis, Olausson et al. found that OFA significantly reduced adverse postoperative events in many common interventions, such as gynecological, upper gastrointestinal, and breast surgeries [8].

The comparison between studies is complex because each trial has its own OFA protocol for the reduction or even suppression of intraoperative opioids, and the judgment criteria are not standardized.

To our knowledge, this study is the first to focus on ORA in major cervicofacial oncologic surgery, where patients are intrinsically at high risk of pain due to the tumor localization, but also because of multi-site nature of the surgery. This study specifically informs us concerning an understudied, yet morbid, population regarding anesthesia.

This study has some limitations. The first is its retrospective nature and its limited sample size, which results in a lack of ability to detect differences between the two groups. The use of remifentanil, even in low target concentrations, might be questionable; however, anesthesia providers at the time of the study were not familiar with opioid reduced anesthesia and preferred to have a back up "ready to use" opioid in case of severe sympathetic response to nociceptive stimulation. Additionally, the inclusion of patients with preoperative opioid consumption could also be questioned; as this was not a randomized study, but a retrospective case-controlled investigation, we preferred to check the effect of this protocol on these patients as well. In a previous study, we described an increase of 40% regarding opioid requirements in these patients undergoing major cancer surgery, and we hypothesized that any opioid-saving effect would be beneficial to these patients [24]. Finally, major cervicofacial surgery includes multiple types of surgery, and the most complex types are those with free flap reconstruction. Usually, free flaps are harvested from a distant site, such as the fibula, quadriceps, or scapula, and intense postoperative pain can emanate from the harvest site. In addition to those at the cervical site, we believe that regional blocks performed by anesthesiologists are truly beneficial in this category of patients (in contrast to catheters placed by surgeons) [18]; therefore, since this was a retrospective study, it was not permitted to exclude patients who had peripheral regional blocks. However, there was no cervical site block in any case (since these blocks are not performed in our institution); therefore, the pain emanating from the cervicofacial site is constant and significant. The groups were not totally comparable, as there were patients in the control group who were more critical and who underwent more complex procedures, which limited the interpretation of the results. This initial difference between the 2 groups can be explained by an important selection bias, since, despite the broad inclusion criteria, patients in the ORA group were pre-selected based on the absence of comorbidities as part of the introduction of a new protocol. Nevertheless, we tried to adjust the two groups for the main endpoints by using additional linear regression and multivariate analysis, and we did not find differences in comparison to our initial results. Intraoperative nociception was not monitored, with opioid administration left to the discretion of the clinician based on the hemodynamic response to nociceptive stimuli that was potentially minimized by using

α-2 agonists. The monitoring of nociception by a pupilometer or a nociception monitor was not possible due to the sympatholytic mechanism of action of dexmedetomidine and the surgery site. Unfortunately, we did not have other means of measuring nociception, which was not routinely monitored at the time of the study.

To date, there are few randomized controlled studies using large numbers to validate opioid-reduced anesthesia. The comparison of existing studies is complex because different endpoints are studied—postoperative pain, hypoxemia, respiratory complications, PONV—and each OFA or ORA protocol is specific to the anesthesia team that implements it. The use of dexmedetomidine in these protocols is not without risk, and the POFA study [22] suggests more caution regarding its use in the face of severe bradycardia, which led to its premature withdrawal.

The opioid health crisis alone does not justify denigrating one of the historical pillars of anesthesia and postoperative analgesia. It is important to contextualize the use of opioids, which is necessary in 3% of postoperative patients after 3 months [2], while chronic postoperative pain persists in 12% of patients [5].

To date, postoperative analgesia, although a key issue in perioperative management, has not been optimized. Multimodal analgesia, although its effectiveness has been demonstrated in the literature, is far from being ubiquitous. In Ladha's study, only 56% of the patients received non-opioid multimodal analgesia postoperatively [25]. Similarly, it is estimated that only 3% of patients benefit from regional analgesia compared to the 25% who are eligible [26]. The reduction in opioids would be the logical consequence of a better postoperative analgesic management. In the absence of a "one size fits all" policy, it would be judicious to adapt anesthesia and postoperative analgesia to each patient according to their risk factors and the surgery that awaits them by favoring multimodal anesthesia and analgesia, which would allow for opioid sparing.

Cervicofacial oncologic surgery is an excellent example of the complexity of perioperative analgesic management, and it could be the target of a multimodal anesthesia that could include α-2 agonists as adjuvants, but not replacements, for opioids.

5. Conclusions

Except for in the first postoperative hours, this retrospective study did not find a significant improvement in the management of post-operative analgesia after the implementation of an opioid-reduced anesthesia protocol in major cervicofacial oncologic surgery. Prospective studies are necessary regarding this type of complex surgery to better manage postoperative pain in these patients.

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Data Availability Statement: Data are available on demand (L.B.).

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References

1. Mozon, E.; Richard, N. *État des Lieux de la Consommationdes Antalgiques Opioïdes et Leurs Usages Problématiques*; ANSM: Saint-Denis, France, 2019.
2. Clarke, H.; Soneji, N.; Ko, D.T.; Yun, L.; Wijeysundera, D.N. Rates and risk factors for prolonged opioid use after major surgery: Population based cohort study. *BMJ* **2014**, *348*, g1251. [CrossRef] [PubMed]
3. Khanna, A.K.; Bergese, S.D.; Jungquist, C.R.; Morimatsu, H.; Uezono, S.; Lee, S.; Ti, L.K.; Urman, R.D.; McIntyre, R., Jr.; Tornero, C.; et al. Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. *Anesth. Analg.* **2020**, *131*, 1012–1024. [CrossRef] [PubMed]
4. Koivuranta, M.; Laara, E.; Snare, L.; Alahuhta, S. A survey of postoperative nausea and vomiting. *Anaesthesia* **1997**, *52*, 443–449. [CrossRef] [PubMed]
5. Fletcher, D.; Martinez, V. Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. *Br. J. Anaesth.* **2014**, *112*, 991–1004. [CrossRef] [PubMed]
6. Mercadante, S.; Arcuri, E.; Santoni, A. Opioid-Induced Tolerance and Hyperalgesia. *CNS Drugs* **2019**, *33*, 943–955. [CrossRef]
7. Egan, T.D. Are opioids indispensable for general anaesthesia? *Br. J. Anaesth.* **2019**, *122*, e127–e135. [CrossRef]
8. Olausson, A.; Svensson, C.J.; Andrell, P.; Jildenstal, P.; Thorn, S.E.; Wolf, A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: A systematic review and meta-analysis. *Acta Anaesthesiol. Scand.* **2022**, *66*, 170–185. [CrossRef]
9. Frauenknecht, J.; Kirkham, K.R.; Jacot-Guillarmod, A.; Albrecht, E. Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: A systematic review and meta-analysis. *Anaesthesia* **2019**, *74*, 651–662. [CrossRef]
10. Salome, A.; Harkouk, H.; Fletcher, D.; Martinez, V. Opioid-Free Anesthesia Benefit-Risk Balance: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Clin. Med.* **2021**, *10*, 2069. [CrossRef]
11. Breivik, H.; Cherny, N.; Collett, B.; De Conno, F.; Filbet, M.; Foubert, A.J.; Cohen, R.; Dow, L. Cancer-related pain: A pan-European survey of prevalence, treatment, and patient attitudes. *Ann. Oncol.* **2009**, *20*, 1420–1433. [CrossRef]
12. Sommer, M.; Geurts, J.W.J.M.; Stessel, B.; Kessels, A.G.H.; Peters, M.L.; Patijn, J.; van Kleef, M.; Kremer, B.; Marcus, M.A.E. Prevalence and predictors of postoperative pain after ear, nose, and throat surgery. *Arch. Otolaryngol. Neck Surg.* **2009**, *135*, 124–130. [CrossRef]
13. Bobian, M.; Gupta, A.; Graboyes, E.M. Acute Pain Management Following Head and Neck Surgery. *Otolaryngol. Clin. N. Am.* **2020**, *53*, 753–764. [CrossRef]
14. Yung, K.C.; Piccirillo, J.F. The incidence and impact of comorbidity diagnosed after the onset of head and neck cancer. *Arch. Otolaryngol. Head Neck Surg.* **2008**, *134*, 1045–1049. [CrossRef]
15. Perisanidis, C.; Herberger, B.; Papadogeorgakis, N.; Seemann, R.; Eder-Czembirek, C.; Tamandl, D.; Heinze, G.; Kyzas, P.A.; Kanatas, A.; Mitchell, D.; et al. Complications after free flap surgery: Do we need a standardized classification of surgical complications? *Br. J. Oral Maxillofac. Surg.* **2012**, *50*, 113–118. [CrossRef]
16. Decotte, A.; Woisard, V.; Percodani, J.; Pessey, J.J.; Serrano, E.; Vergez, S. Respiratory complications after supracricoid partial laryngectomy. *Eur. Arch. Otorhinolaryngol.* **2010**, *267*, 1415–1421. [CrossRef]
17. Ferri, A.; Varazzani, A.; Valente, A.; Pedrazzi, G.; Bianchi, B.; Ferrari, S.; Sesenna, E. Perioperative pain management after fibular free flap harvesting for head-and-neck reconstruction using mini-catheters to inject local anesthetic: A pilot study. *Microsurgery* **2018**, *38*, 295–299. [CrossRef]
18. Motamed, C.; Plantevin, F.; Mazoit, J.X.; Julieron, M.; Bourgain, J.L.; Billard, V. Continuous Ropivacaine Peroneal Nerve Infiltration for Fibula Free Flap in Cervicofacial Cancer Surgery: A Randomized Controlled Study. *J. Clin. Med.* **2022**, *11*, 6384. [CrossRef]
19. Ng, K.T.; Shubash, C.J.; Chong, J.S. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: Systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* **2019**, *74*, 380–392. [CrossRef]
20. Mulier, J.P.; Wouters, R.; Dillemans, M.; Dekock, M. A Randomized Controlled, Double-Blind Trial Evaluating the Effect ofOpioid-Free Versus Opioid General Anaesthesia on Postoperative Painand Discomfort Measured by the QoR-40. *J. Clin. Anesth. Pain Med.* **2018**, *6*, 2.
21. Bhardwaj, S.; Garg, K.; Devgan, S. Comparison of opioid-based and opioid-free TIVA for laparoscopic urological procedures in obese patients. *J. Anaesthesiol. Clin. Pharmacol.* **2019**, *35*, 481–486.
22. Beloeil, H.; Garot, M.; Lebuffe, G.; Gerbaud, A.; Bila, J.; Cuvillon, P.; Dubout, E.; Oger, S.; Nadaud, J.; Becret, A.; et al. Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanil for Major or Intermediate Noncardiac Surgery. *Anesthesiology* **2021**, *134*, 541–551. [CrossRef] [PubMed]
23. Demiri, M.; Antunes, T.; Fletcher, D.; Martinez, V. Perioperative adverse events attributed to alpha2-adrenoceptor agonists in patients not at risk of cardiovascular events: Systematic review and meta-analysis. *Br. J. Anaesth.* **2019**, *123*, 795–807. [CrossRef] [PubMed]
24. Motamed, C.; Audibert, J.; Albi-Feldzer, A.; Bouroche, G.; Jayr, C. Postoperative pain scores and opioid consumption in opioid-dependent patients with cancer after intraoperative remifentanil analgesia: A prospective case-controlled study. *J. Opioid Manag.* **2017**, *13*, 221–228. [CrossRef] [PubMed]

25. Ladha, K.S.; Patorno, E.; Huybrechts, K.F.; Liu, J.; Rathmell, J.P.; Bateman, B.T. Variations in the Use of Perioperative Multimodal Analgesic Therapy. *Anesthesiology* **2016**, *124*, 837–845. [CrossRef]
26. Gabriel, R.A.; Ilfeld, B.M. Use of Regional Anesthesia for Outpatient Surgery Within the United States: A Prevalence Study Using a Nationwide Database. *Anesth. Analg.* **2018**, *126*, 2078–2084. [CrossRef]

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Review

Inhaled Sedation with Volatile Anesthetics for Mechanically Ventilated Patients in Intensive Care Units: A Narrative Review

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Abstract: Inhaled sedation was recently approved in Europe as an alternative to intravenous sedative drugs for intensive care unit (ICU) sedation. The aim of this narrative review was to summarize the available data from the literature published between 2005 and 2023 in terms of the efficacy, safety, and potential clinical benefits of inhaled sedation for ICU mechanically ventilated patients. The results indicated that inhaled sedation reduces the time to extubation and weaning from mechanical ventilation and reduces opioid and muscle relaxant consumption, thereby possibly enhancing recovery. Several researchers have reported its potential cardio-protective, anti-inflammatory or bronchodilator properties, alongside its minimal metabolism by the liver and kidney. The reflection devices used with inhaled sedation may increase the instrumental dead space volume and could lead to hypercapnia if the ventilator settings are not optimal and the end tidal carbon dioxide is not monitored. The risk of air pollution can be prevented by the adequate scavenging of the expired gases. Minimizing atmospheric pollution can be achieved through the judicious use of the inhalation sedation for selected groups of ICU patients, where the benefits are maximized compared to intravenous sedation. Very rarely, inhaled sedation can induce malignant hyperthermia, which prompts urgent diagnosis and treatment by the ICU staff. Overall, there is growing evidence to support the benefits of inhaled sedation as an alternative for intravenous sedation in ICU mechanically ventilated patients. The indication and management of any side effects should be clearly set and protocolized by each ICU. More randomized controlled trials (RCTs) are still required to investigate whether inhaled sedation should be prioritized over the current practice of intravenous sedation.

Keywords: volatile anesthetics; sedation; intensive care unit; mechanical ventilation; isoflurane; sevoflurane; desflurane

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1. Introduction

Inhaled sedation for critically ill patients with volatile anesthetic agents were recently revisited during the current coronavirus disease COVID-19 pandemic in view of the shortage in intravenous sedative agents. Many governments took action to address this issue by centrally managing the supply chains affected by the lockdown policies and the international travel restrictions [1–4]. Isoflurane, one of the volatile anesthetic agents, is now approved for intensive care unit (ICU) sedation in several European countries. Intravenous sedatives and their active metabolites are organ-dependent for elimination, and this can lead to unpredictable pharmacokinetics and pharmacodynamics, drug accumulation, poor clearance, and slow wake-up in critically ill patients. In contrast, volatile anesthetics are

independently exhaled by the lungs and require minimal metabolism [5–11]. The objectives of this narrative review were to identify and discuss the published literature concerning the role of volatile anesthetics as sedatives for mechanically ventilated patients in the ICU. This review focused on lessons learned and the precautions required.

2. Materials and Methods

The study was approved by the local research and ethics committee (IRB KFHH No. H-05-HS-065) of King Fahad Hospital, Hofuf city, Saudi Arabia. The research approval number is RCA NO: 12-E-2021.

In this narrative review, databases including Embase, CINAHL, Scopus, Google Scholar, Google, Science Direct, ProQuest, ISI Web of Knowledge, and PubMed were searched to obtain the related literature published in the English language. The key words were: Inhalation Sedation; volatile anesthetic agents; Intensive Care Unit; Mechanical ventilation; Isoflurane; Sevoflurane; and Desflurane.

Study selection: Randomized controlled trials (RCT), observational studies, retrospective studies, and reviews were included. The patients were adult humans (age >18 years) under mechanical ventilation in medical, surgical, and specialized cardiac ICUs, but not neurosurgical ICUs. The recorded data included the volatile anesthesia sedation effects on ventilation and weaning, hemodynamics stability, organ dysfunction, cognitive function, recovery, and the risk of air pollution.

3. Results

The literature search focused on the period between 2005 and 2023. Seventy-four peer-reviewed studies were selected as a result of the initial reading of the abstracts and reviewing the full text for each article. Sixty-seven peer-reviewed studies were included that identified and covered different aspects of inhalation sedation practice. Six recent and different studies summarized the various practical aspects of concern with inhaled sedation among COVID-19 patients during the last pandemic. (Table 1).

Inhaled sedation reduced the extubation and weaning times of mechanical ventilation, lowered opioids (analgesic sparing effect) and muscle relaxants consumption, enhanced recovery and minimized delirium. Table 2 demonstrates the published controlled trials that demonstrated the analgesic sparing effect of inhalation sedation compared to the other, traditional intravenous sedatives. The improvement in the quality of recovery was demonstrated by Ostermann and his colleagues in their systematic review, Mesnil et al. in their clinical trial, and Blondonnet et al. in their national survey [12–14]. Inhaled sedation must utilize anesthesia reflection devices (ACD-s), such as the Sedaconda Anesthetic Conserving device (Sedaconda-ACD. Sedana Medical, Danderyd, Sweden) and the MIRUS system (Pall Medical, Dreieich, Germany). An Illustration of ICU setup for inhalation sedation presented in Figure 1. These devices significantly increase the dead space and require tidal volumes greater than 350 mL and increasing the respiratory rate of the ventilators to avoid hypercapnia, together with the monitoring of any potential auto-positive end expiratory pressure (PEEP) [15–17]. This led to the development of smaller reflection devices, with only 50 mL dead space (ACD-S), in 2017. These ACD-s were not associated with hypercapnia with the tidal volumes > 200 mL [18]. Table 2 presents two randomized controlled trials and one prospective study demonstrating the ability of analgesic drugs' sparing effects of the inhaled sedation [8,19,20]. Table 3 summarizes the controlled trials that support the role of volatile agents in preserving systemic hemodynamics compared to intravenous propofol [7,21,22]. Fifteen studies also addressed the organ-protective properties of these volatile anesthetic agents. Other studies addressed different topics and will be discussed in sequence.

Table 1. Published studies in chronological on sedating COVID-19 mechanically ventilated patients with volatile anesthetic agents.

Study	Study Type and Population	Sedative Agents	Conclusion
Flinspach A et al. [12] (2020)	Retrospective analysis of five COVID-19 patients admitted to the ICU and requiring mechanical ventilation	Isoflurane	Feasibility of inhaled sedation in ICU and patients undergoing ECMO. Adequate sedation to facilitate ventilator synchrony, prone positioning
Kermad et al. [13] (2021)	Retrospective study included 20 patients with COVID-19 ARDS admitted to the ICU	Isoflurane as inhalational and propofol as intravenous sedative	Isoflurane provides sufficiently deep sedation with less polypharmacy, less NMBA use and lower opioid doses.
Nieuwenhuijs-Moeke et al. [14] (2020)	Editorial	Sevoflurane	Feasibility of volatiles anesthetics and their potential beneficial effects of volatile anesthetics on systemic inflammation, sepsis, and ARDS in mechanically ventilated COVID-19 patients
Suleiman A et al. [15] (2021)	Review of literature	Isoflurane, Sevoflurane and Desflurane	Short-term sedation with volatile anesthetics may be beneficial in severe stages of COVID-19 ARDS. They have proven benefits at the molecular, cellular, and tissue levels.
Kaura and Hopkins [16] (2020)	Editorial	Sevoflurane	Theoretical risk of MH among COVID-19 and educating ICU staff to manage MH
Bellgardt et al. [17] (2021)	Review of Critically ill COVID-19 patients undergoing ECMO	Isoflurane	Benefit of spontaneous breathing and deep sedation in prone position.

ARDS: acute respiratory distress syndrome, COVID-19: coronavirus disease, ECMO: Extracorporeal membrane oxygenation, ICU: intensive care unit, IV: intravenous, MH: malignant hyperthermia, NMBA: neuromuscular blocker agents.

Table 2. Published trials in a chronological order demonstrating the analgesic drugs sparing effect of inhaled sedation compared to intravenous sedation.

Study	Study Type and Population	Inhaled Sedation Group (Drug, *n*)	Intravenous Sedation Group (Drug, *n*)	Mean Sedation Duration	Target Sedation Level	Outcomes
Jung S. et al. [8] (2020)	Prospective study of Patients scheduled for elective head and neck surgery with tracheostomy (post-operative ICU sedation)	Sevoflurane (n = 25)	Propofol (n = 24)	Inhaled: 771.0 ± 388.4 min Propofol: 1508.2 ± 2074.7 min	RASS −2 to −3 CPOT < 3	Post-operative opioid consumption. Monitored the proper initial end-tidal concentration of Sevoflurane in patients underwent head and neck surgery with tracheostomy
Mesnil et al. [19] (2011)	Randomized controlled trial included ICU patients who need more than 24 h of sedation	Sevoflurane (n = 19)	Propofol (n = 14) Midazolam (n = 14)	Inhaled: 50 h Propofol: 57 h Midazolam: 50 h	RSS 3–4	Awakening and extubation time, RSS monitored, post extubation opioid consumption, post extubation hallucination, renal and hepatic function.
Meiser A et al. [21] (2005)	Randomized, controlled of Adult ICU patients who are expected to need at least 24 h of sedation	Isoflurane (n = 146)	Propofol (n = 146)	Inhaled: 48 h Propofol: 48 h	RASS −1 to −4	RASS, adverse events monitored, opioid consumption, ventilation setting and awakening and extubation times monitored

ICU: intensive care units, RSS: The Ramsay Sedation Scale, RASS: Richmond Agitation Sedation Scale.

Table 3. Published randomized controlled trials in a chronological order demonstrating the inhaled sedation preserving effect on the hemodynamics as compared to intravenous propofol sedation.

Study	Study Type and Population	Inhaled Sedation Group (Drug, *n*)	Intravenous Sedation Group (Drug, *n*)	Observation Duration	Target Sedation Level	Included Outcomes
Yassen K et al. [7] (2016)	Prospective randomized hospital based comparative study of Liver transplant adult patients planned for weaning of mechanical ventilation	Desflurane (n = 30)	Propanol (n = 30)	Inhaled:6 h Propofol:8 h	PSI 50–75/h	HR, MAP, CO, SVR, Fetch, consumption of vasoactive drugs, Fentanyl requirements, estuation time, psychometric tests, and total cost.
Migliari, M. [22] (2009)	Randomized controlled trail of hemodynamically stable adult ICU patients requiring sedation for Mechanical Ventilation	Sevoflurane (n = 17)	Propofol and Remifentanil (n = 17)	Inhaled Phase: 2 h Propofol and Remifentanil Phase: 2 h	Ramsay score ≥ 4 and a RASS ≤ -3	Vt, RR, MV, Fio2, Et CO2, HR, IBP, CVP, SpO2, and internal body temperature, C rs, R aw, PEEPi, time to action /awake and Ambient contamination from sevoflurane.
Miser A et al. [23] (2021)	Randomized, controlled trail of Adult ICU patients who are expected to need at least 24 h of sedation	Isoflurane (n = 146)	Propanol (n = 146)	Inhaled: 48 h Propanol: 48 h	RASS −1 to −4	RASS, adverse (hemodynamic), events, opioid consumption, ventilation setting and awakening and estuation time.
Souk up et al. [24] (2023)	Prospective, randomized-controlled phase-Ibis monocentric clinical-trial	Sevoflurane (n = 39)	Propofol (n = 40)	Inhaled >48 h Propofol: 48 h	RASS −1 to −4	RASS, hemodynamics, opioid consumption, ventilation, extubation time, Length of hospital stay

ICU: intensive care unit, RASS: Richmond agitation sedation scale, VT: Tidal Volume, RR: Respiratory Rate, MV: Minute Ventilation, FiO2: inspiratory oxygen fraction, Et CO2: End Tidal Co2, HR: Heart Rate, IBP: invasive arterial blood pressure, CVP: central venous pressure, SpO2: peripheral oxygen saturation, C rs: respiratory system compliance, R aw: airway resistance, PEEPi: intrinsic PEEP, PSI: Patient Sate Index, MAP: Mean Arterial Pressure. CO: Cardiac Output. SVR: systemic vascular resistance. FTc: corrected flow time.

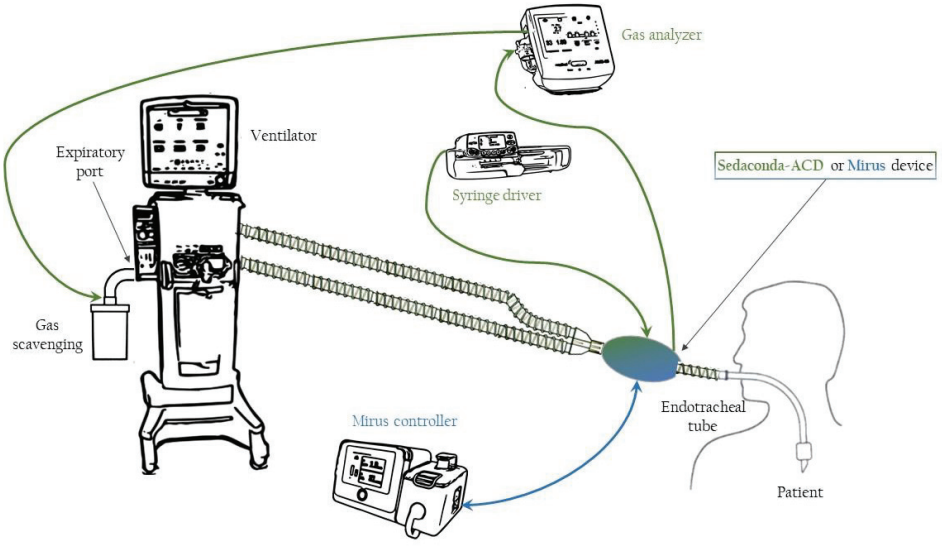

Figure 1. An Illustration of ICU setup for inhalation sedation. Reproduced with permission from Jabaudon M, et al. Anaesth Crit Care Pain Med. 2022. [25].

4. Discussion

Inhaled sedation is an effective and safe alternative to intravenous sedation in ICUs, as reported by Bisbal et al. in their prospective observational study (2011) [26]. However, further discussion is needed to guide towards the best clinical practice and the selection of appropriate patients for inhaled sedation.

4.1. Sedating COVID-19 Patients

The shortage in the supply of intravenous sedatives during the COVID-19 pandemic led to the need for an alternative method of sedation. The use of inhalational agents was explored by several intensivists. In a case series and a systematic analysis by Flinspach A et al. in 2020, they noted that sedation by volatile anesthetic agents leads to deep sedation in critically ill COVID-19 patients [12]. This facilitated the mechanical ventilation during the prone position and improved the degree of synchronization with ICU ventilators. Deep sedation reduced the aerosol generation associated with coughing and decreased the inadvertent extubation. Kermad and his colleagues, in their retrospective chart review (2021), reported that the COVID-19 patients were adequately sedated with isoflurane and, hence, consumed less neuromuscular blocking agents and opioids compared to those sedated with propofol. However, in the severe forms of COVID-19, higher sedative doses of both isoflurane and propofol were required [13].

In 2020, the Nieuwenhuijs-Moeke et al. editorial presented other beneficial effects of inhaled sedation among mechanically ventilated COVID-19 patients suffering from inflammation and sepsis [14]. A recent literature review by Suleiman A et al. (2021) suggested that short-term sedation with volatile anesthetics could be beneficial with severe COVID-19 ARDS based on the molecular, cellular and tissue evidence [15].

One important concern was raised by Kaura and Hopkins about the possibility to induce malignant hyperthermia (MH) among COVID-19 or non-COVID-19 patients, if applied in a wider scale. They emphasized the need to take this into consideration and recommended the need to educate ICU staff about the methods of the diagnosis and management of MH [16].

On the other hand, a review by Bellgardt and his colleagues (2021) focused on the technical details of administrating volatile anesthetic agents to COVID-19 patients on extracorporeal membrane oxygenation (ECMO) [17].

4.2. Analgesic Drugs Sparing Effect

Critically ill patients in need of mechanical ventilation are particularly challenging because they require polypharmacy. Inhaled sedation can lower the requirement of analgesic drugs, as reported by Meiser A et al. in their RCT (2005) [21] and in a review (2012) by Misra et al. [27]. Both reported a notable reduction in the consumption of opioids with sevoflurane and isoflurane sedation when compared to intravenous propofol. The RCT of Mesnil et al. (2011) also observed a reduction in post-extubation morphine consumption among critical ill patients sedated with sevoflurane vs. propofol or midazolam [19]. Mo et al., in their systematic review (2019), provided evidence that inhalational sedation was not inferior to other standard intravenous sedatives regarding pain relief [28].

Lower remifentanil consumption with sevoflurane sedation was also reported in comparison to propofol by Jung, S. et al. in their prospective study (2020) [8]. These findings can be explained by the ability of inhaled sedatives to block the N-methyl-D-aspartate receptors (antagonist activity). However, in a recently published prospective, randomized-controlled phase-IIb monocentric clinical-trial by Soukup et al. (2023), sevoflurane sedation (>48 h) compared to propofol had a lower opioid requirement of remifentanil (400 μg/h vs. 500 μg/h, $p = 0.007$) and of sufentanil 40 μg/h vs. 30 μg/h, $p = 0.007$) [28]. More RCTs are still required (Table 2).

4.3. Preserved Systemic Hemodynamics

Migliari et al. reported a significant increase in heart rate with sevoflurane vs. propofol, despite comparable arterial and central venous pressures [22]. A recently published randomized, controlled trial (RCT) in 2021, by Meiser et al., demonstrated how Isoflurane sedation was not inferior to propofol and with no significant differences in hemodynamics [23]. Desflurane is rarely used as an inhalation sedative. In a prospective randomized hospital based comparative study (2016) by Yassen et al., they investigated the postoperative sedation with desflurane vs. propofol among mechanically ventilated liver transplant recipients and reported the beneficial effects on systemic vascular resistance and mean arterial blood pressure with Desflurane sedation [7].

Recently, Soukup et al. (2023) compared sevoflurane sedation to propofol and found that the hemodynamics were not different [28] (Table 3).

4.4. Organ-Protective Properties

A reduction in the need for inotropic support following coronary bypass graft surgery with sevoflurane vs. propofol was mentioned in Soukup et al.'s review in 2009, Steurer et al. (RCT) in 2012 and Soro et al. (RCT) in 2012 [29–31]. A significant reduction in troponin T concentrations were also reported by Steurer et al. [29]. A review conducted by Orriach et al. (2013) reported that sevoflurane postoperative sedation reduced oxygen consumption and lowered the troponin I concentrations in the blood levels [32]. However, the RCTs by Flier et al. in 2010 [33] and Wasowicz M et al. in 2018 [34] only detected limited evidence of cardiac protection. Soukup et al. [29], Steurer et al. [30] and others did observe these organ protective effects in other organs, such as the brain, lung, liver and bowels in their studies published between 2003 and 2014 [35–40]. In reviews by Jerath et al. and O'Gara et al. in 2016 and an RCT by Jabaudon et al. in 2017, attributed these organ protective properties to the anti-inflammatory effects of the volatile anesthetic agents and the reduced production of pro-inflammatory markers and cytokines [41–43].

4.5. Potential Effects on Respiratory Functions

Volatile anesthetics can benefit injured alveoli and improve arterial oxygenation with their anti-inflammatory properties, as demonstrated by several researchers, particularly in patients with acute respiratory distress syndrome (ARDS). Steurer, M. et al., in their randomized controlled trial (2012), reported an improvement in the oxygenation index with sevoflurane sedation following cardiac surgery compared with propofol [30]. In a prospective cross-over study (2009) by Migliari et al., an increase in arterial carbon dioxide tension ($PaCO_2$) was noted, which was only resolved by increasing the tidal volumes [22].

Meiser et al. [21] and Krannich et al. [44] both confirmed these beneficial respiratory effects of the volatile anesthetics, but also recommended monitoring the $PaCO_2$ levels frequently. Jabaudon et al., in their RCT among patients with ARDS, also observed that sevoflurane improved oxygenation and decreased epithelial injury when compared with midazolam sedation.

Furthermore, Ruszkai et al., in their case report (2014), reported the successful management of a patient suffering from an acute attack of bronchial asthma with inhaled sedation [45]. Blondonnet et al. designed a RCT and named it the SESAR trial (Sevoflurane for Sedation in ARDS), which is currently investigating the efficacy of sevoflurane compared to propofol, but the results are not yet available [46].

Finally, the effect of inhalation agents on the hypoxic pulmonary vasoconstriction (HPV) response has been discussed by several reviewers. HPV physiological redirects the blood flow from the non-ventilated hypoxic areas of the lung to other ventilated lung alveoli, this helps to limit intrapulmonary shunting and optimize the ventilation/perfusion (V/Q) ratio, which then minimizes the fall in arterial oxygen pressure (PaO_2). Volatile anesthetics, in a dose-dependent manner, can attenuate the HPV response far more than intravenous sedatives. However, the administration of volatile anesthetics, between 0.5 to

1.5 MAC, demonstrated only a mild effect because of their compensatory bronchodilator and anti-inflammatory effects [47–49].

4.6. Renal Function under Inhaled Sedation

In a double-blinded, placebo-controlled, multicenter study (2003), Julier K et al. demonstrated the sevoflurane renal protective effect among cardiac patients following cardiac bypass surgery [35]. Röhm et al. also noted, in a prospective, randomized, single-blinded study (2009), that the renal integrity remained unchanged, despite the increase in the inorganic fluoride blood levels [50]. Sedation with volatile anesthetics is characterized by rapid pulmonary elimination which makes it suitable for patients with hepatic or renal failure [51]. In a prospective controlled study (2014) by Perbet et al., they reported that, despite the increase in the plasma fluoride levels during the 48-h inhaled sedation period, they observed no signs of nephrotoxicity [52]. Mesnil et al., Meiser et al. and Jabaudon et al., and all reported no adverse effects with sevoflurane sedation [19,21,43]. In contrast, intravenous anesthetic/sedative agents depend on end-organ elimination, and this leads to unpredictable pharmacokinetics, pharmacodynamics, and adverse outcomes. This can range between delirium and life-threatening propofol infusion syndrome.

However, inhaled sedation is not without precautions; Muyldermans et al. described a case in 2016 of partial nephrogenic diabetes insipidus that developed in a burned patient following prolonged sedation with low expired fractions of sevoflurane [53]. They advised that anesthesiologists and intensivists should always be aware of this rare incidence that can develop with sevoflurane, whether used for general anesthesia or for inhaled sedation, particularly following prolonged surgery or sedation. L'Heudé et al. also described similar findings in their retrospective study (2019). They encountered the rare development of nephrogenic diabetes insipidus (NDI) with the prolonged exposure to high-doses of sevoflurane. They recommended that these clinical findings need to be better investigated via future prospective studies [54]. Jerath A et al. demonstrated, in a pilot randomized controlled trial (2020), that isoflurane sedation increases the levels of serum fluoride concentrations in the blood, but without any significant reduction in the renal functions [55].

4.7. Enhancing Recovery and Cognitive Functions

In a small randomized controlled trial, Mesnil et al. demonstrated that long-term sedation with inhaled sevoflurane, compared to propofol, did reduce the wake-up time, extubation time and post-extubation morphine consumption [19]. Their results are in accordance with the studies by Meiser et al., Soukup et al., and Sackey et al. [19,29,56] and supported by Jerath et al. and Landoni et al.'s systematic reviews and meta-analysis [10,57]. However, no significant differences could be detected in terms of the hospital/ICU durations of stay. Hellström et al., in another randomized controlled clinical trial in 2012, confirmed that a significant reduction in the wake-up time post-cardiac surgery was observed with sevoflurane sedation vs. propofol [58]. Foudraine et al. added, in an observational propensity score-matched study (2021), that the delirium incidence was reduced among post-cardiac arrest patients when sevoflurane sedation was combined with targeted temperature management [59]. In another study, by Hanafy et al., that included 24 post-cardiac surgical patients, they found that the time to be extubated with isoflurane sedation was significantly shorter compared to midazolam sedation [60].

4.8. Air Pollution Risk

Strategies to minimize the individual exposure to air pollution with inhaled sedatives vary between countries. Exposure to low concentrations of volatile anesthetic agents, as measured by passive dosimeter scan, can only be achieved through improvements in hospital ventilation, scavenging systems and reducing exposure time to less than 8 h. Many countries do not have a time limit for exposure. Herzog-Misery et al. (2018) reviewed the effects on occupational health and presented strategies to minimize exposure and

pollution [61]. Sackey et al. reported, in a prospective observational study (2005), that isoflurane levels in the air were less than the recommended international exposure limits when AnaConDa was in use [62]. Both Herzog-Niescery J et al. and Sackey et al., in their observational studies, recommended that an effective air conditioner, with at least 6–8 air changes per hour, is essential if room pollution is to be minimized. Migliari et al. and Accorsi et al. stated that sevoflurane concentrations in the air should not exceed the limit defined by the National Institute for Occupational Safety and Health in USA (2 ppm). Few studies looked into and identified the medical side effects that can develop from the prolonged exposure to the inhaled anesthetic agents [22,63].

The air-pollution and global warming risks from volatile anesthetics are well known. The fact that inhaled anesthetics are greenhouse gases and/or ozone-depleting agents emphasizes their contribution towards global warming.

Inhalation anesthesia agents undergo minimal metabolism and are eliminated, unchanged, as waste gas with each exhalation. This leads to the pollution of the environment and lasts for years. The air global warming effects of these gases have variable atmospheric lifetimes depending on their carbon dioxide content. Varughese and Ahmed, in their narrative review (2021), discussed the measures necessary to minimize the impact on the environment by these volatile anesthetic agents [64]. They advised using well-maintained ventilation and scavenging systems, coupled with the monitoring of the environmental air concentrations, for these anesthesia agents.

The process of the handling and preparation of inhalation devices are considered sources for volatile agent leakage, as reported by Alexander et al. in 2017. It is crucial to consider the long-term and cumulative effects of the volatile agents in order to pursue strategies to mitigate the associated risks to the environment.

Environmental pollution and the effect on the ozone layer by specific volatile anesthetics have a prolonged, lifetime effect. Specific volatile agents, such as Desflurane and N_2O, need to be reduced. The carbon dioxide equivalent of Desflurane is higher than that of sevoflurane and isoflurane, which makes Desflurane not environment friendly [65,66].

The judicious use of the volatile anesthetics should only be indicated to selected groups of ICU patients, where the benefits outweigh the risks.

The use of activated charcoal filters in the expiratory limb of the ventilator cycle will help to reduce the degree of air pollution in the surroundings, but this method has its own limitation and cost. ICU ventilators still require high oxygen and air mixture flows, which mandates an increase in the volatile agent inspired percentage in order to stabilize the inhaled concentration.

Another important recommendation to reduce leaks and environment pollution is the adoption of a routine maintenance program that checks all of the equipment involved in the process of inhaled sedation, this includes the scavenging system. Training and educating both the operating rooms and ICU staff is also necessary. Herzog-Niescery J et al. recommended that extra care is required with MIRUS, particularly during the process of refilling, to reduce leaks and, hence, air pollution [67].

4.9. Is Sedation Depth Monitoring Essential?

Sedation depth varies one from patient to another. Individual variations can affect the systemic hemodynamic, weaning and recovery. Orriach et al. (2013) and Jabaudon et al. (2017) monitored sedation with the bispectral index (BIS) [32,43]. Romagnoli et al. adopted the Richmond Agitation Sedation Scale (RASS), and they reported that the minimum alveolar concentration (MAC) of the inhaled agents correlates negatively with the RASS values [68]. Nitzschke et al. demonstrated, in their prospective, controlled, sequential two-arm clinical study (2014), that BIS-guided sedation significantly reduced the sevoflurane plasma concentration and rescue doses of noradrenaline during on-pump cardiac surgery [69]. In a RCT (2015) by Sayed et al., the monitoring sedation depth among liver transplant recipients, post-operatively, with the patient state index (PSI) helped to preserve the systemic hemodynamics and enhanced recovery. The total consumed doses of sedatives

guided by PSI were less than those guided by RASS [70]. In a prospective interventional study (2020), Blanchard et al. demonstrated that the minimum alveolar concentration of inhaled anesthetic agents (MAC) can be used as a sedative depth monitor. The increase in MAC was in correlation with the decrease in the RASS values ($r = -0.83$, $p < 0.001$). Monitoring the sedation depth preserves the spontaneous breathing activity and reduces the need for muscle relaxants [71].

Applying the consensual/international recommendations on sedation is necessary, and prioritizing the use of a score for sedation as a regular assessment tool is recommended to reduce delirium and prevent ventilator patient dys-synchrony [72]. The authors of this current review believe in the multi-modal monitoring approach and the respect of individual variations.

4.10. Which Inhalation Agent(s) Should Be Used?

Isoflurane was reported by several experienced research groups as their preferred inhalation agent. Isoflurane is cheaper and more potent than sevoflurane. The potency of Isoflurane allows the consumption of lower drug volumes, reduces the cost, and is currently approved for the sedation of ICU patients in Europe [23]. Inhalation anesthetics are metabolized at varying degrees. Sevoflurane, Isoflurane and Desflurane are metabolized by the liver, at rates of 2–5%, 0.2% and 0.02%, respectively. Sevoflurane has been associated with some cases of reversible polyuria when used at high doses and for prolonged durations. Desflurane requires pressurized vaporizers. The MIRUS device can provide inhalation sedation with isoflurane, sevoflurane and desflurane. However, Sedaconda can only be used with Isoflurane and Sevoflurane [23,56].

4.11. Which Patients Could Be the Best Candidates for Inhaled Sedation?

Patients receiving intravenous sedatives for prolonged durations may benefit from an alternative sedative technique, such as inhaled sedation, which is characterized by a very low metabolism. This approach would allow time for the accumulated intravenous sedatives and opioids to be metabolized and cleared. Critically ill patients under mechanical ventilation can benefit from inhaled sedation to facilitate weaning, as it reduces the requirement of opioids and neuromuscular drugs. Elderly patients may also benefit from volatile anesthetics as they can preserve the cognitive functions and reduce the incidence of delirium compared to other intravenous sedatives. Post-cardiac arrest patients are considered good candidates. Foudraine et al. reported decreased delirium and reduced hospital stay when sevoflurane sedation was combined with a targeted temperature management in post-cardiac arrest patients [59]. In a retrospective study from Hellstrom et al. that included 12 post-cardiac arrest patients, isoflurane sedation allowed for early neurologic assessment [73]. Krannich et al. (2017) also suggest that inhaled sedation could specifically benefit cardiac arrest survivors [44].

Patients who require deep sedation to facilitate ventilator synchronization in prone positioning, such as critically ill COVID-19 patients, are good candidates for inhaled sedation [12,17,74]. However, Becher T et al. conducted a multicenter randomized controlled trial (2022) and observed less pronounced improvements in the oxygenation index and V/Q mismatching in patients with (ARDS) and acute hypoxemic respiratory failure (AHRF) in the isoflurane group compared to IV sedation with propofol. The authors attributed this difference in the results from the previous studies to the fact that Isoflurane has fewer organ-protective properties than Sevoflurane [75].

4.12. Prolonged Inhalation Sedation Pros and Cons?

Critically ill patients who are expected to be sedated for a prolonged duration on mechanical ventilators will require daily wake up trials in order to reduce the duration of ventilation and enhance the return of spontaneous breathing. In their clinical trial (2004), Sackey et al. found that prolonged isoflurane sedation >12 h was safe and possessed a low risk of drug accumulation compared to other intravenous sedatives [76]. Inhaled

anesthetics had also been recommended by Redaelli et al. in 2013 for the sedation of ventilator-dependent ICU patients and for those with drug abuse or with severe ARDS in need for long periods of sedation and paralysis [77]. Gallego et al., in a comparative study (2014), looked into the renal and hepatic integrity following long-term sevoflurane sedation among animals. They came to the conclusion that neither sevoflurane nor propofol had any negative effects on the renal or hepatic functions following prolonged exposure [78].

Prolonged sedation (>24 h) with inhaled sevoflurane was reported by Mesnil et al., in their (RCT) (2011), as an effective alternative for propofol or midazolam. They also noted an enhanced recovery and reduced analgesics consumption with sevoflurane [19].

In another recently published RCT (2023), by Soukup and his colleagues, the sedated ICU patients in their trial with sevoflurane (>48 h) required less opioids and less time to breath spontaneously when compared to the propofol-based sedation regime. Based on this RCT, sevoflurane could be considered safe for long-term sedation and non-inferior to propofol [28].

The risk–benefit analysis is always important prior to initiating an alternative method for sedation. The refractory status epilepticus and status asthmaticus are two examples of short and early clinical indications for inhaled sedation, where the benefits outweigh the risks. However, this should not be the case with elderly, critically ill patients or patients with brain trauma who are highly susceptible to neurotoxicity. The theoretical concern of compound A and fluoride nephrotoxicity was investigated and could be linked to prolonged sevoflurane sedation. Inhalation sedation as an alternative method, if practiced in a judicious way, should be associated with reduced cognitive dysfunction (POCD). More research in this field is still required [79,80].

4.13. Practical Aspects and Clinical Application

The lack of familiarity in practicing inhaled sedation is a major obstacle that needs to be addressed. Training and awareness about the benefits of inhaled sedation as an alternative to intravenous sedation among intensivists represents the main challenge, particularly in countries where the intensive care training track is separated from the anesthesia training track. Furthermore, sufficient studies of a RCT nature are required to compare inhalation sedation to intravenous sedation. Other obstacles facing the application logistics of volatile anesthesia need to be addressed inside each hospital.

4.14. What Are the Other Obstacles and Precautions with Inhaled Sedation Practice?

ICU vaporizer SedaConda-ACD is cheaper than the MIRUS, but requires additional monitors for the inhaled and expired anesthetic agent's concentrations. This is usually not available in ordinary ICU settings and varies between countries.

ARDs patients with severe pulmonary disease require high minute volumes, which could be a challenge during inhalation sedation. Increasing the tidal volumes may take care of the dead space effects of volatile agent devices; however, in ARDS, such as patients who suffer from high dead spaces as a result of a very high VQ mismatch, this might be difficult. In this situation, volatiles should be delivered at high minute ventilation (15–25 L/min) by an anesthesia machine or by an ICU ventilator that is coupled with a miniature vaporizer. The increase in the minute ventilation requires that the volatile anesthetics infusion rate needs to be increased hand to hand in order to keep the volatile agents' end tidal concentrations constant [81–83].

Finally, the availability and cost of ACD in many countries around the world, particularly in developing countries, remains a challenge that needs to be addressed by the manufactures.

5. Conclusions

There is growing evidence from the published literature in support of volatile anesthetic agents as sedatives for mechanically ventilated ICU patients, but in specific clinical situations. The refractory status epilepticus, status asthmaticus and patients with hepatic

or renal impairment are among those specific indications, as the benefits outweigh the risks. Several studies have demonstrated their cardio-protective, anti-inflammatory and bronchodilator properties, alongside their minimal metabolism. Inhaled sedation reduces the time of mechanical ventilation and lowers opioid consumption, as well as enhancing recovery and weaning from ventilators. Providing intermittent periods of inhaled sedation as an alternative to a prolonged intravenous sedative regime will provide time for the body to metabolize and excrete the accumulated intravenous sedatives and their active metabolites.

Indications for inhaled sedation should be set upon by each ICU team, according to the patient's needs and the training of the staff. More clinical RCTs to compare inhalation sedation to intravenous sedation are needed. Developing strict measures to reduce the effect of volatile anesthetics on the environment is essential to avoid any harm.

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References

1. Charbonneau, H.; Mrozek, S.; Pradere, B.; Cornu, J.-N.; Misrai, V. How to resume elective surgery in light of COVID-19 post-pandemic propofol shortage: The common concern of anaesthesists and surgeons. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 593–594. [CrossRef]
2. Pourrat, X.; Huon, J.F.; Laffon, M.; Allenet, B.; Roux-Marson, C. Implementing clinical pharmacy services in France: One of the key points to minimise the effect of the shortage of pharmaceutical products in anaesthesia or intensive care units? *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 367–368. [CrossRef]
3. FDA Drug Shortages. Book FDA Drug Shortages. 2020. Available online: https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm (accessed on 21 February 2020).
4. Government of Canada. Exceptional Importation and Sale of Drugs in Relation to COVID-19: Tier 3 Drug Shortages. 2020. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/covid19-interim-order-drugs-medical-devices-special-foods/information-provisions-related-drugs-biocides/tier-3-shortages.html (accessed on 1 May 2020).
5. Zhang, Z.; Chen, K.; Ni, H.; Zhang, X.; Fan, H. Sedation of mechanically ventilated adults in intensive care unit: A network meta-analysis. *Sci. Rep.* **2017**, *7*, 44979. [CrossRef]
6. Hughes, C.G.; McGrane, S.; Pandharipande, P.P. Sedation in the intensive care setting. *Clin. Pharmacol.* **2012**, *4*, 53–63.

7. Yassen, K.A.; Awaad, E.K.E.-D.; Refaat, E.K.; Soliman, N.M.; Yehia, M.F. Inhaled Desflurane vs. Propofol for Postoperative Sedation Guided with Patient State Index of SEDline in Mechanically Ventilated Liver Transplant Recipient. *J. Anesth. Clin. Res.* **2016**, *7*, 623.
8. Jung, S.; Na, S.; Bin Kim, H.; Joo, H.J.; Kim, J. Inhalation sedation for postoperative patients in the intensive care unit: Initial sevoflurane concentration and comparison of opioid use with propofol sedation. *Acute Crit. Care* **2020**, *35*, 197–204. [CrossRef]
9. Kim, H.Y.; Lee, J.E.; Kim, H.Y.; Kim, J. Volatile sedation in the intensive care unit: A systematic review and meta-analysis. *Medicine* **2017**, *96*, e8976. [CrossRef]
10. Jerath, A.; Panckhurst, J.; Parotto, M.; Lightfoot, N.; Wasowicz, M.; Ferguson, N.D.; Steel, A.; Beattie, W.S. Safety and Efficacy of Volatile Anesthetic Agents Compared with Standard Intravenous Midazolam/Propofol Sedation in Ventilated Critical Care Patients: A Meta-analysis and Systematic Review of Prospective Trials. *Anesth. Analg.* **2017**, *124*, 1190–1199. [CrossRef]
11. Lönnqvist, P.A.; Bell, M.; Karlsson, T.; Wiklund, L.; Höglund, A.S.; Larsson, L. Does prolonged propofol sedation of mechanically ventilated COVID-19 patients contribute to critical illness myopathy? *Br. J. Anaesth.* **2020**, *125*, e334–e336. [CrossRef]
12. Flinspach, A.N.; Zacharowski, K.M.; Ioanna, D.; Adam, E.H. Volatile Isoflurane in Critically Ill Coronavirus Disease 2019 Patients-A Case Series and Systematic Review. *Crit. Care Explor.* **2020**, *2*, e0256. [CrossRef]
13. Kermad, A.; Speltz, J.; Danziger, G.; Mertke, T.; Bals, R.; Volk, T.; Lepper, P.M.; Meiser, A. Comparison of isoflurane and propofol sedation in critically ill COVID-19 patients-a retrospective chart review. *J. Anesth.* **2021**, *35*, 625–632. [CrossRef] [PubMed]
14. Nieuwenhuijs-Moeke, G.J.; Jainandunsing, J.S.; Struys, M.M.R.F. Sevoflurane, a sigh of relief in COVID-19? *Br. J. Anaesth.* **2020**, *125*, 118–121. [CrossRef] [PubMed]
15. Suleiman, A.; Qaswal, A.; Alnouti, M.; Yousef, M.; Suleiman, B.; Jarbeh, M.; Alshawabkeh, G.; Bsisu, I.; Santarisi, A.; Ababneh, M. Sedating Mechanically Ventilated COVID-19 Patients with Volatile Anesthetics: Insights on the Last-Minute Potential Weapons. *Sci. Pharm.* **2021**, *89*, 6. [CrossRef]
16. Kaura, V.; Hopkins, P.M. Sevoflurane may not be a complete sigh of relief in COVID-19. *Br. J. Anaesth.* **2020**, *125*, e487–e488. [CrossRef] [PubMed]
17. Bellgardt, M.; Özcelik, D.; Breuer-Kaiser, A.F.C.; Steinfort, C.; Breuer, T.G.K.; Weber, T.P.; Herzog-Niescery, J. Extracorporeal membrane oxygenation and inhaled sedation in coronavirus disease 2019-related acute respiratory distress syndrome. *World J. Crit. Care Med.* **2021**, *10*, 323–333. [CrossRef]
18. Ostermann, M.E.; Keenan, S.P.; Seiferling, R.A.; Sibbald, W.J. Sedation in the intensive care unit: A systematic review. *JAMA* **2000**, *283*, 1451–1459. [CrossRef]
19. Mesnil, M.; Capdevila, X.; Bringuier, S.; Trine, P.-O.; Falquet, Y.; Charbit, J.; Roustan, J.-P.; Chanques, G.; Jaber, S. Long-term sedation in intensive care unit: A randomized comparison between inhaled sevoflurane and intravenous propofol or midazolam. *Intensive Care Med.* **2011**, *37*, 933–941. [CrossRef]
20. Blondonnet, R.; Quinson, A.; Lambert, C.; Futier, E.; Bazin, J.-E.; Pereira, B.; Bastarache, J.; Ware, L.; Constantin, J.-M.; Jabaudon, M. Use of volatile agents for sedation in the intensive care unit: A national survey in France. *PLoS ONE* **2021**, *16*, e0249889. [CrossRef]
21. Meiser, A.; Laubenthal, H. Inhalational anaesthetics in the ICU: Theory and practice of inhalational sedation in the ICU, economics, risk-benefit. *Best Pract. Res. Clin. Anaesthesiol.* **2005**, *19*, 523–538. [CrossRef]
22. Migliari, M.; Bellani, G.; Rona, R.; Isgrò, S.; Vergnano, B.; Mauri, T.; Patroniti, N.; Pesenti, A.; Foti, G. Short-term evaluation of sedation with sevoflurane administered by the anesthetic conserving device in critically ill patients. *Intensive Care Med.* **2009**, *35*, 1240–1246. [CrossRef]
23. Meiser, A.; Volk, T.; Wallenborn, J.; Guenther, U.; Becher, T.; Bracht, H.; Schwarzkopf, K.; Knafelj, R.; Faltlhauser, A.; Thal, S.C.; et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation of invasively ventilated patients in intensive care units in Germany and Slovenia: An open-label, phase 3, randomised controlled, non-inferiority trial. *Lancet Respir. Med.* **2021**, *9*, 1231–1240. [CrossRef] [PubMed]
24. Soukup, J.; Michel, P.; Christel, A.; Schittek, G.A.; Wagner, N.-M.; Kellner, P. Prolonged sedation with sevoflurane in comparison to intravenous sedation in critically ill patients—A randomized controlled trial. *J. Crit. Care* **2023**, *74*, 154251. [CrossRef]
25. Jabaudon, M.; Zhai, R.; Blondonnet, R.; Bonda, W.L.M. Inhaled sedation in the intensive care unit. *Anaesth. Crit. Care Pain Med.* **2022**, *41*, 101133.
26. Bisbal, M.; Arnal, J.M.; Passelac, A.; Sallée, A.; Demory, D.; Donati, S.-Y.; Granier, I.; Corno, G.; Durand-Gasselin, J. Efficacité, tolérance et coût d'une sédation par sévoflurane en réanimation [Efficacy, safety and cost of sedation with sevoflurane in intensive care unit]. *Ann. Fr. Anesth. Reanim.* **2011**, *30*, 335–341. [CrossRef] [PubMed]
27. Misra, S.; Koshy, T. A review of the practice of sedation with inhalational anaesthetics in the intensive care unit with the AnaConDa device. *Indian J. Anaesth.* **2012**, *56*, 518. [CrossRef] [PubMed]
28. Mo, J. Inhalation Sedation: A Systematic Review and Meta-Analysis. *J. Acute Care Surg.* **2019**, *9*, 45–53. [CrossRef]
29. Soukup, J.; Schärff, K.; Kubosch, K.; Pohl, C.; Bomplitz, M.; Kompardt, J. State of the art: Sedation concepts with volatile anesthetics in critically Ill patients. *J. Crit. Care* **2009**, *24*, 535–544. [CrossRef]
30. Steurer, M.P.; Steurer, M.A.; Baulig, W.; Piegeler, T.; Schläpfer, M.; Spahn, D.R.; Falk, V.; Dreessen, P.; Theusinger, O.M.; Schmid, E.R.; et al. Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. *Crit. Care* **2012**, *16*, R191. [CrossRef]

31. Soro, M.; Gallego, L.; Silva, V.; Ballester, M.T.; Lloréns, J.; Alvariño, A.; García-Perez, M.L.; Pastor, E.; Aguilar, G.; Martí, F.J.; et al. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: A double-blind randomised study. *Eur. J. Anaesthesiol.* **2012**, *29*, 561–569. [CrossRef]
32. Orriach, J.L.G.; Aliaga, M.R.; Ortega, M.G.; Navarro, M.R.; Arce, I.N.; Manas, J.C. Sevoflurane in intraoperative and postoperative cardiac surgery patients. Our experience in intensive care unit with sevoflurane sedation. *Curr. Pharm. Des.* **2013**, *19*, 3996–4002. [CrossRef]
33. Flier, S.; Post, J.; Concepcion, A.; Kappen, T.; Kalkman, C.; Buhre, W. Influence of propofol-opioid vs isoflurane-opioid anaesthesia on postoperative troponin release in patients undergoing coronary artery bypass grafting. *Br. J. Anaesth.* **2010**, *105*, 122–130. [CrossRef]
34. Wąsowicz, M.; Jerath, A.; Luksun, W.; Sharma, V.; Mitsakakis, N.; Meineri, M.; Katznelson, R.; Yau, T.; Rao, V.; Beattie, W.S. Comparison of propofol-based versus volatile-based anaesthesia and postoperative sedation in cardiac surgical patients: A prospective, randomized, study. *Anaesthesiol. Intensive Ther.* **2018**, *50*, 200–209. [CrossRef]
35. Julier, K.; da Silva, R.F.; Garcia, C.; Bestmann, L.; Frascarolo, P.; Zollinger, A.; Chassot, P.-G.; Schmid, E.R.; Turina, M.I.; Von Segesser, L.K.; et al. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. *Anesthesiology* **2003**, *98*, 1315–1327. [CrossRef]
36. Kitano, H.; Kirsch, J.R.; Hurn, P.D.; Murphy, S.J. Inhalational anesthetics as neuroprotectants or chemical preconditioning agents in ischemic brain. *J. Cereb. Blood Flow Metab.* **2007**, *27*, 1108–1128. [CrossRef]
37. Beck-Schimmer, B.; Breitenstein, S.; Urech, S.; De Conno, E.; Wittlinger, M.; Puhan, M.; Jochum, W.; Spahn, D.R.; Graf, R.; Clavien, P.-A. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann. Surg.* **2008**, *248*, 909–918. [CrossRef]
38. De Conno, E.; Steurer, M.P.; Wittlinger, M.; Zalunardo, M.P.; Weder, W.; Schneiter, D.; Schimmer, R.C.; Klaghofer, R.; Neff, T.A.; Schmid, E.R.; et al. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. *Anesthesiology* **2009**, *110*, 1316–1326. [CrossRef]
39. Wu, L.; Zhao, H.; Wang, T.; Pac-Soo, C.; Ma, D. Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection. *J. Anesth.* **2014**, *28*, 740–758. [CrossRef]
40. Kim, M.; Park, S.W.; Kim, M.; D'Agati, V.D.; Lee, H.T. Isoflurane post-conditioning protects against intestinal ischemia-reperfusion injury and multiorgan dysfunction via transforming growth factor-β1 generation. *Ann. Surg.* **2012**, *255*, 492–503. [CrossRef]
41. Jerath, A.; Parotto, M.; Wasowicz, M.; Ferguson, N.D. Volatile Anesthetics. Is a New Player Emerging in Critical Care Sedation? *Am. J. Respir. Crit. Care Med.* **2016**, *193*, 1202–1212. [CrossRef]
42. O'Gara, B.; Talmor, D. Lung protective properties of the volatile anesthetics. *Intensive Care Med.* **2016**, *42*, 1487–1489. [CrossRef]
43. Jabaudon, M.; Boucher, P.; Imhoff, E.; Chabanne, R.; Faure, J.-S.; Roszyk, L.; Thibault, S.; Blondonnet, R.; Clairefond, G.; Guérin, R.; et al. Sevoflurane for Sedation in Acute Respiratory Distress Syndrome. A Randomized Controlled Pilot Study. *Am. J. Respir. Crit. Care Med.* **2017**, *195*, 792–800. [CrossRef] [PubMed]
44. Krannich, A.; Leithner, C.; Engels, M.; Nee, J.; Petzinka, V.; Schröder, T.; Jörres, A.; Kruse, J.; Storm, C. Isoflurane Sedation on the ICU in Cardiac Arrest Patients Treated with Targeted Temperature Management: An Observational Propensity-Matched Study. *Crit. Care Med.* **2017**, *45*, e384–e390. [CrossRef]
45. Ruszkai, Z.; Bokrétás, G.P.; Bartha, P.T. Sevoflurane therapy for life-threatening acute severe asthma: A case report. *Can. J. Anaesth.* **2014**, *61*, 943–950. [CrossRef]
46. Blondonnet, R.; Simand, L.-A.; Vidal, P.; Borao, L.; Bourguignon, N.; Morand, D.; Bernard, L.; Roszyk, L.; Audard, J.; Godet, T.; et al. Design and Rationale of the Sevoflurane for Sedation in Acute Respiratory Distress Syndrome (SESAR) Randomized Controlled Trial. *J. Clin. Med.* **2022**, *11*, 2796. [CrossRef] [PubMed]
47. Sylvester, J.T.; Shimoda, L.A.; Aaronson, P.I.; Ward, J.P.T. Hypoxic pulmonary vasoconstriction. *Physiol. Rev.* **2012**, *92*, 367–520, Erratum in *Physiol. Rev.* **2014**, *94*, 989. [CrossRef] [PubMed]
48. Licker, M.; Hagerman, A.; Jeleff, A.; Schorer, R.; Ellenberger, C. The hypoxic pulmonary vasoconstriction: From physiology to clinical application in thoracic surgery. *Saudi J. Anaesth.* **2021**, *15*, 250–263. [CrossRef] [PubMed]
49. Pang, Q.-Y.; An, R.; Liu, H.-L. Effects of inhalation and intravenous anesthesia on intraoperative cardiopulmonary function and postoperative complications in patients undergoing thoracic surgery. *Minerva Anestesiol.* **2018**, *84*, 1287–1297. [CrossRef]
50. Röhm, K.D.; Mengistu, A.; Boldt, J.; Mayer, J.; Beck, G.; Piper, S.N. Renal integrity in sevoflurane sedation in the intensive care unit with the anesthetic-conserving device: A comparison with intravenous propofol sedation. *Anesth. Analg.* **2009**, *108*, 1848–1854. [CrossRef]
51. Mazze, R.I.; Callan, C.M.; Galvez, S.T.; Delgado-Herrera, L.; Mayer, D.B. The effects of sevoflurane on serum creatinine and blood urea nitrogen concentrations: A retrospective, twenty-two-center, comparative evaluation of renal function in adult surgical patients. *Anesth. Analg.* **2000**, *90*, 683–688. [CrossRef]
52. Perbet, S.; Bourdeaux, D.; Sautou, V.; Pereira, B.; Chabanne, R.; Constantin, J.M.; Chopineau, J.; Bazin, J.E. A pharmacokinetic study of 48-hour sevoflurane inhalation using a disposable delivery system (AnaConDa®) in ICU patients. *Minerva Anestesiol.* **2014**, *80*, 655–665.

53. Muyldermans, M.; Jennes, S.; Morrison, S.; Soete, O.; François, P.M.; Keersebilck, E.; Rose, T.; Pantet, O. Partial Nephrogenic Diabetes Insipidus in a Burned Patient Receiving Sevoflurane Sedation with an Anesthetic Conserving Device—A Case Report. *Crit. Care Med.* **2016**, *44*, e1246–e1250. [CrossRef]
54. L'Heudé, M.; Poignant, S.; Elaroussi, D.; Espitalier, F.; Ferrandière, M.; Laffon, M. Nephrogenic diabetes insipidus associated with prolonged sedation with sevoflurane in the intensive care unit. *Br. J. Anaesth.* **2019**, *122*, e73–e75. [CrossRef]
55. Jerath, A.; Wong, K.; Wasowicz, M.; Fowler, T.; Steel, A.; Grewal, D.; Huszti, E.; Parotto, M.; Zhang, H.; Wilcox, M.; et al. Use of Inhaled Volatile Anesthetics for Longer Term Critical Care Sedation: A Pilot Randomized Controlled Trial. *Crit. Care Explor.* **2020**, *2*, e0281. [CrossRef]
56. Sackey, P.V.; Martling, C.R.; Carlswärd, C.; Sundin, O.; Radell, P.J. Short- and long-term follow-up of intensive care unit patients after sedation with isoflurane and midazolam—A pilot study. *Crit. Care Med.* **2008**, *36*, 801–806. [CrossRef]
57. Landoni, G.; Pasin, L.; Cabrini, L.; Scandroglio, A.M.; Baiardo Redaelli, M.; Votta, C.D.; Bellandi, M.; Borghi, G.; Zangrillo, A. Volatile Agents in Medical and Surgical Intensive Care Units: A Meta-Analysis of Randomized Clinical Trials. *J. Cardiothorac. Vasc. Anesth.* **2016**, *30*, 1005–1014. [CrossRef]
58. Hellström, J.; Öwall, A.; Sackey, P.V. Wake-up times following sedation with sevoflurane versus propofol after cardiac surgery. *Scand. Cardiovasc. J.* **2012**, *46*, 262–268. [CrossRef]
59. Foudraine, N.A.; Algargoush, A.; van Osch, F.H.; Bos, A.T. A multimodal sevoflurane-based sedation regimen in combination with targeted temperature management in post-cardiac arrest patients reduces the incidence of delirium: An observational propensity score-matched study. *Resuscitation* **2021**, *159*, 158–164. [CrossRef]
60. Hanafy, M.A. Clinical Evaluation of Inhalational Sedation Following Coronary Artery Bypass Grafting. *Egypt. J. Anaesth.* **2005**, *21*, 237–242.
61. Herzog-Niescery, J.; Seipp, H.M.; Weber, T.P.; Bellgardt, M. Inhaled anesthetic agent sedation in the ICU and trace gas concentrations: A review. *J. Clin. Monit. Comput.* **2018**, *32*, 667–675. [CrossRef]
62. Sackey, P.V.; Martling, C.R.; Nise, G.; Radell, P.J. Ambient isoflurane pollution and isoflurane consumption during intensive care unit sedation with the Anesthetic Conserving Device. *Crit. Care Med.* **2005**, *33*, 585–590. [CrossRef]
63. Accorsi, A.; Valenti, S.; Barbieri, A.; Raffi, G.B.; Violante, F.S. Proposal for single and mixture biological exposure limits for sevoflurane and nitrous oxide at low occupational exposure levels. *Int. Arch. Occup. Environ. Health* **2003**, *76*, 129–136. [CrossRef]
64. Varughese, S.; Ahmed, R. Environmental and occupational considerations of anesthesia: A narrative review and update. *Anesth. Analg.* **2021**, *133*, 826. [CrossRef]
65. Alexander, R.; Andrew, P.; Stephan, M. Greenhouse Gases: The Choice of Volatile Anesthetic Does Matter. *Can. J. Anesth./J. Can. D'anesthésie* **2017**, *65*, 221–222. [CrossRef]
66. Meyer, M.J. Desflurane should des-appear: Global and financial rationale. *Anesth. Analg.* **2020**, *131*, 1317–1322. [CrossRef]
67. Herzog-Niescery, J.; Vogelsang, H.; Gude, P.; Seipp, H.M.; Uhl, W.; Weber, T.P.; Bellgardt, M. Environmental safety: Air pollution while using MIRUS™ for short-term sedation in the ICU. *Acta Anaesthesiol. Scand.* **2019**, *63*, 86–92. [CrossRef]
68. Romagnoli, S.; Chelazzi, C.; Villa, G.; Zagli, G.; Benvenuti, F.; Mancinelli, P.; Arcangeli, G.; Dugheri, S.; Bonari, A.; Tofani, L.; et al. The New MIRUS System for Short-Term Sedation in Postsurgical ICU Patients. *Crit Care Med.* **2017**, *45*, e925–e931. [CrossRef]
69. Nitzschke, R.; Wilgusch, J.; Kersten, J.F.; Trepte, C.J.; Haas, S.A.; Reuter, D.A.; Goepfert, M.S. Bispectral index guided titration of sevoflurane in on-pump cardiac surgery reduces plasma sevoflurane concentration and vasopressor requirements: A prospective, controlled, sequential two-arm clinical study. *Eur. J. Anaesthesiol.* **2014**, *31*, 482–490. [CrossRef]
70. Sayed, E.; Refaat, E.; Yassen, K. SEDLine Monitored Sedation and Recovery for Postoperative Ventilated Recipients of Living Donor Liver Transplantation: A Randomized Controlled Trial. *J. Anesth. Clin. Res.* **2015**, *6*, 1–6.
71. Blanchard, F.; Perbet, S.; James, A.; Verdonk, F.; Godet, T.; Bazin, J.E.; Pereira, B.; Lambert, C.; Constantin, J.M. Minimal alveolar concentration for deep sedation (MAC-DS) in intensive care unit patients sedated with sevoflurane: A physiological study. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 429–434. [CrossRef]
72. Stollings, J.L.; Kotfis, K.; Chanques, G.; Pun, B.T.; Pandharipande, P.P.; Ely, E. Delirium in critical illness: Clinical manifestations, outcomes, and management. *Intensive Care Med.* **2021**, *47*, 1089–1103. [CrossRef]
73. Hellström, J.; Öwall, A.; Martling, C.R.; Sackey, P.V. Inhaled isoflurane sedation during therapeutic hypothermia after cardiac arrest: A case series. *Crit. Care Med.* **2014**, *42*, e161–e166. [CrossRef] [PubMed]
74. Duque, M.G.; Medina, R.; Enciso, C.; Beltran, E.; Hernandez, K.; Franco, D.M.; Masclans, J.R. Usefulness of Inhaled Sedation in Patients with Severe ARDS Due to COVID-19. *Respir. Care* **2022**, *22*, 10371. [CrossRef] [PubMed]
75. Becher, T.; Meiser, A.; Guenther, U.; Bellgardt, M.; Wallenborn, J.; Kogelmann, K.; Bracht, H.; Falthauser, A.; Nilsson, J.; Sackey, P.; et al. Isoflurane vs. propofol for sedation in invasively ventilated patients with acute hypoxemic respiratory failure: An a priori hypothesis substudy of a randomized controlled trial. *Ann. Intensive Care.* **2022**, *12*, 116. [CrossRef] [PubMed]
76. Sackey, P.V.; Martling, C.-R.; Granath, F.; Radell, P.J. Prolonged isoflurane sedation of intensive care unit patients with the Anesthetic Conserving Device. *Crit. Care Med.* **2004**, *32*, 2241–2246. [CrossRef]
77. Redaelli, S.; Mangili, P.; Ormas, V.; Sosio, S.; Peluso, L.; Ponzoni, F.; Patroniti, N.; Pesenti, A. Prolonged sedation in ARDS patients with inhaled anesthetics: Our experience. *Crit. Care* **2013**, *17* (Suppl. S2), 386. [CrossRef]
78. Gallego, L.; Soro, M.; Alvariño, A.; Noguera, I.; Belda, F. Renal and hepatic integrity in long-term sevoflurane sedation using the anesthetic conserving device: A comparison with intravenous propofol sedation in an animal model. *Rev. Esp. Anestesiol. Reanim.* **2015**, *62*, 191–203. [CrossRef]

79. Turner, G.B.; O'rourke, D.; Scott, G.O.; Beringer, T.R.O. Fatal hepatotoxicity after re-exposure to isoflurane: A case report and review of the literature. *Eur. J. Gastroenterol. Hepatol.* **2000**, *12*, 955–959. [CrossRef] [PubMed]
80. Manatpon, P.; Kofke, W.A. Toxicity of inhaled agents after prolonged administration. *J. Clin. Monit. Comput.* **2018**, *32*, 651–666. [CrossRef]
81. Meiser, A.; Bellgardt, M.; Belda, J.; Röhm, K.; Laubenthal, H.; Sirtl, C. Technical performance and reflection capacity of the anaesthetic conserving device—A bench study with isoflurane and sevoflurane. *J. Clin. Monit. Comput.* **2009**, *23*, 11–19. [CrossRef]
82. Fan, E.; Beitler, J.R.; Brochard, L.; Calfee, C.S.; Ferguson, N.D.; Slutsky, A.S.; Brodie, D. COVID-19-associated acute respiratory distress syndrome: Is a different approach to management warranted? *Lancet Respir. Med.* **2020**, *8*, 816–821. [CrossRef]
83. Landoni, G.; Belloni, O.; Russo, G.; Bonaccorso, A.; Carà, G.; Jabaudon, M. Inhaled Sedation for Invasively Ventilated COVID-19 Patients: A Systematic Review. *J. Clin. Med.* **2022**, *29*, 2500. [CrossRef] [PubMed]

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Relationship between Middle Cerebral Artery Pulsatility Index and Delayed Neurocognitive Recovery in Patients undergoing Robot-Assisted Laparoscopic Prostatectomy

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Abstract: A steep Trendelenburg (ST) position combined with pneumoperitoneum may cause alterations in cerebral blood flow with the possible occurrence of postoperative cognitive disorders. No studies have yet investigated if these alterations may be associated with the occurrence of postoperative cognitive disorders. The aim of the study was to evaluate the association between an increased middle cerebral artery pulsatility index (Pi), measured by transcranial doppler (TCD) 1 h after ST combined with pneumoperitoneum, and delayed neurocognitive recovery (dNCR) in 60 elderly patients undergoing robotic-assisted laparoscopic prostatectomy (RALP). Inclusion criteria were: ≥65 years; ASA class II–III; Mini-Mental Examination score > 23. Exclusion criteria were: neurological or psychiatric pathologies; any conditions that could interfere with test performance; severe hypertension or vascular diseases; alcohol or substance abuse; chronic pain; and an inability to understand Italian. dNCR was evaluated via neuropsychological test battery before and after surgery. Anesthesia protocol and monitoring were standardized. The middle cerebral artery Pi was measured by TCD, through the trans-temporal window and using a 2.5 MHz ultrasound probe at specific time points before and during surgery. In total, 20 patients experiencing dNCR showed a significantly higher Pi after 1 h from ST compared with patients without dNCR (1.10 (1.0–1.19 95% CI) vs. 0.87 (0.80–0.93 95% CI); $p = 0.003$). These results support a great vulnerability of the cerebral circulation to combined ST and pneumoperitoneum in patients who developed dNCR. TCD could be used as an intraoperative tool to prevent the occurrence of dNCR in patients undergoing RALP.

Keywords: transcranial doppler; postoperative cognitive dysfunction; robotic-assisted prostatectomy

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1. Introduction

It is known that a steep Trendelenburg (ST) position, especially when combined with pneumoperitoneum, can cause alterations of brain regulatory mechanisms [1] that, in elderly patients, may lead to the onset of postoperative cognitive dysfunction (pCD) [2]. At present, there are no studies investigating the possible relationship between changes in

cerebral blood flow, caused by ST combined with pneumoperitoneum, and the occurrence of postoperative cognitive disorders.

Transcranial Doppler (TCD) ultrasonography allows repeated, non-invasive investigations of rapid changes in intracerebral perfusion by assessing middle cerebral artery flow. The most commonly used hemodynamic index is the Gosling pulsatility index (Pi) [3] which has traditionally been interpreted as a descriptor of non-invasive intracranial pressure (ICP) in brain injury as well as in the normal brain [4,5].

The main objective of this study was to evaluate the association between a higher Pi at 1 h from the onset of ST combined with pneumoperitoneum and the occurrence of delayed neurocognitive recovery (dNCR). The association between dNCR and emergence agitation (EA) or postoperative delirium (POD) was also explored.

2. Materials and Methods

This single-center, prospective study was approved by the local Institutional Ethic Committee (ID 1781). Written informed consent was obtained from each patient before the study. All patients scheduled for robotic-assisted laparoscopic prostatectomy (RALP) were screened for enrolment. Patients aged ≥65 years with an ASA physical status classification class II–III and a Mini-Mental Examination (MMSE) score (corrected for age and educational level) of >23 were included. Patients who refused to participate, with known neurological or psychiatric diseases, under chronic psychiatric drugs or other conditions that could interfere with test performance (e.g., blindness and deafness), a history of severe hypertension, a significant carotid or cerebral vascular disease, alcohol or substance abuse, chronic pain, and an inability to understand the Italian language were excluded.

2.1. Anesthesia Protocol

All patients underwent standard monitoring: electrocardiogram, non-invasive arterial blood pressure, pulse oximetry, expiratory gas concentration, bispectral index (BIS), and diuresis. Anesthesia was induced with fentanyl 3 μg/kg, propofol 2 mg/kg, whilst tracheal intubation was facilitated by the administration of rocuronium 0.6 mg/kg. Anesthesia was then maintained with Sevoflurane adjusted according to the BIS value which was kept between 40 and 60. All patients were mechanically ventilated with a tidal volume of 7 mL/kg and the respiratory rate was adjusted to maintain the carbon dioxide end-tidal between 35 and 45 mmHg. Rocuronium 0.15 mg/kg was then repeated in order to keep a deep neuromuscular block (Post Tetanic Count ≤ 2). For intraoperative analgesia, remifentanil was administered in continuous infusion at concentrations varying from 0.05 to 0.25 mcg/kg/min, depending on heart rate and mean arterial pressure variations. Balanced solutions were administered at 1–5 mL/kg/h intraoperatively and 1000 mL for 24 h postoperatively.

After prostate removal, remifentanil infusion was stopped and a 2 mL/h elastomeric pump with Tramadol 400 mg in 48 mL of 0.9% NaCl solution was started [6]. For all patients, before extubation, Paracetamol 1 gr and Ketorolac 30 mg were administered.

Boluses of morphine (0.03 mg/kg; maximum dose 10 mg) were used to treat postoperative pain in the recovery room (RR), while intravenous Tramadol 100 mg was the rescue dose therapy for pain control during ward stay and was administered if the Numeric Rating Scale (NRS) value was ≥5. All patients received Paracetamol 1 gr every 8 h for the first 24 h after surgery.

2.2. Data Collection and Measurements

(1) For the diagnosis of dNCR, the following tests were performed on the day before surgery and on the 2nd day postoperatively: the Rey Auditory Verbal Learning Test (RAVLT), the Raven's Progressive Matrices test, the trail-making test (part A and part B), the Clock drawing test, a phonemic and semantic verbal fluency test, and the Rey–Osterrieth complex figure test (ROCF). dNCR (dichotomous variable) was diagnosed in the individual patient when there was a postoperative decrement of

≥1 standard deviation (SD) (of the whole group at baseline) in a single test and no improvement (score ≥ 1 SD) in the other tests [7]. An improvement in a test score—between the first and the second assessment—smaller than 1 SD of the whole group at baseline was interpreted as a consequence of the practice effect [8].

(2) The onset of POD was assessed by the Confusion Assessment Method (CAM). CAM was administered in the RR and daily until discharge [9].

(3) Anxiety and depression were also assessed on the day before surgery using the State-Trait Anxiety Inventory (STAI) [10] and the Beck Depression Inventory Second Edition (BDI-II) [11], respectively.

(4) During surgery, mean blood pressure, heart rate, BIS, carbon dioxide end-tidal, and pneumoperitoneum-pressure values were recorded (when applicable): before (T1) and after (T2) the induction of anesthesia; thirty minutes (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). ST, a position used routinely during RALP, involves lowering (by 45 degrees) the top of the operating table from the head side and maintaining this position for almost the entire duration of the surgery. Pneumoperitoneum pressure was applied immediately before ST application and maintained at values < 12 mmHg.

With appropriate equipment (Hitachi) and a 2.5 MHz ultrasound probe, the Trans Cranial Doppler (TCD) was performed through the trans-temporal window—located in the middle point between the tragus and the external angle of the ipsilateral eye—at all the time points listed above. The middle cerebral artery (MCA) which is located approximately 30–60 mm deep, and its flow, approaching the probe, appears as a positive wave. Pi was measured according to Gosling's method [12]. Resistivity index (Ri) was also assessed [11].

(5) Pain was assessed using NRS ranging from 0 with no pain to 10 with the worst pain ever felt at the following times: at the patient's arrival in the recovery room, and after 1, 2, 8, 12, 24 and 48 h.

(6) The 36-Item Short Form Health Survey (SF-36) was assessed on the day before surgery and on the 2nd day postoperatively [13].

The following data were also recorded: demographic parameters (age, Body Mass Index, years of education); risk stratification variables (ASA physical, status, Charlson Comorbidity Index); duration of surgery and anesthesia; amount of infused balanced solution; ST duration; diuresis; remifentanil consumption; morphine use in the recovery room and tramadol administration in the ward and hospital stay.

2.3. Statistical Analysis

The a priori power analysis for the calculation of the sample size was based on differences between means (power analysis with Student's unpaired *t*-test) and performed with G*Power 3.1.5 software. Considering a 25% incidence of dNCR and a 50% difference in Pi after pneumoperitoneum + ST between patients with and without dNCR (effect size d = 1), a minimum of 52 patients was considered necessary by calculating an allocation ratio of 4/1 for a two-tailed test with $\beta = 0.80$ and $\alpha = 0.05$. A total of 60 patients were foreseen for enrolment to deal with any dropouts.

Clinical and demographic characteristics were indicated using descriptive statistics. Quantitative variables were described using the mean and a 95% confidence interval (CI). The qualitative variables were summarized using absolute values. The *t*-test for continuous variables and Yates corrected chi-square for dichotomous or discrete variables were used to evaluate the differences between patients with and without dNCR. Furthermore, repeated measures ANOVA with Bonferroni correction was performed for variables assessed at different times. Logistic regression was used to identify possible dNCR predictors, including only variables significant at univariate analysis. The cut-off of significant predictors was calculated using non-parametric ROC (Receiver Operating Characteristic) analysis

and establishing a sensitivity ≥ 0.8. The data were analyzed using the Statistica software (version 8.0) or STATA (version 14.0).

3. Results

Sixty-three patients were assessed for eligibility, three of whom were excluded for the reasons shown in Figure 1 and sixty were finally enrolled. Patients' characteristics and intraoperative data are shown in Table 1. No differences were found for demographic and anesthesia/surgery variables (Table 1).

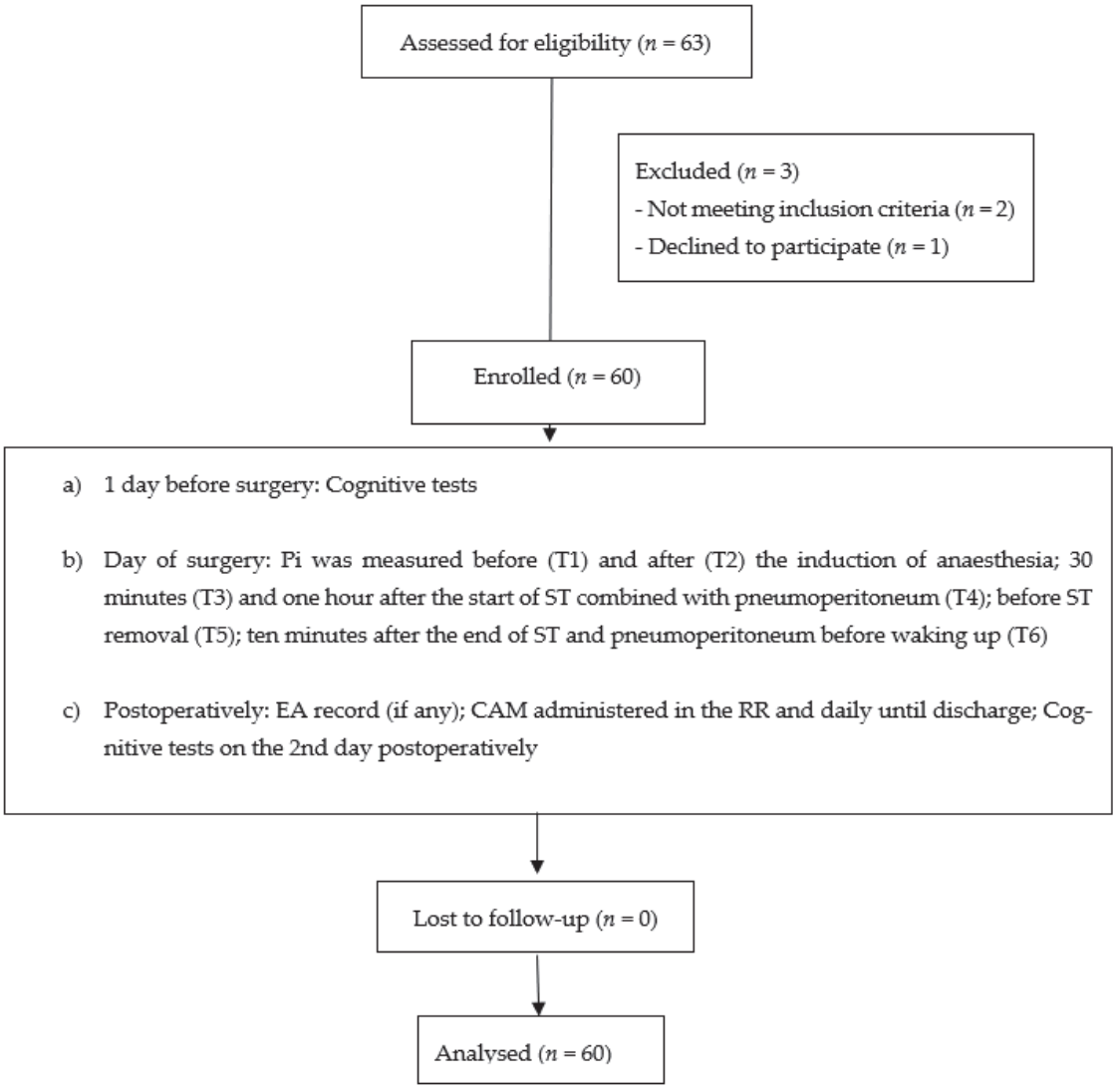

Figure 1. Study diagram flow with the description of study design. ST, steep Trendelenburg; Pi, pulsatility index; EA, emergence agitation; CAM, Confusion Assessment Method; RR, recovery room.

Table 1. Main pre-, intra-, and postoperative parameters in patients with and without dNCR. Values are means (95% confidence intervals) or numbers. BMI: Body Mass Index; ASA: American Society of Anesthesiologists physical status classification; CCI: Charlson Comorbidity Index; MMSE: mini-mental state examination score corrected for age and educational level; STAI: State-Trait Anxiety Inventory; Y1: state anxiety; Y2: trait anxiety; BDI-II: Beck Depression Inventory Second Edition; ST: Steep Trendelenburg; I.O.: intraoperative; P.O.: postoperative; EA: emergence agitation; POD: postoperative delirium.

	Patients without dNCR (*n* = 40)	**Patients with dNCR (*n* = 20)**	**t or χ2 (df)**	***p***
Age, years	69.6 (68.6–70.6)	70.6 (68.4–72.6)	−1.04 (58)	0.30
BMI, kg/m^2	26.2 (25.3–27.2)	25.7 (24.4–27.0)	0.72 (58)	0.47
ASA, II/III	38/2	19/1	0.39 (2)	0.53
CCI	4.6 (4.3–4.8)	4.7 (4.3–5.0)	−0.63 (58)	0.53
MMSE	25.3 (24.2–26.5)	26.0 (25.5–26.4)	1.28 (58)	0.21
STAI-Y1	34.7 (30.8–38.6)	35.5 (30.2–40.8)	−0.24 (58)	0.80
STAI-Y2	31.3 (29.4–33.2)	33.1 (29.0–37.3)	−0.93 (58)	0.35
DBI-II	7.6 (5.9–9.4)	8.7 (5.4–12.0)	−0.67 (58)	0.50
Balanced solution, ml	620.0 (535.8–704.2)	605.0 (448.1–761.9)	0.19 (58)	0.85
Surgery duration, min	178.1 (162.7–193.6)	176.8 (158.0–195.7)	0.10 (58)	0.92
Anesthesia duration, min	207.2 (190.8–223.6)	208.2 (188.2–228.2)	−0–07 (58)	0.94
ST duration, min	145.3 (132.1–158.5)	150.1 (134.2–165.9)	−0.44 (58)	0.66
Diuresis, ml	234.7 (200.7–268.8)	303.0 (208.7–397.3)	−1.72 (58)	0.09
I.O. Remifentanil, mcg	745.5 (621.9–869.1)	984.7 (708.6–1260.9)	−1.89 (58)	0.06
P.O. Morphine, Yes/No	5/35	4/16	0.15 1)	0.70
P.O. Tramadol, Yes/No	13/27	6/14	0.01 (1)	0.92
EA, Yes/No	5/35	6/14	1.68 (1)	0.19
POD, Yes/No	0/40	3/17	3.55 (1)	0.03
Hospital stay (days)	5.1 (4.7–5.5)	5.7 (4.4–6.9)	−1.06 (58)	0.29

Of the 60 enrolled patients, 11 experienced emergence agitation upon awakening in the operating room, 3 had POD in the recovery room, and 20 patients were diagnosed with dNCR by the assessment on the 2nd postoperative day (n = 17).

All three patients who experienced POD were subsequently diagnosed with dNCR, showing a statistically significant association between POD and dNCR (p = 0.03).

The ANOVA results showed a significant effect of the Group per Time interaction (F (5290) = 2.35; p = 0.04) for Pi. In the group of patients with dNCR, a significantly higher Pi at t4 was found compared with patients without dNCR (1.10 (1.0–1.19 95% CI) vs. 0.87 (0.80–0.93 95% CI); p = 0.003) (Figure 2). The increase in Pi at 1 h after ST compared to the values after anesthesia induction was significantly higher in the dNCR group (0.12 ± 0.25 vs. −0.05 ± 0.15; t: −3.34; p = 0.008). The other variables measured during (mean arterial pressure, heart rate, end-tidal CO_2, BIS, pneumoperitoneum) and after anesthesia including NRS (see Figures S1–S6 (Supplementary Materials)), as well as morphine and tramadol consumption (see Table 1), were comparable between the two groups. While the ANOVA showed a significant effect of the interaction Group per Time (F (1290) =3.00; p = 0.01) for Ri (see Figure S7), no significant differences were found between the two groups at post hoc analyses. Logistic regression showed that Pi at 1 h after ST (p = 0.002) was a predictor of dNCR (Likelihood Ratio chi^2 = 13.26; p = 0.003). Moreover, a Pi of 0.9 was identified as the determinant cut-off for dNCR (sensitivity = 80.0%; specificity = 65.0%; AUC: 0.76).

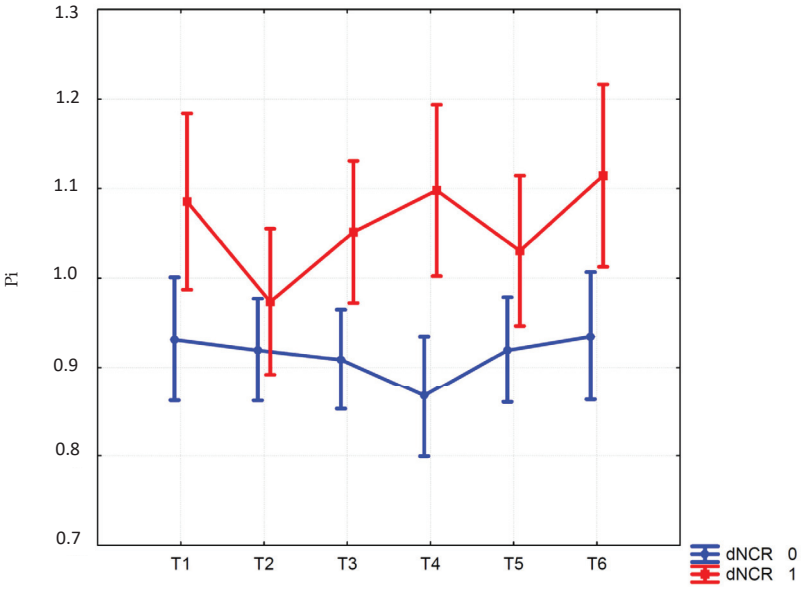

Figure 2. Pulsatility index (Pi) at different time points: baseline (T1), after the induction of anesthesia (T2); 30 min after the start of the Trendelenburg position (T3); one hour from the start of ST (T4), before ST removal (T5); before waking up, ten minutes after the end of ST (T6). Vertical bars denote 95% CI.

The significantly altered neuropsychological tests after surgery were the Rey Auditory Verbal Learning Test (RAVLT) and the Rey–Osterrieth complex figure (ROCF) test recall (see Table 2).

Table 2. Neuropsychological tests (difference between postoperative and preoperative values) in patients with and without dNCR. RAVLT, Rey Auditory Verbal Learning Test; stm, short-term memory; ltm, long-term memory; re, recency effect; PPMT, Raven's Progressive Matrices test; TMT, trail making test; CDT, clock drawing test; pVFT, phonemic verbal fluency test; sVFT, semantic verbal fluency test; ROCF, Rey–Osterrieth complex figure test. Values are means (95% confidence intervals).

	Patients without dNCR (n = 40)	**Patients with dNCR (n = 20)**	**t (df = 58)**	p
RAVLT, stm	1.3 (0.6–2.1)	0.1 (−0.8–1.0)	2.03	0.04
RAVLT, ltm	4.2 (3.2–5.1)	1.4 (−0.2–3.1)	3.19	0.002
RAVLT, re	1.5 (0.9–2.2)	−0.4 (−1.3–0.5)	3.55	0.0007
RPMT	−0.01 (−0.8–0.8)	0.09 (−1.3–1.5)	−0.14	0.89
TMT-A	8.7 (−1.8–19.2)	−4.8 (−20.1–10.3)	1.51	0.14
TMT-B	3.7 (−13.6–21.0)	−2.6 (−30.3–25.1)	0.41	0.68
CDT	−0.3 (−0.6–0.01)	0.05 (−0.6–0.7)	−1.12	0.27
pVFT	0.6 (−1.2–2.5)	−0.14 (−3.4–3.1)	0.46	0.65
sVFT	0.8 (−0.5–2.2)	0.16 (−1.5–1.9)	0.63	0.53
ROCF, copy	−2.8 (−5.2–−0.4)	−3.5 (−5.5–−1.6)	0.41	0.68
ROCF, recall	4.6 (3.0–6.3)	1.2 (−0.9–3.2)	2.60	0.01

As regards health status, there was a significant reduction in both "Emotional Well-being" ($p < 0.0001$) and "Energy-Fatigue" ($p = 0.0008$) items on the 2nd day postoperatively compared to basal values (before surgery) only in patients with dNCR. Moreover, the "Emotional well-being" item was significantly lower in patients with dNCR compared to those without dNCR ($p = 0.028$) (see Table S1).

4. Discussion

Our results show that one-third of the population studied was diagnosed with dNCR. These data are confirmed in the literature which shows a higher incidence in elderly patients [14]. In this study, we found a statistically significant association between a higher value of Pi one hour from the start of ST combined with pneumoperitoneum and the onset of dNCR. Pi measured at this time point was chosen as the main variable as we hypothesized that time length in ST contributes to altering cerebral hemodynamics.

The combination of pneumoperitoneum and ST can increase ICP as proven by ultrasonographic measurement of Pi [1] or optic nerve sheath diameter [15]. In our study, the increase in Pi 1 h after ST compared to that after anesthesia induction (before the application of ST and Trendelenburg) was significant in patients with dNCR, reinforcing this interpretation. Kalmar et al., also hypothesized that venous congestion due to Trendelenburg was the main determinant of the increase in ICP [16].

Based on our results, Trendelenburg degrees could be reduced until the Pi drops below the cut-off of 0.9. Maintaining a stable ultralow pneumoperitoneum pressure using a valveless insufflation system could be another possible protective strategy to avoid the occurrence of dNCR [17].

The association between cerebral hemodynamics and cognitive outcome after anesthesia has been poorly investigated. Chen et al., indirectly measured the ICP during RALP through the variation of the ONSD and found a potential indirect link between the increase in ICP during the combination of pneumoperitoneum and ST and the onset of short-term cognitive disorders [2]. However, Chen et al., reported, among the limitations of their study, the use of MMSE [2], which is a screening test for of evaluating cognitive impairment in older adults while dNCR needs a battery of more specific tests to be diagnosed [7]. On the contrary, Goettel et al. and Kim et al. [14] showed that impaired intraoperative cerebral autoregulation seems not to be predictive of dNCR in elderly patients after major non-cardiac surgery [18].

The relationship between the increase in ICP determined by ST and pneumoperitoneum with dNCR has never been systematically investigated. However, one of the pathophysiological hypotheses of pCD concerns cerebral hypoperfusion during surgery. This variation could be the epiphenomenon of a greater vulnerability of these patients to the venous congestion caused by ST with consequent hypoperfusion and reduced metabolic oxygen supply. However, brain oxygenation was not measured in our study, thus this cause–effect relationship cannot be confirmed.

Moreover, a previous review on the onset of pCD in non-cardiac surgery highlighted that the correlation between pCD and intraoperative cerebral hypoxemia is not so strong and more limited to inflammatory mediators triggered by stress caused by anesthesia, surgery, and hospitalization [19]. The inflammation mediators could also have had an essential role in dNCR pathophysiology in our study due to a possibly elevated permeability of the blood–brain barrier in patients with dNCR [20]. Thus, the concomitant increase in ICP with consequent stasis at the cerebral level in susceptible patients could have facilitated the entrance of cytokines in the brain during surgical stress causing neuroinflammation.

Among the other risk factors for the onset of postoperative cognitive disorders, monitoring of the depth of anesthesia was discussed in several papers as a preventive measure [21,22]. Chan et al., have shown that a guided BIS anesthesia reduced the occurrence of both short and long-term pCD and POD [23]. Similarly, Kotekar et al., argued that intraoperative monitoring of the depth of anesthesia, especially in older patients, can help

reduce the onset of pCD [24]. However, in our study, the mean BIS did not differ between patients with and without dNCR.

An important limitation of the study is the lack of long-term follow-up to assess either the persistence of cognitive dysfunction or the impact of pCD on quality of life over time. It would be interesting for future studies to investigate if these changes may also occur in long-lasting surgeries such as robotic cystectomy.

Another limitation is that Pi was considered an indirect index of the ICP, even if this issue deserves further investigation. However, the absence of significant differences in Ri between patients with and without dNCR in our study could confirm that, when compared with the PI, the RI index is less sensitive to ICP variations [25]. Moreover—even though expired CO_2 did not show significant changes—we cannot exclude an influence of the $PaCO^2$ increase during pneumoperitoneum [26] on Pi, which may increase in response to hypercapnia.

In conclusion, the most relevant result of this study is the association between the increase in Pi after one hour from ST under pneumoperitoneum and dNCR. These results support a great vulnerability of the cerebral circulation to the ST combined with pneumoperitoneum in patients who develop dNCR. Even if further studies are needed to confirm these findings, middle cerebral artery Pi could be used as a prognostic indicator of an unfavorable cognitive outcome and constitutes a deterrent to modifying the perioperative therapeutic strategy in patients with risk factors for dNCR. The findings of the present study had relevant clinical implications for the chance to predict and prevent dNCR and the consequent impairment in quality of life after surgery.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12031070/s1, Figure S1: Numerical rate scale (NRS) for pain in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: at patient's arrival in the recovery room (RR), after 1, 2, 8, 12, 24 and 48 h. Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery; Figure S2: Mean arterial pressure (MAP) in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: before (T1) and after (T2) the induction of anesthesia; 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Figure S3: Heart rate in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: before (T1) and after (T2) the induction of anesthesia; 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Figure S4: End tidal CO_2 (mmHg) values in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: after the induction of anesthesia (T2); 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Figure S5: Bispectral index (BIS) in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: before (T1) and after (T2) the induction of anesthesia; 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Figure S6: Pneumoperitoneum pressure (mmHg) in patients with dNCR (red line) versus patients without dNCR (blu line) at the following times: 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Figure S7: Resistivity index in patients with

dNCR (red line) versus patients without dNCR (blu line) at the following times: before (T1) and after (T2) the induction of anesthesia; 30 min (T3) and one hour after the start of ST combined with pneumoperitoneum (T4); before ST and pneumoperitoneum removal (T5); ten minutes after the end of ST and pneumoperitoneum before waking up (T6). Values are shown as mean ± 95% confidence interval. Interaction F (Group per Time) is shown. dNCR, delayed neurocognitive recovery. ST, Steep Trendelenburg; Table S1: ANOVAs Group (dNCR vs No dNCR) × Time (T0 vs T1) on each item of SF-36 (n = 60). T0 = Before surgery; T1 = After surgery (2nd day postoperatively). Values are shown as mean (M) ± standard deviation (SD).

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Data Availability Statement: Data presented in this study are available upon request.

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References

1. Robba, C.; Cardim, D.; Donnelly, J.; Bertuccio, A.; Bacigaluppi, S.; Bragazzi, N.; Cabella, B.; Liu, X.; Matta, B.; Lattuada, M.; et al. Effects of pneumoperitoneum and Trendelenburg position on intracranial pressure assessed using different non-invasive methods. *Br. J. Anaesth.* **2016**, *117*, 783–791. [CrossRef] [PubMed]
2. Chen, K.; Wang, L.; Wang, Q.; Liu, X.; Lu, Y.; Li, Y.; Wong, G.T.C. Effects of pneumoperitoneum and steep Trendelenburg position on cerebral hemodynamics during robotic-assisted laparoscopic radical prostatectomy: A randomized controlled study. *Medicine* **2019**, *98*, e15794. [CrossRef] [PubMed]
3. Bellner, J.; Romner, B.; Reinstrup, P.; Kristiansson, K.A.; Ryding, E.; Brandt, L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surg. Neurol.* **2004**, *62*, 45–51. [CrossRef]
4. Gosling, R.G.; King, D.H. Arterial assessment by Doppler-shift ultrasound. *Proc. R. Soc. Med.* **1974**, *67*, 447–449.
5. Budohoski, K.P.; Schmidt, B.; Smielewski, P.; Kasprowicz, M.; Plontke, R.; Pickard, J.D.; Klingelhöfer, J.; Czosnyka, M. Non-invasively estimated ICP pulse amplitude strongly correlates with outcome after TBI. *Acta Neurochir.* **2012**, *114*, 121–125. [CrossRef]
6. Russo, A.; Romanò, B.; Papanice, D.; Cataldo, A.; Gandi, C.; Vaccarella, L.; Totaro, A.; Sacco, E.; Bassi, P.; Aceto, P.; et al. InTrathecal mORphine, traNsversus Abdominis Plane Block, and tramaDOl Infusion for Catheter-Related Bladder Discomfort in Patients Undergoing Robot-Assisted Laparoscopic Prostatectomy (TORNADO): A Pilot Prospective Controlled Study. *J. Clin. Med.* **2022**, *11*, 2136. [CrossRef]
7. Evered, L.; Silbert, B.; Knopman, D.S.; Scott, D.A.; DeKosky, S.T.; Rasmussen, L.S.; Oh, E.S.; Crosby, G.; Berger, M.; Eckenhoff, R.G. Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br. J. Anaesth.* **2018**, *121*, 1005–1012. [CrossRef]
8. Collie, A.; Maruff, P.; Darby, D.G.; McStephen, M. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J. Int. Neuropsychol. Soc.* **2003**, *9*, 419–428. [CrossRef] [PubMed]
9. Aldecoa, C.; Bettelli, G.; Bilotta, F.; Sanders, R.D.; Audisio, R.; Borozdina, A.; Cherubini, A.; Jones, C.; Kehlet, H.; MacLullich, A.; et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur. J. Anaesthesiol.* **2017**, *34*, 192–214. [CrossRef]
10. Spielberger, C.D.; Sydeman, S.J. State-trait anxiety inventory and state-trait anger expression inventory. In *The Use of Psychological Testing for Treatment Planning and Outcome Assessment*; Maruish, M.E., Ed.; Lawrence Erlbaum Associates: Hillsdale, NJ, USA, 1994; pp. 292–321.
11. Beck, A.; Brown, G.; Steer, R. *Beck Depression Inventory-II Manual*; Psychological Corporation: San Antonio, TX, USA, 1996.

12. D'Andrea, A.; Conte, M.; Scarafile, R.; Riegler, L.; Cocchia, R.; Pezzullo, E.; Cavallaro, M.; Carbone, A.; Natale, F.; Russo, M.G.; et al. Transcranial Doppler Ultrasound: Physical Principles and Principal Applications in Neurocritical Care Unit. *J. Cardiovasc. Echogr.* **2016**, *26*, 28–41. [CrossRef]
13. Apolone, G.; Mosconi, P. The Italian SF-36 Health Survey: Translation, validation and norming. *J. Clin. Epidemiol.* **1998**, *51*, 1025–1036. [CrossRef] [PubMed]
14. Aceto, P.; Incalzi, R.A.; Bettelli, G.; Carron, M.; Chiumiento, F.; Corcione, A.; Crucitti, A.; Maggi, S.; Montorsi, M.; Pace, M.C.; et al. Perioperative Management of Elderly patients (PriME): Recommendations from an Italian intersociety consensus. *Aging Clin. Exp. Res.* **2020**, *32*, 1647–1673. [CrossRef] [PubMed]
15. Kim, M.-S.; Bai, S.-J.; Lee, J.-R.; Choi, Y.D.; Kim, Y.J.; Choi, S.H. Increase in intracranial pressure during carbon dioxide pneumoperitoneum with steep Trendelenburg positioning proven by ultrasonographic measurement of optic nerve sheath diameter. *J. Endourol.* **2014**, *28*, 801–806. [CrossRef] [PubMed]
16. Kalmar, A.F.; Foubert, L.; Hendrickx, J.F.; Mottrie, A.; Absalom, A.; Mortier, E.P.; Struys, M.M. Influence of steep Trendelenburg position and CO_2 pneumoperitoneum on cardiovascular, cerebrovascular, and respiratory homeostasis during robotic prostatectomy. *Br. J. Anaesth.* **2010**, *104*, 433–439. [CrossRef] [PubMed]
17. La Falce, S.; Novara, G.; Gandaglia, G.; Umari, P.; De Naeyer, G.; D'Hondt, F.; Beresian, J.; Carette, R.; Penicka, M.; Mo, Y.; et al. Low Pressure Robot-assisted Radical Prostatectomy with the AirSeal System at OLV Hospital: Results from a Prospective Study. *Clin. Genitourin. Cancer* **2017**, *15*, e1029–e1037. [CrossRef]
18. Goettel, N.; Burkhart, C.S.; Rossi, A.; Cabella, B.C.; Berres, M.; Monsch, A.U.; Czosnyka, M.; Steiner, L.A. Associations Between Impaired Cerebral Blood Flow Autoregulation, Cerebral Oxygenation, and Biomarkers of Brain Injury and Postoperative Cognitive Dysfunction in Elderly Patients After Major Noncardiac Surgery. *Anesth. Analg.* **2017**, *124*, 934–942. [CrossRef]
19. Aceto, P.; Lai, C.; De Crescenzo, F.; Crea, M.A.; Di Franco, V.; Pellicano, G.R.; Perilli, V.; Lai, S.; Papanice, D.; Sollazzi, L. Cognitive decline after carotid endarterectomy: Systematic review and meta-analysis. *Eur. J. Anaesthesiol.* **2020**, *37*, 1066–1074. [CrossRef]
20. Cheng, C.; Wan, H.; Cong, P.; Huang, X.; Wu, T.; He, M.; Zhang, Q.; Xiong, L.; Tian, L. Targeting neuroinflammation as a preventive and therapeutic approach for perioperative neurocognitive disorders. *J. Neuroinflamm.* **2022**, *19*, 297. [CrossRef]
21. Aceto, P.; Beretta, L.; Cariello, C.; Claroni, C.; Esposito, C.; Forastiere, E.M.; Guarracino, F.; Perucca, R.; Romagnoli, S.; Sollazzi, L.; et al. Joint consensus on anesthesia in urologic and gynecologic robotic surgery: Specific issues in management from a task force of the SIAARTI, SIGO, and SIU. *Minerva Anestesiol.* **2019**, *85*, 871–885. [CrossRef]
22. Aceto, P.; Perilli, V.; Lai, C.; Ciocchetti, P.; Vitale, F.; Sollazzi, L. Postoperative cognitive dysfunction after liver transplantation. *Gen. Hosp. Psychiatry* **2015**, *37*, 109–115. [CrossRef]
23. Chan, M.T.V.; Cheng, B.C.P.; Lee, T.M.C.; Gin, T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J. Neurosurg. Anesthesiol.* **2013**, *25*, 33–42. [CrossRef] [PubMed]
24. Kotekar, N.; Shenkar, A.; Nagaraj, R. Postoperative cognitive dysfunction—Current preventive strategies. *Clin. Interv. Aging* **2018**, *13*, 2267–2273. [CrossRef] [PubMed]
25. Ursino, M.; Giulioni, M.; Lodi, C.A. Relationships among cerebral perfusion pressure, autoregulation, and transcranial Doppler waveform: A modeling study. *J. Neurosurg.* **1998**, *89*, 255–266. [CrossRef] [PubMed]
26. Ripa, M.; Schipa, C.; Kopsacheilis, N.; Nomikarios, M.; Perrotta, G.; De Rosa, C.; Aceto, P.; Sollazzi, L.; De Rosa, P.; Motta, L. The Impact of Steep Trendelenburg Position on Intraocular Pressure. *J. Clin. Med.* **2022**, *11*, 2844. [CrossRef] [PubMed]

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Effect of Supplemental Oxygen on von Willebrand Factor Activity and Ristocetin Cofactor Activity in Patients at Risk for Cardiovascular Complications Undergoing Moderate-to High-Risk Major Noncardiac Surgery—A Secondary Analysis of a Randomized Trial

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Abstract: Increased von Willebrand Factor (vWF) activity mediates platelet adhesion and might be a contributor to the development of thrombotic complications after surgery. Although in vitro studies have shown that hyperoxia induces endovascular damage, the effect of perioperative supplemental oxygen as a possible trigger for increased vWF activity has not been investigated yet. We tested our primary hypothesis that the perioperative administration of 80% oxygen concentration increases postoperative vWF activity as compared to 30% oxygen concentration in patients at risk of cardiovascular complications undergoing major noncardiac surgery. A total of 260 patients were randomly assigned to receive 80% versus 30% oxygen throughout surgery and for two hours postoperatively. We assessed vWF activity and Ristocetin cofactor activity in all patients shortly before the induction of anesthesia, within two hours after surgery and on the first and third postoperative day. Patient characteristics were similar in both groups. We found no significant difference in vWF activity in the overall perioperative time course between both randomization groups. We observed significantly increased vWF activity in the overall study population throughout the postoperative time course. Perioperative supplemental oxygen showed no significant effect on postoperative vWF and Ristocetin cofactor activity in cardiac risk patients undergoing major noncardiac surgery. In conclusion, we found no significant influence of supplemental oxygen in patients undergoing major non-cardiac surgery on postoperative vWF activity and Ristocetin cofactor activity.

Keywords: von Willebrand factor; ristocetin; endothelial demage; noncardiac surgery

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1. Introduction

Major surgery is an independent risk factor for the development of postoperative thromboembolic events [1]. It has been shown that surgical trauma, anesthesia, intraoperative hemodynamic and fluid perturbations, and perioperative inflammation are important causes vascular endothelial damage [2]. This is an important fact, since the activation of endothelial cells by damage leads to the expression of adhesion molecules including P-selectin, E-selectin, and vWF [3,4]. Von Willebrand Factor (vWF) is a large multimeric glycoprotein and a key component in hemostasis [5,6]. VWF is synthesized in megakaryocytes and endothelial cells and stored in Weibel–Palade bodies [7]. It is known that vWF is a strong mediator for platelet adhesion, aggregation and thrombus formation, and more importantly, increases significantly after surgery [8,9]. Therefore, increased vWF activity

caused by activated endothelial cells might be one cause for the increased incidence of postoperative thromboembolic events.

Previous studies indicated that hyperoxia induces endovascular damage [10–12]. In detail, it has been shown in in vitro studies that an oxygen concentration of 95% is associated with the occurrence of DNA damage of endothelial cells and fibroblasts [12]. Although it is becoming more evident that supplemental oxygen has no effect on wound healing or cardiovascular complications, a strong consensus about the most beneficial concentration does still not exist [13–15]. Subsequently, intraoperative administered oxygen concentration is still varying and mainly dependent on the attending anesthesiologists [16]. In this context, possible effects of perioperative supplemental oxygen on the integrity of endothelial cells are clinically relevant; however, data from the perioperative setting are still lacking.

Thus, we tested in this pre-planned secondary analysis of a prospective randomized clinical trial the hypothesis that perioperative administration of 80% oxygen concentration increases postoperative vWF activity as compared to 30% oxygen concentration in patients at risk of cardiovascular complications undergoing major noncardiac surgery. We further evaluated if supplemental oxygen increases postoperative Ristocetin cofactor activity.

2. Materials and Methods

This is a pre-planned secondary analysis of a double-blinded randomized clinical trial that investigated the effect of supplemental oxygen on postoperative maximum N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations in patients at risk for cardiovascular complications undergoing major noncardiac surgery [17]. The study was conducted at the Medical University of Vienna according to the Declaration of Helsinki and Good Clinical Practice. The study was approved by the local Institutional Review Board and was registered at ClinicalTrials.gov (Registration number: NCT 03388957; Principal Investigator: Prof. Dr. Edith Fleischmann; Date of registration: 2 December 2017) and at the European Trial Database (EudraCT 2017-003714-68). This study was approved by the University's Ethics Committee (Ethikkomission Medizinische Universität Wien; Borschkegasse 8b/6, 1090, Vienna, Austria; EK-Number 1744/2017; Chairperson Prof. Martin Brunner) on 13 November 2017. We obtained written informed consent from all patients before randomization. Inclusion and exclusion criteria and a detailed description of our study protocol and the randomization procedure were published previously [17].

We recorded demographic data including age, sex, BMI, American Society of Anesthesiologists (ASA) physical status, comorbidities, long-term medication, type of surgery, ABO blood type, and preoperative laboratory values from all patients. We further recorded duration of anesthesia and surgery, fluid and anesthesia management, and intra- and postoperative blood pressure. Blinded research personnel drew all study specific pre- and postoperative blood samples. We assessed vWF activity, Ristocetin cofactor activity, and static oxidation-reduction potential (sORP) in all patients shortly before induction of anesthesia, within two hours after surgery and on the first and third postoperative day. We further measured ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme that cleaves vWF, before surgery in all patients.

Blinded research personnel obtained all data. All data were recorded and stored in the data management system 'Clincase'(v2.7.0.12, Berlin, Germany) hosted by IT Systems & Communications, Medical University of Vienna, Vienna, Austria.

We included all patients who were enrolled into the main trial for this secondary analysis. The study was originally planned for the main study outcome, the maximum BNP value over the first 3 days. We re-estimated the sample size for this secondary analysis based on previous results on vWF to get an evaluation of the available sample size. It was shown previously that adverse cardiac events after noncardiac surgery were associated with postoperative vWF activity of 150% $\pm$ 60% compared with postoperative maximum vWF activity of 125% $\pm$ 50% in patients without postoperative cardiac events [18]. Therefore, based on the aforementioned study, we assumed an absolute difference of 17% in postop-

erative vWF activity as clinically meaningful. Using the given assumptions, a two-sided t-test, we calculated that at least 123 patients per group are needed to detect a significant difference between both groups at a significance level of 0.05 with 90% power. Thus, the given sample size of 260 patients (130 patients per group) may be adequately powered.

Descriptive statistics (mean, standard deviation and quantiles) for vWF activity and Ristocetin cofactor activity were calculated separately for each time point and the 80% and 30% oxygen group. To investigate the difference in time course of vWF activity and Ristocetin cofactor activity between both randomization groups, first linear regression models for vWF activity and Ristocetin cofactor activity were performed accounting for time, group and the interaction between time and group as fixed factor and patient as random factor. Further, we used univariable linear regression models (with random factor patient) for the possible influence factors including time as well as the baseline covariates age, BMI, sex, ASA, history of coronary artery disease, peripheral artery disease, stroke, heart failure, diabetes, hypertension, type of procedure (open versus laparoscopic), type of surgery, ABO blood type, and preoperative ADAMTS13 and blood loss on perioperative vWF and Ristocetin cofactor activity. All factors being significant (with a $p < 0.05$) in the simple models where then included in a multivariable regression model (with random factor patient). To evaluate a possible correlation between the perioperative trend of vWF activity and oxidative stress—assessed via sORP measurements—we performed a linear regression model for vWF as the dependent variable, accounting for time, sORP and the interaction between time and sORP as well as patient as a random factor. All p-values < 0.05 were considered statistically significant. We used R.4.2.2 (SAS Institute, Cary, NC, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA) for statistical analysis.

3. Results

We present the analysis of 258 patients who were enrolled in our main trial between December 2017 and December 2019 at the Medical University of Vienna. A total of 130 patients were randomly assigned to receive 80% oxygen throughout surgery and for two hours postoperatively, and 130 patients were randomly assigned to receive 30% oxygen throughout surgery and for two hours postoperatively. Two patients in the 80% group were excluded from analysis because surgery was postponed. Thus, overall, 258 patients were analyzed. Baseline characteristics as well as intra- and postoperative characteristics were published previously and did not differ between the groups [19].

3.1. Primary Outcome

Descriptive statistics of vWF activity separately for each randomization group and time are shown in Table 1. The perioperative trends of vWF activity for both study groups are shown in Figure 1. We found no significant difference in vWF activity in the overall perioperative time course between the 80% and the 30% oxygen groups (estimated effect: 0.297; 95% CI −4.154 to 4.749; $p = 0.896$). Furthermore, a significant difference between the 80% and 30% oxygen group was found at no time point (Table 1).

Table 1. Descriptive statistics for vWF activity and Ristocetin cofactor activity. VWF activity and Ristocetin cofactor activity at each timepoint are presented as median (25th quartile; 75th quartile). All p-values are for two-tailed Mann–Whitney U tests.

	80% Oxygen		30% Oxygen		p-Value
vWF activity, %					
Baseline	156.5	[112.75; 212.5]	155.5	[119; 200.75]	0.78
2 h postoperative	211	[160; 274.5]	214	[163; 266]	0.85
Postoperative day 1	228	[180; 315.75]	219.5	[186; 279.5]	0.45
Postoperative day 3	244	[199.5; 302]	256	[193; 317]	0.82

Table 1. *Cont.*

	80% Oxygen		30% Oxygen		*p*-Value
Ristocetin cofactor activity, %					
Baseline	142.5	[113.75; 208.75]	152	[116.5; 199.5]	0.88
2 h postoperative	227.5	[164.25; 306.25]	247	[198; 315]	0.19
Postoperative day 1	255.5	[190; 359.75]	245	[201; 286]	0.56
Postoperative day 3	247.5	[199.25; 311]	270	[203.5; 340]	0.36

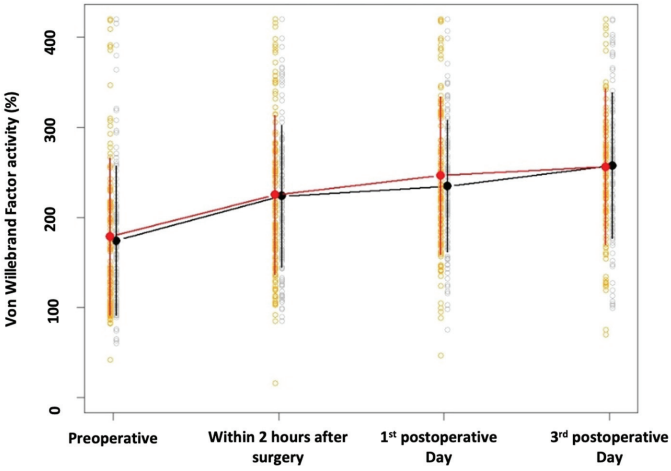

Figure 1. Time course for von Willebrand Factor activity. Mean values (dots) and standard deviations (vertical lines) for vWF separately for time and the 30%-group (black) as well as the 80%-group (red). The blank dots give the values of the observed individuals, separately for the two groups.

We observed significantly increased vWF activity in the overall study population over time ($p < 0.001$) as compared to baseline. vWF activity increased on average by 19.264 (95% CI 17.040 to 21.488) per day.

3.2. Secondary Outcome: Ristocetin Cofactor Activity

Descriptive statistics of Ristocetin cofactor activity separately for randomization group and time are shown in Table 1.

We found no significant difference in Ristocetin cofactor activity in the overall perioperative time course between the 80% and the 30% oxygen groups (estimated effect: 1.003; 95% CI 20.500 to 32.528; $p = 0.818$). Furthermore, a significant difference between the 80% and 30% oxygen group was found at no time point (Table 1).

We observed significantly higher Ristocetin cofactor activity in the overall study population over time ($p < 0.001$) as compared to baseline. On average, Ristocetin cofactor activity increased by 26.969 (95% CI 22.954 to 30.984) per day.

3.3. Analyses of Possible Confounding Factors

3.3.1. Von Willebrand Factor Activity

Significantly higher postoperative vWF activities were observed for females as compared to males ($p = 0.044$) for patients with a history of peripheral artery disease ($p = 0.036$), patients with a blood type other than O ($p < 0.001$), and patients with pancreatic surgery ($p < 0.001$) in the univariable model. Patients undergoing renal surgery ($p = 0.002$) or prostatectomy ($p = 0.012$) had significantly smaller vWF activity. Age, BMI, ASA, history of coronary artery disease, stroke, heart failure, diabetes, hypertension or preoperative ADAMTS13 or blood loss did not show evidence for an association with vWF activity.

For all time points, patients with laparoscopic surgery showed lower postoperative vWF activity as compared to open procedures ($p < 0.001$) (Table 2).

Table 2. Univariable regression models vWF. The estimated effect sizes, confidence levels (CL) and *p*-values were calculated using univariable regression models. pre, preoperative; 2 h post, within two hours after surgery; POD, postoperative day; BMI, body mass index; ASA, American Society of Anesthesiologists.

Variable	Comparison	Effect	Lower CL	Upper CL	*p*-Value
Time	Overall Trend Test	19.264	17.040	21.488	<0.001
	pre vs. 2 h post	−46.672	−55.050	−38.295	<0.001
	pre vs. POD 1	−62.434	−70.973	−53.894	<0.001
	pre vs. POD 3	−80.874	−89.720	−72.028	<0.001
Time × Group	Overall Trend Test	0.297	−4.154	4.749	0.896
	Group 30% vs. 80% pre	−2.964	−23.547	17.619	0.777
	Group 30% vs. 80% 2 h post	0.099	−20.528	20.726	0.993
	Group 30% vs. 80% POD 1	−11.570	−32.475	9.335	0.277
	Group 30% vs. 80% POD 3	0.507	−20.852	21.866	0.963
	Group 30% pre vs. 2 h post	−48.180	−59.995	−36.365	<0.001
	Group 30% pre vs. POD 1	−57.891	−70.157	−45.625	<0.001
	Group 30% pre vs. POD 3	−82.617	−95.187	−70.048	<0.001
	Group 80% pre vs. 2 h post	−45.117	−57.009	−33.224	<0.001
	Group 80% pre vs. POD 1	−66.497	−78.401	−54.584	<0.001
	Group 80%: pre vs. POD 3	−79.146	−91.610	−66.682	<0.001
Type of surgery	Laparoscopic vs. Open	−48.264	−66.232	−30.297	<0.001
Time × Type of surgery	Overall Trend Test	1.523	−3.171	6.216	0.524
Liver	Yes vs. No	10.534	−19.790	40.858	0.495
Colorectal	Yes vs. No	−11.296	−31.163	13.330	0.431
Pancreatic	Yes vs. No	55.257	29.981	80.534	<0.001
Renal	Yes vs. No	−38.300	−62.435	−14.166	0.002
Prostatectomy	Yes vs. No	−36.031	−64.046	−8.017	0.012
Cystectomy	Yes vs. No	−17.482	−48.574	13.610	0.269
Gynecological	Yes vs. No	27.488	−19.689	74.660	0.252
Other	Yes vs. No	3.228	−26.021	32.477	0.828
Age		1.059	−0.134	2.252	0.082
BMI		0.301	−1.552	2.154	0.750
Sex	Female vs. Male	19.584	0.561	38.607	0.044
ASA	3,4 vs. 1,2	15.168	−4.580	34.916	0.132
History of Coronary Artery Disease	Yes vs. No	2.912	−18.077	23.901	0.785
History of Peripheral Artery Disease	Yes vs. No	26.660	1.698	51.622	0.036
History of stroke	Yes vs. No	−2.287	−34.760	30.186	0.890
History of Heart failure	Yes vs. No	8.693	−26.490	43.875	0.627
Diabetes	Yes vs. No	−0.345	−20.530	19.839	0.973
History of Hypertension	Yes vs. No	−26.494	−61.876	8.889	0.142
Blood type	0 vs. A,B,AB	51.242	32.961	69.523	<0.001

Table 2. *Cont.*

Variable	Comparison	Effect	Lower CL	Upper CL	*p*-Value
pre ADAMTS		0.002	−0.100	0.105	0.962
Type of surgery	Laparoscopic vs. Open	−48.264	−66.232	−30.297	<0.001
Blood Loss		0.007	−0.007	0.021	0.345

The factors time point, type of surgery, sex, history of peripheral artery disease, blood type, pancreatic or renal surgery as well as prostatectomy were included in the multivariable model. All parameters except renal surgery and prostatectomy remained significant in the multivariable model (Table 3).

Table 3. Multivariable regression model vWF. The estimated effect sizes, confidence levels and p-values were calculated using multivariable regression models (with random factor patient). pre, preoperative; 2 h post, within two hours after surgery; POD, postoperative day; CL, confidence level.

Variable	Comparison	Effect	Lower CL	Upper CL	*p*-Value
Time	pre vs. 2 h post	−45.736	−54.239	−37.233	<0.001
	pre vs. POD 1	−61.587	−70.243	−52.931	<0.001
	pre vs. POD 3	−80.248	−80.305	−89.272	<0.001
Type of surgery	Laparoscopic vs. Open	−30.367	−50.177	−10.557	0.003
Sex	Female vs. Male	18.570	1.194	35.946	0.036
History of Peripheral Artery Disease	Yes vs. No	26.305	4.018	48.592	0.021
Blood type	0 vs. A,B,AB	55.529	38.568	72.489	<0.001
Pancreatic	Yes vs. No	28.625	5.024	52.225	0.018
Renal	Yes vs. No	−16.297	−41.125	8.531	0.197
Prostatectomy	Yes vs. No	−25.026	−52.736	2.685	0.077

3.3.2. Ristocetin Cofactor Activity

Significantly higher postoperative Ristocetin cofactor activity was found for increasing age ($p = 0.019$), females as compared to males ($p = 0.027$), patients with peripheral artery disease ($p = 0.001$), patients without history of hypertension ($p = 0.001$), patients with blood type other than O ($p < 0.001$) and patients having pancreatic surgery ($p < 0.001$) in the univariable model. Significantly lower Ristocetin cofactor activity was found in patients having renal surgery ($p = 0.003$). BMI, ASA, history of coronary artery disease, stroke, heart failure, diabetes or preoperative ADAMTS13 or blood loss did not show evidence for an association with Ristocetin cofactor activity. For all time points, patients with laparoscopic surgeries showed lower postoperative Ristocetin cofactor activity ($p < 0.001$) (Supplemental Materials, Table S1: Univariable regression model Ristocetin). The factors time point, type of surgery, age, sex, history of peripheral artery disease, history of hypertension, blood type, pancreatic, and renal surgery were included in the multivariable model. All parameters except for pancreatic or renal surgery remained significant in the multivariable model (Supplemental Materials, Table S2: Multivariable regression model Ristocetin).

3.3.3. vWF Activity and SORP

Over the perioperative time course, a significant positive correlation between the trend of vWF activity and sORP was observed in the overall study population (estimated effect: 0.380; 95% CI 0.170 to 0.590; $p < 0.001$).

4. Discussion

In this secondary analysis, we assessed endothelial damage via consecutive vWF activity measurements. We observed no significant effect of perioperative 80% oxygen concentration on postoperative vWF activity as compared to perioperative 30% oxygen concentration. Furthermore, we did not observe a significant difference in postoperative Ristocetin cofactor activity between the two groups.

In the original trial, we showed that the administration of supplemental oxygen was not associated with significant changes in postoperative maximum NT-proBNP and Troponin T concentrations [19]. Previous secondary analyses of this trial showed that supplemental oxygen was also not associated with significant changes in postoperative catecholamine levels [20] as well as postoperative Copeptin or oxidative stress levels [21,22].

A previous trial showed no adverse effects of supplemental oxygen on the incidence of myocardial injury after noncardiac surgery (MINS) in patients with cardiovascular risk factors undergoing major noncardiac surgery [23]. In another trial that evaluated the effect of supplemental oxygen in surgical site infections, the authors did not detect any significant effect of supplemental oxygen [14]. A post hoc analysis of this trial also showed that supplemental oxygen did not increase overall postoperative mortality [24]. Therefore, it seems likely that supplemental oxygen does not significantly affect the development of postoperative complications after major noncardiac surgery.

Surgery leads to postoperative inflammation, stress, and hypercoagulation [18,25–28]. We observed a significant increase in vWF activity after surgery in the overall patient population independent of the administered oxygen concentration. Supplemental oxygen is associated with increased inflammatory response, specifically in alveolar epithelium and in human cardiac myocytes [29,30]. Pure oxygen causes increased reactive oxygen stress leading to inflammation and ultimately to alveolar cell death [29]. In contrast to these findings, we observed that vWF activity was independent of the administered oxygen concentration. This is also true regarding oxidative stress. In a previous sub-analysis, we showed that the increase in oxidative stress did not differ significantly between the 80% and the 30% oxygen group [22]. Based on the current evidence, we are convinced that surgical trauma, anesthesia, fluid, and hemodynamic perturbations are the predominant factors for endothelial dysfunction rather than the administration of higher oxygen concentrations. To evaluate if oxidative stress might have affected vWF activity, we also performed a post hoc correlation. We found that postoperative oxidative stress correlates significantly with postoperative vWF activity. This further confirms that surgical trauma might be the most reasonable cause for increased oxidative stress and might therefore be the most important trigger factor for postoperative vascular damage represented by our increased vWF activity.

Nearly all of our patients underwent surgery for cancer. It is known that vWF activity is increased in cancer patients, which might explain the higher incidence of coagulopathies in these patients [31]. Moreover, even the type of cancer plays a significant role [32]. Specifically, patients with pancreatic cancer have a high risk of developing thromboembolic events [32]. This is consistent with our observations. We observed significantly higher vWF activity in patients with pancreatic cancer. Therefore, it seems reasonable that vWF activity might be an important contributor for coagulopathies, specifically in patients undergoing surgery for pancreatic cancer.

Peripheral artery disease is strongly associated with atherosclerosis, vascular damage, hypercoagulability, and an increased incidence of thromboembolic events [33]. We found significantly higher vWF and Ristocetin cofactor activity in patients with peripheral artery disease. A possible explanation might be that peripheral artery disease is associated with endothelial dysfunction, especially in the perioperative period, where endothelial dysfunction is caused by surgical trauma [34–36]. Since vWF is a potent clotting factor, it might very well be that vWF plays an important role in the postoperative pathogenesis of thromboembolic events.

Interestingly, in contrast to vWF activity, we observed significantly higher Ristocetin cofactor activity in hypertensive patients. It is known that hypertension is associated with

vascular injury [37] which might have resulted in higher Ristocetin cofactor activity due to vascular damage.

Plasma levels of vWF are approximately 25% higher in patients with blood type A, B, or AB as compared to blood type O [38]. While the molecular mechanisms for these differences have not been entirely clarified, it is of high clinical importance, as the risk of venous as well as arterial thromboembolic events is significantly higher in patients with blood type A, B, or AB [39,40]. Patients presenting with blood type AB are shown to have the highest rate of venous thrombotic events as compared to blood group O, followed by B and A [41]. Several other studies also linked the incidence of myocardial infarction (MI) and coronary artery disease (CAD) to the ABO blood type, where group O has the lowest risk for MI and CAD [42,43].

This study has some limitations. This was a pre-planned secondary analysis. The study was powered to detect the effect between 80% versus 30% perioperative oxygen concentration on postoperative maximum NT-proBNP concentration [19]. We only included patients undergoing major noncardiac cancer surgery. Therefore, we were not able to compare perioperative vWF activity between patients undergoing cancer versus non-cancer surgery, which might have helped to underline the high risk of postoperative thromboembolic events in patients having cancer surgery. Our rate of thromboembolic events was far too small to evaluate the association between postoperative vWF activity and the incidence of thromboembolic events. In fact, only four patients developed pulmonary embolism within 30 days after surgery. Therefore, the clinical impact of our results needs to be evaluated in a large observational study with adequate power to detect a higher number of postoperative thromboembolic events. Further it is well known that endothelial damage is associated with an increase in various biomarkers. In detail, endothelial damage leads to an increase in fibrinogen [44]. Additionally, excess endothelial stimulation in patients with peripheral artery disease is associated with D-Dimer and Thrombin-Antithrombin III levels [44]. Lastly, in our study, patients in the non-intervention group received a FiO_2 of 0.3, which is still higher than the physiological level of 0.21. Hafner et al. showed in an in vitro study that even slight increases in the oxygen concentration are associated with increases in VEGF secretion [30]. Therefore, it cannot be ruled out that oxygen might have affected vWF activity in our non-intervention group. However, the use of 21% oxygen during surgery is relatively uncommon; thus, 30% oxygen might better reflect current clinical practice.

5. Conclusions

In conclusion, we found no significant influence of supplemental oxygen in patients undergoing major non-cardiac surgery on postoperative vWF activity and Ristocetin cofactor activity.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12031222/s1, Table S1: Univariable regression model Ristocetin, Table S2: Multivariable regression model Ristocetin.

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Institutional Review Board Statement: The study was conducted at the Medical University of Vienna according to the Declaration of Helsinki and Good Clinical Practice. The study was approved by the local Institutional Review Board and was registered at ClinicalTrials.gov (Registration number: NCT 03388957; Principal Investigator: Prof. Dr. Edith Fleischmann; Date of registration: 2 December 2017) and at the European Trial Database (EudraCT 2017-003714-68). This study was

approved by the University's Ethics Committee (Ethikkomission Medizinische Universität Wien; Borschkegasse 8b/6, 1090, Vienna, Austria; EK-Number 1744/2017; Chairperson Prof. Martin Brunner) on 13 November 2017.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Heit, J.A. Epidemiology of venous thromboembolism. *Nat. Rev. Cardiol.* **2015**, *12*, 464–474. [CrossRef] [PubMed]
2. Stevens, J.L.; Feelisch, M.; Martin, D.S. Perioperative Oxidative Stress: The Unseen Enemy. *Anesth. Analg.* **2019**, *129*, 1749–1760. [CrossRef] [PubMed]
3. Williams, M.; Azcutia, V.; Newton, G.; Alcaide, P. Emerging mechanisms of neutrophil recruitment across endothelium. *Trends Immunol.* **2011**, *32*, 461–469. [CrossRef] [PubMed]
4. Ley, K.; Laudanna, C.; Cybulsky, M.I.; Nourshargh, S. Getting to the site of inflammation: The leukocyte adhesion cascade updated. *Nat. Rev. Immunol.* **2007**, *7*, 678–689. [CrossRef]
5. Randi, A.M.; Laffan, M.A. Von Willebrand factor and angiogenesis: Basic and applied issues. *J. Thromb. Haemost.* **2017**, *15*, 13–20. [CrossRef]
6. Kawecki, C.; Lenting, P.J.; Denis, C.V. von Willebrand factor and inflammation. *J. Thromb. Haemost.* **2017**, *15*, 1285–1294. [CrossRef]
7. Bierings, R.; Voorberg, J. Up or out: Polarity of VWF release. *Blood* **2016**, *128*. [CrossRef]
8. Ikeda, M.; Iwamoto, S.I.; Imamura, H.; Furukawa, H.; Kawasaki, T. Increased platelet aggregation and production of platelet-derived microparticles after surgery for upper gastrointestinal malignancy. *J. Surg. Res.* **2003**, *115*, 174–183. [CrossRef]
9. Marc Samama, C.; Thiry, D.; Elalamy, I.; Diaby, M.; Guillosson, J.J.; Kieffer, E.; Coriat, P. Perioperative activation of hemostasis in vascular surgery patients. *Anesthesiology* **2001**, *94*, 74–78. [CrossRef]
10. D'Amore, P.A.; Sweet, E. Effects of hyperoxia on microvascular cells in vitro. *Vitr. Cell. Dev. Biol.* **1987**, *23*, 123–128. [CrossRef]
11. Junod, A.F.; Jornot, L.; Petersen, H. Differential effects of hyperoxia and hydrogen peroxide on DNA damage, polyadenosine diphosphate-ribose polymerase activity, and nicotinamide adenine dinucleotide and adenosine triphosphate contents in cultured endothelial cells and fibroblasts. *J. Cell Physiol.* **1989**, *140*, 177–185. [CrossRef] [PubMed]
12. Singer, M.; Young, P.J.; Laffey, J.G.; Asfar, P.; Taccone, F.S.; Skrifvars, M.B.; Meyhoff, C.S.; Radermacher, P. Dangers of hyperoxia. *Crit. Care* **2021**, *25*, 440. [CrossRef]
13. Allegranzi, B.; Zayed, B.; Bischoff, P.; Kubilay, N.Z.; de Jonge, S.; de Vries, F.; Gomes, S.M.; Gans, S.; Wallert, E.D.; Wu, X.; et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: An evidence-based global perspective. *Lancet Infect. Dis.* **2016**, *16*, e288–e303. [CrossRef] [PubMed]
14. Kurz, A.; Kopyeva, T.; Suliman, I.; Podolyak, A.; You, J.; Lewis, B.; Vlah, C.; Khatib, R.; Keebler, A.; Reigert, R.; et al. Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. *Br. J. Anaesth.* **2018**, *120*, 117–126. [CrossRef]
15. Meyhoff, C.S.; Wetterslev, J.; Jorgensen, L.N.; Henneberg, S.W.; Høgdall, C.; Lundvall, L.; Svendsen, P.E.; Mollerup, H.; Lunn, T.H.; Simonsen, I.; et al. Effect of High Perioperative Oxygen Fraction on Sugical Site Infection and Pilmonary Complications After abdominal Surgery. *JAMA* **2009**, *302*, 1543–1550. [CrossRef]
16. Kabon, B.; Kurz, A. Optimal perioperative oxygen administration. *Curr. Opin. Anaesthesiol.* **2006**, *19*, 11–18. [CrossRef]
17. Reiterer, C.; Kabon, B.; von Sonnenburg, M.F.; Starlinger, P.; Taschner, A.; Zotti, O.; Goshin, J.; Drlicek, G.; Fleischmann, E. The effect of supplemental oxygen on perioperative brain natriuretic peptide concentration in cardiac risk patients—A protocol for a prospective randomized clinical trial. *Trials* **2020**, *21*, 400. [CrossRef] [PubMed]
18. Zheng, H.; Ma, H.P.; Chen, L.; Zhan, H.T.; Guo, H. Prethrombotic state and cardiac events in patients with coronary heart disease during noncardiac surgery. *Clin. Appl. Thromb. Hemost.* **2014**, *20*, 84–90. [CrossRef]
19. Reiterer, C.; Kabon, B.; Taschner, A.; von Sonnenburg, M.F.; Graf, A.; Adamowitsch, N.; Starlinger, P.; Goshin, J.; Fraunschiel, M.; Fleischmann, E. Perioperative supplemental oxygen and NT-proBNP concentrations after major abdominal surgery—A prospective randomized clinical trial. *J. Clin. Anesth.* **2021**, *73*, 110379. [CrossRef]
20. Taschner, A.; Kabon, B.; Falkner von Sonnenburg, M.; Graf, A.; Adamowitsch, N.; Fraunschiel, M.; Fleischmann, E.; Reiterer, C. Perioperative Supplemental Oxygen and Plasma Catecholamine Concentrations after Major Abdominal Surgery—Secondary Analysis of a Randomized Clinical Trial. *J. Clin. Med.* **2022**, *11*, 1767. [CrossRef]
21. Taschner, A.; Kabon, B.; Graf, A.; Adamowitsch, N.; Falkner von Sonnenburg, M.; Fraunschiel, M.; Horvath, K.; Fleischmann, E.; Reiterer, C. Perioperative Supplemental Oxygen and Postoperative Copeptin Concentration in Cardiac-Risk Patients Undergoing Major Abdominal Surgery—A Secondary analysis of a Randomized Clinical Trail. *J. Clin. Med.* **2022**, *11*, 2085. [CrossRef] [PubMed]
22. Reiterer, C.; Fleischmann, E.; Taschner, A.; Adamowitsch, N.; von Sonnenburg, M.F.; Graf, A.; Fraunschiel, M.; Starlinger, P.; Goschin, J.; Kabon, B. Perioperative supplemental oxygen and oxidative stress in patients undergoing moderate- to high-risk major abdominal surgery—A subanalysis of randomized clinical trial. *J. Clin. Anesth.* **2022**, *77*, 110614. [CrossRef] [PubMed]

23. Holse, C.; Aasvang, E.K.; Vester-Andersen, M.; Rasmussen, L.S.; Wetterslev, J.; Christensen, R.; Jorgensen, L.N.; Pedersen, S.S.; Loft, F.C.; Troensegaard, H.; et al. Hyperoxia and Antioxidants for Myocardial Injury in Noncardiac Surgery: A 2 × 2 Factorial, Blinded, Randomized Clinical Trial. *Anesthesiology* **2022**, *136*, 408–419. [CrossRef] [PubMed]
24. Jiang, Q.; Kurz, A.; Zhang, X.; Liu, L.; Yang, D.; Sessler, D.I. Supplemental Intraoperative Oxygen and Long-term Mortality: Subanalysis of a Multiple Crossover Cluster Trial. *Anesthesiology* **2021**, *134*, 709–721. [CrossRef]
25. Devereaux, P.J.; Goldman, L.; Cook, D.J.; Gilbert, K.; Leslie, K.; Guyatt, G.H. Perioperative cardiac events in patients undergoing noncardiac surgery: A review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. *Cmaj* **2005**, *173*, 627–634. [CrossRef]
26. Kalinin, R.E.; Suchkov, I.A.; Mzhavanadze, N.D.; Zhurina, O.N.; Klimentova, E.A.; Povarov, V.O. Coagulation factor activity and hemostatic markers of endothelial dysfunction in patients with peripheral arterial disease. *Vasc. Spec. Int.* **2021**, *37*, 26. [CrossRef]
27. Obradovic, M.; Kurz, A.; Kabon, B.; Roth, G.; Kimberger, O.; Zotti, O.; Bayoumi, A.; Reiterer, C.; Stift, A.; Fleischmann, E. The effect of intraoperative goal-directed crystalloid versus colloid administration on perioperative inflammatory markers- Asubstudy of a randomized controlled trial. *BMC Anesthesiol.* **2020**, *20*, 210. [CrossRef]
28. Noblett, S.E.; Snowden, C.P.; Shenton, B.K.; Horgan, A.F. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br. J. Surg.* **2006**, *93*, 1069–1076. [CrossRef]
29. Pagano, A.; Barazzone-Argiroffo, C. Alveolar Cell Death in Hypoeroxia-Induces Lung Injury. *Ann. N Y Acad. Sci.* **2003**, *1010*, 405–416. [CrossRef]
30. Hafner, C.; Wu, J.; Tiboldi, A.; Hess, M.; Mitulovic, G.; Kaun, C.; Krychtiuk, K.A.; Wojta, J.; Ullrich, R.; Tretter, E.V.; et al. Hyperoxia induces inflammation and cytotoxicity in human adult cardiac monocytes. *Shock* **2017**, *47*, 436–444. [CrossRef]
31. Patmore, S.; Dhami, S.P.S.; O'Sullivan, J.M. Von Willebrand factor and cancer; metastasis and coagulopathies. *J. Thromb. Haemost.* **2020**, *18*, 2444–2456. [CrossRef]
32. Wun, T.; White, R.H. Epidemiology of cancer-related venous thromboembolism. *Best Pract. Res. Clin. Haematol.* **2009**, *22*, 9–23. [CrossRef] [PubMed]
33. Narula, N.; Olin, J.W.; Narula, N. Pathologic Disparities between Peripheral Artery Disease and Coronary Artery Disease. *Arterioscler. Thromb. Vasc. Biol.* **2020**, *40*, 1982–1989. [CrossRef] [PubMed]
34. Makin, A.J.; Chung, N.A.Y.; Silverman, S.H.; Lip, G.Y.H. Alterations of thrombogenesis, endothelial damage and oxidative stress with reperfusion during femoral artery bypass surgery for peripheral vascular disease. *Pathophysiol. Haemost. Thromb.* **2002**, *32*, 158–164. [CrossRef] [PubMed]
35. Blann, A.D.; Seigneur, M.; Steiner, M.; Boisseau, M.R.; Mccollum, C.N. Circulating endothelial cell markers in peripheral vascular disease: Relationship to the location and extent of atherosclerotic disease. *Eur. J. Clin. Investig.* **1997**, *27*, 916–921. [CrossRef] [PubMed]
36. Heeschen, C.; Dimmeler, S.; Hamm, C.W.; van den Brand, M.J.; Boersma, E.; Zeiher, A.M.; Simoons, M.L. Soluble CD40 Ligand in Acute Coronary Syndromes. *N. Engl. J. Med.* **2003**, *348*, 1104–1111. [CrossRef]
37. Touyz, R.M. Molecular and cellular mechanisms in vascular injury in hypertension: Role of angiotensin II. *Curr. Opin. Nephrol. Hypertens.* **2005**, *14*, 125–131. [CrossRef]
38. Jenkins, P.V.; O'Donnell, J.S. ABO blood group determines plasma von Willebrand factor levels: A biologic function after all? *Transfusion* **2006**, *46*, 1836–1844. [CrossRef]
39. Ward, S.E.; O'Sullivan, J.M.; O'Donnell, J.S. The relationship between ABO blood group, von Willebrand factor, and primary hemostasis. *Blood* **2020**, *136*, 2864–2874. [CrossRef]
40. Jick, H.; Westerholm, B.; Vessey, M.; Lewis, G.; Slone, D.; Inman, W.W.; Shapiro, S.; Worcester, J. Venous thromboembolic disease and abo blood type. A cooperative study. *Obstet. Gynecol. Surv.* **1969**, *24*, 539–542. [CrossRef]
41. Wiggins, K.L.; Smith, N.L.; Glazer, N.L.; Rosendaal, F.R.; Heckbert, S.R.; Psaty, B.M.; Rice, K.M.; Lumley, T. ABO genotype and risk of thrombotic events and hemorrhagic stroke. *J. Thromb. Haemost.* **2009**, *7*, 263–269. [CrossRef] [PubMed]
42. Carpeggiani, C.; Coceani, M.; Landi, P.; Michelassi, C.; L'Abbate, A. ABO blood group alleles: A risk factor for coronary artery disease. An angiographic study. *Atherosclerosis* **2010**, *211*, 461–466. [CrossRef] [PubMed]
43. Sari, I.; Ozer, O.; Davutoglu, V.; Gorgulu, S.; Eren, M.; Aksoy, M. ABO blood group distribution and major cardiovascular risk factors in patients with acute myocardial infarction. *Blood Coagul. Fibrinolysis* **2008**, *19*, 231–234. [CrossRef] [PubMed]
44. Cassar, K.; Bachoo, P.; Ford, I.; Greaves, M.; Brittenden, J. Markers of coagulation activation, endothelial stimulation and inflammation in patients with peripheral arterial disease. *Eur. J. Vasc. Endovasc. Surg.* **2005**, *29*, 171–176. [CrossRef]

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Predictability of Radiologically Measured Psoas Muscle Area for Intraoperative Hypotension in Older Adult Patients Undergoing Femur Fracture Surgery

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Abstract: This retrospective study aimed to determine the predictive value of radiologically measured psoas muscle area (PMA) for intraoperative hypotension (IOH) using receiver operating characteristic (ROC) curves in older adult patients with hip fractures. The cross-sectional axial area of the psoas muscle was measured by CT at the level of the 4th lumbar vertebrae and normalized by body surface area (BSA). The modified frailty index (mFI) was used to assess frailty. IOH was defined as an absolute threshold of mean arterial blood pressure (MAP) < 65 mmHg or a relative decrease in MAP > 30% from baseline MAP. Among the 403 patients, 286 (71.7%) had developed IOH. PMA normalized by BSA in male patients was 6.90 ± 0.73 in the no-IOH group and 4.95 ± 1.20 in the IOH group ($p < 0.001$). PMA normalized by BSA in female patients was 5.18 ± 0.81 in the no-IOH group and 3.78 ± 0.75 in the IOH group ($p < 0.001$). The ROC curves showed that the area under the curve for PMA normalized by BSA and modified frailty index (mFI) were 0.94 for male patients, 0.91 for female patients, and 0.81 for mFI ($p < 0.001$). In multivariate logistic regression, low PMA normalized by BSA, high baseline systolic blood pressure, and old age were significant independent predictors of IOH (adjusted odds ratio: 3.86, 1.03, and 1.06, respectively). PMA measured by computed tomography showed an excellent predictive value for IOH. Low PMA was associated with developing IOH in older adult patients with hip fractures.

Keywords: frailty; sarcopenia; hip fracture; psoas muscle; older adult patients; hypotension

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1. Introduction

Hip fractures are one of the most important causes of disability in the aging population and lead to an increasing socioeconomic health burden [1]. Surgical outcomes of patients with hip fractures are associated with a high 3-month mortality rate (4.7–19.5 %) and physical morbidity [2–4]. Therefore, identifying the predisposing risk factors preoperatively is important to improve surgical outcomes. Preoperative assessment of frailty and sarcopenia, as a surrogate of frailty, have emerged as useful predictors of surgical mortality and morbidity in various surgical conditions in older adults [5–8].

Frailty is defined as a state of vulnerability to poor resolution of homeostasis, characterized by unintentional weight loss, self-reported exhaustion, muscle weakness, slow walking speed, and low physical activity [9]. Sarcopenia, a component of frailty, is defined as the progressive loss of muscle mass and muscle strength [10]. Several frailty assessment tools have been suggested to predict surgical outcomes [11–13]; however, there is no consensus on the measurement of frailty. Assessing frailty using frailty assessment

tools in patients with femur fractures is not always feasible because most have limited physical performance, and some are difficult to communicate with, such as those with neurocognitive or hearing disorders.

Recently, several studies have measured the cross-sectional area of the psoas muscle using computed tomography (CT) imaging as a validated method for quantifying sarcopenia [14–16]. Since pelvic bone CT was performed as a standard diagnostic work-up before surgery, the psoas muscle area (PMA) could be a useful candidate for preoperative risk evaluation along with frailty assessment tools.

Intraoperative hypotension (IOH) is associated with mortality and adverse postoperative outcomes, such as acute kidney injury [17], myocardial injury [18], and stroke [19]. IOH is associated with postoperative outcomes and frequently occurs in frail patients; they typically have a higher sympathetic drive and reduced baroreflex sensitivity, which leads to IOH [20,21]. The association between low PMA and adverse surgical outcomes in older adult patients with hip fractures has been described [5]. To the best of our knowledge, no study has demonstrated the association between sarcopenia, presented as low PMA, and IOH development. Therefore, we hypothesized that CT-measured PMA could predict IOH in older adult patients undergoing hip fracture surgery.

2. Materials and Methods

2.1. Study Design and Patients

This retrospective study was approved by the Institutional Review Board of Ewha Woman's University Hospital (IRB no. 2022-04-039), and the requirement for written informed consent was waived. The data were collected from electronic medical records (EMR) of older adult patients (aged > 65 years) who underwent hip fracture surgery, such as arthroplasty and osteosynthesis, from January 2020 to December 2021 at two hospitals of Ewha Woman's University (Seoul and Mokdong Hospital). The surgical procedure for hip fractures was performed by an orthopedic surgeon at each institution in the same medical school. Patients who underwent surgery under spinal and combined spinal epidural anesthesia, multiple fracture surgery, or had previous hip surgery in whom the cross-sectional area of the psoas could not be obtained using CT images because of artifacts from devices (e.g., metallic hip or spine prostheses), and those with incomplete or follow-up loss data were excluded. Of the 649 patients, 246 were excluded based on these criteria, and 403 were included (Figure 1).

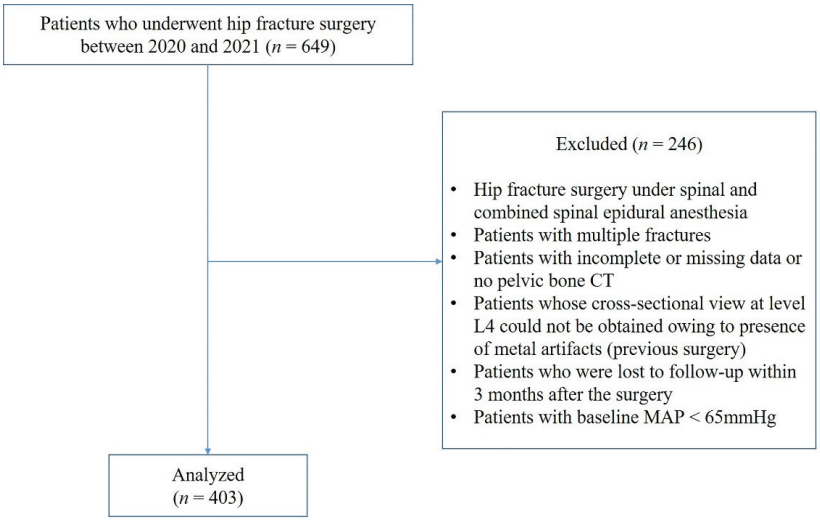

Figure 1. Study flow chart.

2.2. Measurement of Psoas Muscle Area

The cross-sectional axial area (cm^2) of the bilateral psoas muscle at the level of the fourth lumbar vertebra (L4) was assessed from the axial slice image of pelvic bone CT using picture archiving and communication systems (PACS) (Maroview 5.4, Infinitt, Seoul, Republic of Korea), as described previously [5,22]. Pelvic bone CT was performed as part of the patient's routine diagnostic work-up, as ordered by the surgeon at our institution. Bilateral PMAs that were outlined manually at the L4 pedicle level by the freehand region of interest (ROI) program in PACS (Figure 2) were averaged and divided by the body surface area (BSA) for normalization according to Canales et al. [14]. The PMAs from the axial CT image were measured by two anesthesiologists retrospectively: one (Y.Y.L.) measured all images, and the other who was blinded to the outcomes (I.Y.) measured randomly selected 50 images. The inter-class correlation coefficient (ICC) was used to measure inter-observer agreement. The PMA value normalized by BSA was divided into five groups. The highest quintile ($\geq$5.48) was considered as a reference to examine factors associated with developing IOH and 3-month unfavorable outcomes using logistic regression analysis.

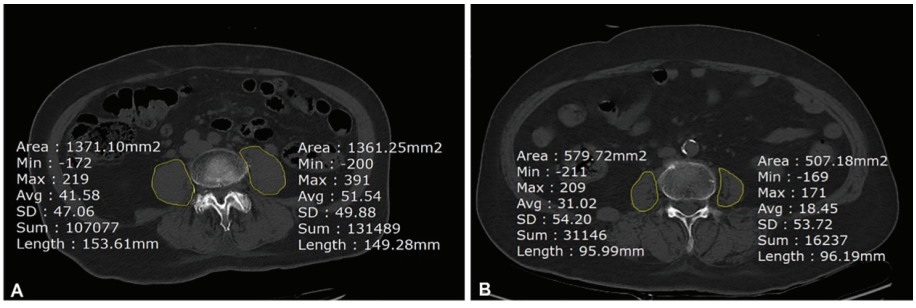

Figure 2. Cross-sectional images of the psoas muscle in pelvic bone CT. Cross-sectional image from the pedicle level of L4 axial view of pelvic bone CT. Right and left psoas muscle areas are measured using free ROI and averaged. Cross-sectional image of psoas muscle for (**A**) measured PMA of the patients in the 5th quintile group and (**B**) measured PMA of the patients in the 1st quintile group. CT, computed tomography; ROI, region of interest; PMA, psoas muscle area; BSA, body surface area.

2.3. Assessment of Frailty and Intraoperative Hypotension

All patients were assessed for frailty using the modified frailty index (mFI) based on EMRs. The mFI originated from the frailty index of the Canadian Study of Health and Aging Frailty Index [11] by matching 70 variables to 11 categories of comorbidities and deficits. Factors of mFI were obtained from the patient's medical history, which consisted of 11 deficit variables (Table S1) calculated by summation of variables and divided by 11. We categorized the patients into two groups: the non-frail (including pre-frail) ($0 \leq$ mFI < 0.27) and frail groups (mFI ≥ 0.27) based on previous studies [23]. In the logistic regression analysis for predicting IOH and 3-month unfavorable outcomes, we used mFI categorical groups by dividing 11 groups based on the mFI score (0 to 1).

The baseline blood pressure was defined as the first value of non-invasive blood pressure (systolic, diastolic, and mean blood pressure) after entering the operating room in the supine position. Radial artery cannulation was conducted under sedation before or right after induction, which was electronically recorded every five minutes (up to 1 min intervals in case of describing in detail) using BESTcare 2.0 (ezCaretech, Seoul, Republic of Korea) program. In some cases in which attending anesthesiologists wanted to describe the hypotensive blood pressure in detail, it was recorded up to 1 min intervals. If the patients showed 30% higher baseline blood pressure than the average blood pressure during the hospitalization period, we allowed the blood pressure to be lowered after premedication with sedatives according to our institutions' routine. In this case, blood pressure before the induction was considered baseline blood pressure. We defined IOH as the absolute

threshold of mean arterial blood pressure (MAP) < 65 mmHg or a relative decrease in MAP > 30% from the baseline, which lasted for at least 1 min [18,24]. For regression analysis, the incidence of IOH was analyzed dichotomously. Data on managing IOH, such as the presence of vasopressors (ephedrine, phenylephrine bolus, or norepinephrine infusion), were also collected from anesthetic charts. Perioperative management was conducted using a standardized hip fracture anesthesia protocol in two hospitals in the same branch of medical school. In all patients, general anesthesia was induced using propofol (1–1.5 mg/kg) and fentanyl (1 μg/kg) and was maintained by inhalation agents (sevoflurane or desflurane). Our standardized protocol included maintenance of normovolemia during anesthesia and management of systolic blood pressure within 20% of the baseline by fluid and/or vasopressors [25]. The transfusion target was hemoglobin 8 g/dL for most of the patients, excluding the patients who needed higher targets (hemoglobin $\geq$ 10 g/dL) for transfusion [26].

2.4. Data Collection

Demographics, medical history, and perioperative laboratory findings were obtained from the EMRs at two institutions: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, and comorbidities. It also included variables such as diabetes mellitus (controlled by diet alone or treated with oral antihyperglycemic therapy or insulin), hypertension (HTN) on medication, type of hypertensive medication, cerebrovascular disease (CVA), transient ischemic accident (TIA), heart diseases (arrhythmia, congestive heart failure, ischemic heart disease, previous myocardial infarction within 6 months, or coronary intervention/bypass graft at any time), pulmonary diseases (pneumonia or chronic obstructive pulmonary disease exacerbation within 30 days), peripheral vascular disease, and cognitive impairment, which were used to calculate mFI. The following preoperative laboratory findings were collected: hemoglobin, platelets, white blood cells, serum albumin, C-reactive protein, blood urea nitrogen, and serum creatinine. Intraoperative variables were collected from the EMRs, including baseline and lowest blood pressure (non-invasive and invasive), presence of IOH, operation type, anesthesia time, operation time, input (intraoperative crystalloid and colloid infusions or blood transfusion) estimated blood loss, and presence of vasopressors. Postoperative data were collected: intensive care unit (ICU) admission, length of hospital stay, presence of postoperative delirium, postoperative deep vein thrombosis, postoperative pneumonia, and CVA during hospitalization. Rehospitalization (including admission to a nursing hospital), death, or falls within 3 months after surgery were regarded as 3-month adverse outcomes using logistic regression analysis [27].

2.5. Study Outcomes

The primary outcome was the predictive value of PMA normalized by BSA for IOH during hip fracture surgery in older adult patients using receiver operating characteristic (ROC) curves. The secondary outcomes were the predictability of IOH by frailty using the mFI score and the association between PMA and frailty measured by the mFI score. Moreover, we analyzed the predictors of developing IOH and the 3-month unfavorable outcomes in older adult patients undergoing hip fracture surgery.

2.6. Statistical Analysis

Continuous variables were analyzed using an independent *t*-test or Mann–Whitney U test after assessment for normality using the Shapiro–Wilk test and are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, whereas categorical variables were analyzed using χ^2 tests or Fisher's exact tests (if > 20% of the expected frequencies were < 5) and were presented as percentages. The ICC with a 95% confidence interval (CI) was calculated by two researchers to determine the reliability of the PMA measurements. ROC curve analysis was used to identify the predictability of PMA normalized by BSA in male and female patients (primary outcome), and frailty measured by the mFI score was used to discriminate with or without IOH groups (secondary outcome).

The data were presented as the area under the curve (AUC) with 95% CI. We suggested cut-offs of PMA normalized by BSA for IOH and frailty by sex using Youden's index and by respective sensitivity and specificity. The Hosmer–Lemeshow goodness-of-fit test and AUC were used to assess the model fit. The association between frailty and PMA normalized by BSA, the factors associated with developing IOH, and 3-month unfavorable outcomes were analyzed using a binary logistic regression model (secondary outcome). Confounding factors, including age, sex, albumin level, and ASA classification (<III or ≥III), were identified from previous studies [28]. Additionally, significant variables, including 11 variables in mFI, were assessed by comparing patients with and without IOH. We also conducted inversed probability of treatment weighting (IPTW) to adjust for confounding factors [29]. Covariates which showed a significant difference in Table 1 were used for calculating propensity scores. Multivariate logistic regression was used to analyze the predictive factors for IOH and 3-month unfavorable outcomes using the backward selection method. In this process, sex and age were considered, and major factors were selected after checking for multicollinearity. The data were presented as area odds ratios (ORs) with 95% CI. Statistical analyses were performed using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA), MedCalc Statistical Software Version 20.1.4 2020 (MedCalc Software Bvba, Ostend), and International Business Machine Statistical Package for the Social Sciences Statistics (version 22.0; IBM Corp., Armonk, NY, USA). Statistical significance was assumed at $p < 0.05$, and two-tailed p-values were used.

Table 1. Demographic and baseline characteristics of participants.

Demographics	All Patients (n = 403)	No-IOH (n = 117)	IOH (n = 286)	p-Value
Age, year	81.34 ± 8.60	78.62 ± 8.43	82.46 ± 8.45	**0.001**
Sex, female	305 (75.7)	81 (69.1)	224 (78.3)	**0.053**
BMI, kg/m^2	22.15 ± 3.76	21.62 ± 2.89	21.77 ± 3.35	0.997
ASA status				0.372
<III	145 (36)	46 (39.3)	99 (34.6)	
≥III	258 (64)	71 (60.7)	187 (65.4)	
Chronic arterial hypertension	316 (78.4)	85 (26.9)	231 (73.1)	**<0.001**
No medication	5 (1.6)	1 (1.2)	4 (1.6)	
ARB	41 (12.9)	9 (10.6)	32 (13.9)	
Ca^{+2} antagonist	127 (39.8)	35 (41.2)	92 (39.8)	
β-Blocker	16 (5.0)	2 (2.3)	14 (6.1)	
ACE inhibitor	2 (0.6)	0 (0)	2 (0.9)	
Diuretics	6 (1.9)	1 (1.2)	5 (2.2)	
Combined drugs	117 (38.2)	37 (43.5)	82 (35.5)	
DM	142 (35.2)	40 (34.2)	102 (35.6)	0.196
Surgical category				0.726
Open reduction internal fixation	186 (46.2)	54 (46.2)	132 (46.2)	
Closed reduction internal fixation	18 (4.5)	4 (3.4)	14 (4.9)	
Bipolar hemiarthroplasty	123 (30.5)	32 (27.4)	91 (31.8)	
Total hip replacement	76 (18.8)	27 (23)	49 (17.1)	
Emergency surgery	72 (17.9)	14 (12)	58 (20.3)	**0.048**

Table 1. *Cont.*

Demographics	All Patients (n = 403)	No-IOH (n = 117)	IOH (n = 286)	p-Value
Preoperative data				
Hemoglobin, g/dL	11.53 ± 7.08	11.41 ± 1.90	10.92 ± 1.95	0.113
Platelet, 10^9/L	209.84 ± 80.76	212.35 ± 82.06	208.74 ± 80.34	0.719
WBC, 10^3/uL	8.90 ±3.21	8.91 ±2.97	8.90 ±3.32	0.992
Albumin, g/dL	3.67 ± 0.28	3.67 ± 0.28	3.67 ± 0.28	0.243
CRP, mg/dL	2.50 ± 3.00	2.50 ± 3.00	2.50 ± 3.00	0.361
BUN, mg/dL	22.29 ± 7.09	22.29 ± 7.09	22.29 ± 7.09	0.596
Creatinine, mg/dL	0.85 ±0.51	0.86 ±0.48	0.84 ±0.52	0.705
Intraoperative data				
Baseline SBP	149.86 ± 21.16	141.46 ± 20.13	153.45 ± 20.61	**<0.001**
Baseline DBP	82.16 ± 14.78	79.85 ± 12.71	83.15 ± 15.51	0.068
Baseline MBP	104.40 ± 15.15	102.39 ± 12.79	106.11 ± 15.77	0.052
Lowest SBP	92.20 ± 13.90	99.18 ± 14.38	89.21 ± 12.59	**<0.001**
Lowest DBP	50.96 ± 10.15	57.12 ± 10.51	48.33 ± 8.79	**<0.001**
Lowest MBP	64.50 ± 10.32	71.14 ± 10.10	61.68 ± 9.05	**<0.001**
Input, mL, (IQR)	801.01 (762.40, 839.62)	792.66 (748.56, 836.76)	820.22 (741.90, 898.55)	**0.035**
Estimated blood loss, mL, (IQR)	227.83 (209.69, 245.96)	243.17 (204.07, 282.26)	221.16 (201.28, 241.04)	0.903
Anesthesia time, min	114.03 ± 29.61	107.24 ± 26.41	114.03 ± 27.30	0.612
Operation time, min	60.21 ± 24.81	57.44 ± 22.17	58.94 ± 22.81	0.649

Values are expressed as means ± standard deviations, medians (interquartile ranges, IQR), or absolute numbers (percentages). BMI, body mass index; ASA, American Society of Anesthesiologists; DM, diabetes mellitus; HTN, hypertension; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; DM, diabetes mellitus; WBC, white blood cell; CRP, C-reactive protein; BUN, blood urine nitrogen; Cr, creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. p-value < 0.05 are in bold.

3. Results

As presented in Table 1, 403 patients were analyzed, of which 286 (71.7%) had developed IOH. The patients had a mean age of 81.34 ± 8.60 years, and 64% (n = 258) of the patients had ASA ≥ III. The population underwent hip surgery, including open reduction internal fixation, hip (n = 186; 46.2%), bipolar hemiarthroplasty (n = 123; 30.5%), and total hip replacement (n = 76; 18.8%). The emergency surgery portion in the IOH group was 20.3%, which was higher than that of 12% in the no-IOH group (p = 0.048). The number of patients with chronic HTN was higher in the IOH group than that in the non-IOH group (231 [73.1%] vs. 85 [26.9%]; p < 0.001). Most patients were on medication, and the largest percentage of the combined drugs were angiotensin-converting enzyme inhibitors (angiotensin receptor blockers) and β-blockers. The baseline systolic blood pressure was higher in the IOH group (153.45 ± 20.61 vs. 141.46 ± 20.13; p < 0.001). Patients in the IOH group were supplemented with a higher intravenous volume to manage hypotension (p = 0.035). Preoperative laboratory findings were not significantly different between the groups.

Frailty and postoperative outcomes are presented in Table 2. PMA normalized by BSA in male patients was 6.90 ± 0.73 in the no-IOH group and 4.95 ± 1.20 in the IOH group (p < 0.001). PMA normalized by BSA in female patients was 5.18 ± 0.81 in the no-IOH group and 3.78 ± 0.75 in the IOH group (p < 0.001). The ICC between the two researchers for measuring PMA was excellent: 0.977 (95% CI, 0.95–0.99; p < 0.001), and measuring PMA from CT images took only less than 1 min. mFI score was significantly higher in the IOH group (0.34 ± 0.15) than that in the no-IOH group (0.17 ± 0.14) (p < 0.001). Frail patients were more included in the IOH group (n = 263; 92.3%) than in the no-IOH group (n = 14; 12%) (p < 0.001). The association between the five categorical groups of PMA normalized by BSA and frailty measured by mFI score was analyzed using logistic regression; OR was 2.735 (95% CI, 2.20–3.40; p < 0.001).

Table 2. Patients' frailty assessment and postoperative 3-month outcomes before and after IPTW.

	All Patients (n = 403)	No-IOH (n = 117)	IOH (n = 286)	p-Value
PMA				
Male	9.35 ± 2.75	11.55 ±3.01	8.20 ±2.48	**<0.001**
Female	6.20 ± 1.64	7.81 ±1.65	5.68 ±1.63	**<0.001**
PMA normalized by BSA				
Male	5.63 ± 1.48	6.90 ± 0.73	4.95 ± 1.20	**<0.001**
Female	4.13 ±1.03	5.18 ± 0.81	3.78 ± 0.75	**<0.001**
mFI score	0.29 ± 0.17	0.17 ± 0.14	0.34 ±0.15	**<0.001**
Not-frail (mFI < 0.27)	125 (31)	103 (88)	23 (7.7)	**<0.001**
Frail (mFI ≥ 0.27)	278 (69)	14 (12)	263 (92.3)	**<0.001**

	Before IPTW adjustment			p-value	After IPTW adjustment		p-Value
	All patients (n = 403)	No-IOH (n = 117)	IOH (n = 286)		No-IOH (n = 394)	IOH (n = 377)	
ICU admission	117 (29)	17 (14.5)	100 (35)	**<0.001**	57 (14.5)	125 (33.2)	**<0.001**
Hospital length of stay, days	14.13 ± 10.13	11.96 ± 6.08	15.02 ±10.00	**0.006**	12.46 ± 6.36	14.60 ± 11.63	**0.002**
Delirium	138 (34.3)	34 (29.3)	104 (36.4)	0.177			
DVT	119 (29.9)	31 (27.2)	88 (31)	0.455			
pneumonia	50 (12.4)	10 (20)	40 (14)	0.140			
CVA	14 (3.5)	1 (0.9)	13 (4.5)	0.068			
3-month outcomes	113 (28.0)	12 (10.2)	101 (35.3)	**<0.001**	62 (15.6)	140 (37.1)	**<0.001**
Rehospitalization	86 (21.3)	10 (25.6)	76 (27.2)	**0.001**	51 (13)	109 (28.9)	**<0.001**
Death	10 (2.5)	0	10 (3.5)	**0.046**	4 (1.0)	12 (3.3)	**0.030**
Falls	17 (4.2)	2 (1.7)	15 (5.4)	0.099			

Values are expressed as means ± standard deviations, medians, or absolute numbers (percentages). IPTW, inverse probability if treatment weighting; mFI, modified frailty index; PMA, psoas muscle area; BSA, body surface area; ICU, intensive care unit, DVT, deep vein thrombosis; CVA, cerebrovascular disease. p-value <0.05 are in bold.

Patients in the IOH group showed a higher rate of ICU admission (35%; n = 100) than those in the no-IOH group (14.5%; n = 17; $p < 0.001$). After being weighted by estimated propensity scores, 125 patients (33.2%) in IOH group and 57 patients (14.5%) in no-IOH group showed a rate of ICU admission ($p < 0.001$). Longer duration of hospital stay was higher in the IOH group (15.02 ± 10.00 days) than that in the no-IOH group (11.96 ± 6.08 days; $p = 0.006$). After being weighted by estimated propensity scores, the duration of hospital stay was significantly longer in the IOH group (14.60 ± 11.63 vs. 12.46 ± 6.36 days; $p = 0.002$). The rates of 3-month adverse outcomes were significantly higher by 35.3% (n = 101) in the IOH group than that in the no-IOH group by 10.2% (n = 12) ($p < 0.001$). After being weighted by estimated propensity scores, the rates of 3-month adverse outcomes were 37.1% (n = 140) in the IOH group and 15.6% (n = 62) in the no-IOH group ($p < 0.001$).

The ROC curves (Figure 3) show that the AUC for PMA normalized by BSA and mFI were 0.94 for male patients (95% CI, 0.87–0.96; $p < 0.001$), 0.91 for female patients (95% CI, 0.87–0.96; $p < 0.001$), and 0.81 for mFI (95% CI, 0.77–0.85; $p < 0.001$). The optimal cut-off values of PMA normalized by BSA for predicting IOH were 6.17 (87.8% sensitivity and 92.9% specificity) and 4.50 (89.0% sensitivity and 88.1% specificity) for male and female patients, respectively.

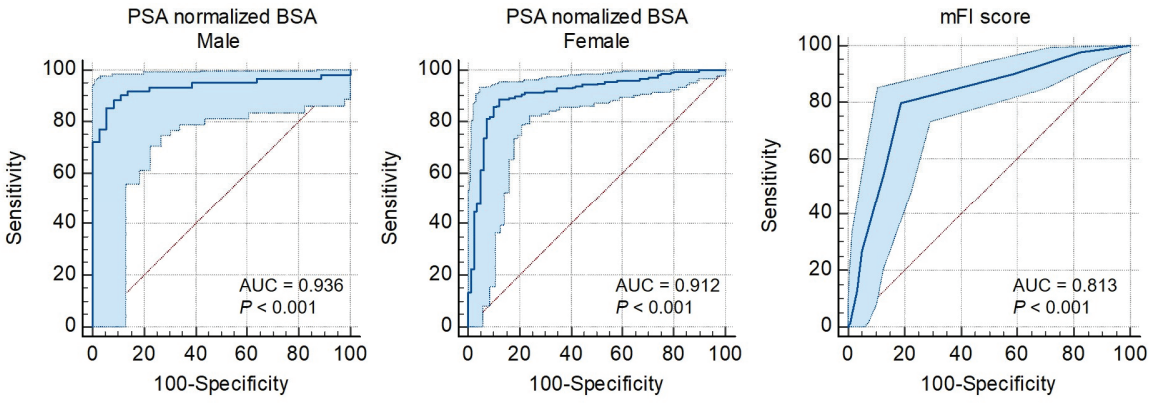

Figure 3. Receiver-operating characteristic curves for discriminating intraoperative hypotension ROC curve for predicting IOH using (**A**) PSA normalized by BSA in male patients, (**B**) PSA normalized by BSA in female patients, and (**C**) mFI score. ROC; receiver operating characteristic AUC; area under the curve; IOH, intraoperative hypotension; PMA, psoas muscle area; BSA, body surface area; mFI, modified frailty index.

The factors associated with IOH are presented in Table 3. Univariate analysis showed that old age, low albumin, hemoglobin levels, high baseline systolic blood pressure, low PMA normalized by BSA, and a greater number of mFI variables were significantly associated with IOH. The highest OR was found in patients with a low PMA normalized by BSA (OR 3.85; 95% CI, 2.92–5.07; $p < 0.001$), followed by the number of mFI variables (OR 2.07; 95% CI, 1.71–2.52; $p < 0.001$). Among the mFI variables, a history of CHF, HTN, TIA, CVA with sequelae, pulmonary diseases, cardiac intervention, and patients' dependent functional status were significantly associated with IOH. Multivariate logistic regression revealed that low PMA (OR 3.86; 95% CI, 2.82–5.29; $p < 0.001$) normalized by BSA, high baseline systolic blood pressure (OR 1.03; 95% CI, 1.01–1.05; $p = 0.001$), and old age (OR 1.06; 95% CI, 1.02–1.10; $p = 0.003$) were significant independent predictors of IOH, whereas the number of mFI variables was not a significant independent predictor of IOH ($p = 0.870$).

Table 3. Unadjusted and adjusted odds ratios for predicting IOH by binary logistic regression.

Variables	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	***p*-Value**	**Odds Ratio (95% CI)**	***p*-Value**
Age (for 1 year increase)	1.047 (1.02, 1.08)	**0.002**	1.06 (1.02, 1.10)	0.003
Sex (female)	1.45 (0.84, 2.49)	0.182	1.23 (0.58, 2.60)	0.580
ASA <III vs. ≥III	1.25 (0.79, 1.90)	0.372	0.68 (0.33, 1.42)	0.305
Emergency	1.02 (0.55, 1.88)	0.945	—	—
Albumin	0.49 (0.30, 0.82)	**0.007**	0.76 (0.40, 1.45)	0.400
Hemoglobin	0.83 (0.72, 0.94)	**0.004**	1.08 (0.87, 1.33)	0.512
Baseline SBP	1.03 (1.02, 1.04)	**<0.001**	1.03 (1.01, 1.05)	**0.001**

Table 3. *Cont.*

Variables	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	***p*-Value**	**Odds Ratio (95% CI)**	***p*-Value**
PMA normalized by BSA (Reference: 5th quintile)	3.85 (2.92, 5.07)	**<0.001**	3.86 (2.82, 5.29)	**<0.001**
mFI variables (categorical)	2.07 (1.71, 2.52)	**<0.001**	1.01 (0.85, 1.21)	0.870
DM	2.39 (1.39, 4.13)	0.502	—	—
CHF	2.97 (1.55, 5.68)	**0.001**	—	—
HTN	3.00 (1.75, 5.13)	**<0.001**	—	—
TIA or CVA	4.25 (2.27, 7.95)	**<0.001**	—	—
Dependent functional status	8.67 (4.99, 15.04)	**<0.001**	—	—
MI	3.61 (0.81, 16.03)	0.091	—	—
Peripheral disease	2.23 (0.89, 5.56)	0.086	—	—
CVA with sequelae	2.79 (1.26, 6.18)	**0.011**	—	—
Pulmonary disease	3.58 (1.63, 7.86)	**0.001**	—	—
Cardiac intervention or angina	3.60 (1.37, 9.47)	**0.009**	—	—
Impaired sensory	1.13 (0.52, 2.44)	0.761	—	—

CI, confidence interval; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; mFI, modified frailty index; PMA, psoas muscle area; BSA, body surface area; mFI, modified frailty index; DM, diabetes mellitus; CHF, congestive heart failure; HTN, hypertension; TIA, transient ischemic attack; CVA, cerebrovascular disease; MI, myocardial infarction.

As presented in Table 4, female sex, ASA classification (<III vs. ≥III), low albumin and hemoglobin levels, presence of IOH, low PMA normalized by BSA, a greater number of categorical mFI variables, and history of TIA were significantly shown to be associated with 3-month adverse outcomes using univariate logistic regression analysis. The results of multivariate logistic regression showed the highest OR for low PMA normalized by BSA (OR 1.62; 95% CI, 1.37–1.91; $p < 0.001$). In addition, old age (OR 1.08; 95% CI, 1.04–1.12; $p < 0.001$) and low albumin levels (OR 0.44; 95% CI, 0.23–0.85; $p = 0.014$) were significantly associated with 3-month unfavorable outcomes, whereas presence of IOH was not a significant independent predictor of 3-month unfavorable outcomes after adjusting for confounders ($p = 0.478$).

Table 4. Unadjusted and adjusted odds ratios for predicting 3-month unfavorable outcomes by binary logistic regression.

Variables	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	***p*-Value**	**Odds Ratio (95% CI)**	***p*-Value**
Age (for 1 year increase)	1.24 (0.6, 2.57)	0.560	1.08 (1.04, 1.12)	**<0.001**
Sex (female)	1.04 (1.00, 1.08)	**0.045**	1.29 (0.58, 2.89)	0.537

Table 4. *Cont.*

Variables	Unadjusted Analysis		Adjusted Analysis	
	Odds Ratio (95% CI)	*p*-Value	Odds Ratio (95% CI)	*p*-Value
ASA <III vs. ≥III	3.19 (1.57, 6.47)	**0.001**	1.30 (0.62, 2.72)	0.482
Emergency	0.61 (0.29, 1.27)	0.185	—	—
Albumin	0.40 (0.22, 0.74)	**0.004**	0.44 (0.23, 0.85)	**0.014**
Hemoglobin	0.79 (0.66, 0.92)	**0.003**	0.93 (0.82, 1.07)	0.300
Baseline SBP	1.02 (1.00, 1.04)	0.057	—	—
IOH	3.00 (1.38, 6.51)	**0.005**	1.42 (0.54, 3.74)	0.478
PMA normalized by BSA (Reference: 5th quintile)	1.44 (1.19, 1.76)	**<0.001**	1.62 (1.37, 1.91)	**<0.001**
mFI score (categorical)	2.38 (1.12, 5.07)	**0.025**	0.95 (0.76, 1.19)	0.658
DM	1.31 (0.78, 2.19)	0.302	—	—
CHF	1.25 (0.72, 2.17)	0.433	—	—
HTN	1.57 (0.87, 2.82)	0.134	—	—
TIA or CVA	2.60 (1.51, 4.47)	**0.001**	—	—
Dependent functional status	1.29 (0.75, 2.22)	0.359	—	—
MI	1.85 (0.64, 5.49)	0.267	—	—
Peripheral disease	0.93 (0.42, 2.04)	0.853	—	—
CVA with sequelae	1.78 (0.92, 3.45)	0.088	—	—
Pulmonary disease	1.18 (0.64, 2.18)	0.591	—	—
Cardiac intervention or angina	1.36 (0.68, 2.73)	0.390	—	—
Impaired sensory	1.20 (0.54, 2.70)	0.655	—	—

CI, confidence interval; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; IOH, intraoperative hypotension; PMA, psoas muscle area; BSA, body surface area; mFI, modified frailty index; DM, diabetes mellitus; CHF, congestive heart failure; HTN, hypertension; TIA, transient ischemic attack; CVA, cerebrovascular disease; MI, myocardial infarction. *p*-values < 0.05 are in bold.

4. Discussion

In this retrospective study, 71.7% of patients experienced hypotensive events during femur fracture surgery. The patients in the IOH group had a lower PMA normalized by BSA than those in the no-IOH group, both in male and female patients. The present study demonstrated that preoperative PMA measured by CT showed an excellent AUC value for predicting IOH in older adult patients undergoing femur fracture surgery. Our results suggest that PMA obtained from pre-existing CT could be used as a simple and feasible method for predicting IOH in older adult patients with hip fractures who are unable to access frailty. It was also significantly associated with 3-month unfavorable outcomes.

Several previous studies have shown that radiologically assessed PMA, as a surrogate of sarcopenia, was related to surgical mortality in various surgical settings, such as tran-

scatheter aortic valve implantation [6], abdominal [7], and femur fracture surgery [5,22]. Based on these results, we considered the underlying relationship between surgical mortality and low PMA. Frail patients have reduced baroreflex sensitivity and vagal function, which may predispose them to IOH [21]. Soysal et al. [30] showed the relationship between the severity of sarcopenia and orthostatic hypotension accompanied by decreased function of their cardiovascular function to maintain blood pressure. Hence, in this context, we hypothesized that CT-measured PMA is not only associated with adverse surgical outcomes but could also be related to IOH in older adult patients undergoing hip fracture surgery.

PMA normalization is necessary to consider its clinical use because it differs according to race, sex, and age. Several PMA normalization methods have been used, such as the psoas: L4 vertebrae index [5,6], which is normalized by BMI, BSA [12], and height [7]. Some studies using CT-measured PMA used height^2 for adjustment; the present study utilized BSA, according to Canales et al. [14]. They demonstrated that the AUC value of PMA (cm^2) normalized by BSA (m^2) was 0.95 (95% CI, 0.89–1.00) for discriminating frailty measured by Fried phenotype frailty assessments, which is higher than that of the BMI 0.80 (95% CI, 0.65–0.95). Similarly, our study showed excellent AUC values using PMA normalized by BSA to discriminate IOH preoperatively in male (0.94 (95% CI, 0.87–0.96; $p < 0.001$)) and female patients (0.91 (95% CI, 0.87–0.96; $p < 0.001$)).

The American College of Surgeons and the American Geriatrics Society recommend routine preoperative evaluation of frailty for all patients aged > 65 years [31]. Beggs et al. [32] reported that adverse surgical outcomes increased two to three-fold in frail patients, regardless of the type of surgery and frailty assessment tools. However, it is difficult to use preoperative frailty assessment clinically because its questionnaire-based method is limited in its application for patients with femur fractures who have restricted physical conditions or inability to provide a medical history owing to altered mental status. Furthermore, no consensus tools or time-consuming measuring procedures have contributed to the restrictions on its routine use. PMA can be readily obtained from axial images of pelvic bone CT preoperatively, and it could be a feasible tool for patients with hip fractures to optimize perioperative risk assessment.

In the present study, we found that PSA normalized by BSA was superior to mFI score in predicting IOH. Measuring PMA from CT images before surgery could be a faster and more simple method than mFI for assessing the risks of IOH. Predicting IOH could improve individual anesthetic management, in terms of preparing for hypotensive situations: meticulous titration of anesthetic agents, preparation of additional peripheral intravenous lines, vasopressors, sufficient pre-induction fluid supplement, and continuous arterial blood pressure monitoring to prevent hypotensive events during the surgery. As a surrogate of frailty before surgery, measuring PMA from CT images took < 1 min and showed a relatively excellent ICC, suggesting it to be an individual prognostic tool for developing IOH.

Predicting IOH is difficult because there are distinct entities of hypotension depending on the phase of anesthesia, including vasodilation by induction agents, massive bleeding, greater anesthesia depth, patient's hypovolemic state, and preoperative use of antihypertensive medications (angiotensin-II receptor blockers and angiotensin-converting enzymes). From our retrospective data, we found that low PMA, advanced old age, and high baseline systolic blood pressure were associated with the development of IOH, of which most IOH events occurred at three-time points: post-induction period, position-changing period supine to lateral or vice-versa, and before-emergence period. Consistent with our study, Sudfeld et al. [28] defined post-induction period hypotension in which the time within 20 min after induction was most prevalent and critical for anesthesiologists since surgical factors can be ruled out at this point. They suggested factors associated with post-induction and early IOH, including emergency surgery, low pre-induction systolic arterial pressure, and advanced age. Consistent with this study, we found that older patients were likely to have more IOH episodes and that more frail patients were included in the IOH group than that in the no-IOH group. Old age is associated with frailty, which leads to IOH. In

contrast, emergency surgery, low pre-induction systolic arterial pressure, ASA class IV, and male sex were not associated with IOH development in our study population. This discrepancy may be attributed to the different populations of the study and the definition of IOH. Regarding the population with hip fractures, older women were more prone to falls than older men [33]. The patients had higher baseline blood pressure owing to pain caused when they were transferred to the operating bed. Moreover, Sudfeld et al. considered IOH only within the post-induction period and early 30 min after the start of surgery, and the incidence of hypotension was approximately 34%, which is approximately half of that in our study. This difference may be attributed to the use of a narrow definition of IOH and the absolute threshold of systolic blood pressure (<90 mmHg) for considering IOH in 30 years younger study population. Interestingly, ASA classification and the number of mFI variables did not show significant associations with IOH prediction and 3-month adverse outcomes in multivariate logistic regression analysis. We assumed that these tools have limitations because they are primarily used for the accumulation of underlying diseases. Radiologically measured PMA showed a closer relationship to functional physical status than ASA classification and mFI variables. Considering the impact of sarcopenia, PMA is related to active daily life [34], and it dynamically reflects patients' physical status. This result indicates that sarcopenia and frailty are interrelated conditions that lead to IOH and adverse outcomes.

Several possible mechanisms may explain the development of IOH in frail patients. First, frailty is associated with impaired autonomic cardiovascular regulation. Decreased sympathetic vasoconstrictor nerve activity in frail patients induces profound vasodilatory effects by propofol induction agents [35] and could develop IOH, particularly during the post-induction period. Reduced baroreceptor responsiveness, represented by decreased heart rate variability, has been previously demonstrated in frail patients [36]. An impaired autonomic nervous system may affect the ability to maintain systemic blood pressure, which is important for cardiovascular homeostasis under stress. Second, the decreased water content in patients with low PMA could lead to hypotension during surgery. The water content in skeletal muscle is approximately 10% to 20% [37], and skeletal muscle mass, as a reservoir of water content, is important for maintaining blood pressure [38]. Low PMA, a surrogate of a sarcopenia-induced low water reservoir, may contribute to impaired blood pressure homeostasis in frail patients. Third, patients with pre-existing HTN were more vulnerable to IOH. Multivariate analysis showed that the adjusted OR of baseline systolic blood pressure for predicting IOH was 1.03, and the number of patients with chronic hypertension was higher in the IOH group than in the no-IOH group. Jor et al. [39] also demonstrated that the degree of preoperative hypertensive systolic blood pressure is associated with the development of IOH. Older patients with HTN are likely to be labile regarding systemic blood pressure. Moreover, the patients continued renin-angiotensin-aldosterone system antagonists till the day before surgery, which may be associated with a higher risk of IOH.

This study had several limitations. First, this was a retrospective study, and unfound confounding factors may exist. We conducted this study from two institutions of the same medical school using standardized anesthesia protocols and excluded neuraxial anesthesia to minimize selection bias due to the different pathophysiology of hypotension, which is attributed to depression of the sympathetic trunk. Despite these efforts, it has inherent limitations according to its design. Second, we could not measure the time-weighted average IOH from restricted data that automatically recorded arterial blood pressure from EMR at 1- to 5-min intervals. As longer exposure to IOH may be related to an increased risk of postoperative outcomes, future prospective studies should be done to clarify the association between IOH and 3-month adverse outcomes considering the time-weighted average IOH. Third, we analyzed the older adult femur-fractured cohort whose distribution was not equal to that of male and female patients because older women have lower bone density and are more prone to falls than older men [33]. Caution is necessary for generalizing our results, which should be validated in a multicenter prospective study in the

future. Fourth, we only used the mFI score to assess frailty, which consisted of comorbidities or deficits that could be retrospectively assessed, unlike questionnaire-based assessment methods [10,11]. However, it is difficult to apply questionnaire-based frailty assessment tools to patients with femur fractures because of their physical disability. In this context, we attempted to suggest a feasible surrogate for frailty in patients with femur fractures, such as PMA, from existing pelvic bone CT. Finally, ICC was not measured for the entire cohort, and PMA was measured independently by anesthesiologists in randomly selected patients; PMA was measured by a trained anesthesiologist, not a radiologist. Nonetheless, the measurement of PMA was easy to learn, and the ICC was known to be high: 0.968 (95% CI, 0.961–0.973) for the right and 0.915 for the left (95% CI, 0.898–0.929) [22]. This advantage could be a strength of PMA for easy application in clinical settings by anesthesiologists.

5. Conclusions

PMA normalized by BSA using pre-existing CT was a significant predictor of IOH occurrence and unfavorable surgical outcomes in older adult patients with hip fractures. Moreover, preoperative simple measurement of PMA was superior to mFI in predicting IOH. To discuss the relationship between IOH and adverse surgical outcomes, further prospective studies using the time-weighted average IOH are warranted.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12041691/s1, Table S1. Factors of modified frailty index.

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Data Availability Statement: The full trial protocol and the data supporting the findings of this study are available from the corresponding author upon request.

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References

1. Lin, K.B.; Yang, N.P.; Lee, Y.H.; Chan, C.L.; Wu, C.H.; Chen, H.C.; Chang, N.T. The incidence and factors of hip fractures and subsequent morbidity in Taiwan: An 11-year population-based cohort study. *PLoS ONE* **2018**, *13*, e0192388. [CrossRef] [PubMed]
2. Ove, T.; Fredrik, H.; Ola, E.D.; Are, H.P.; Olav, R. Clinical and biochemical prediction of early fatal outcome following hip fracture in the elderly. *Int. Orthop.* **2011**, *35*, 903–907.
3. Istianah, U.; Nurjannah, I.; Magetsari, R. Post-discharge complications in postoperative patients with hip fracture. *J. Clin. Orthop. Trauma* **2021**, *14*, 8–13. [CrossRef] [PubMed]
4. Ha, Y.; Cha, Y.; Yoo, J.; Lee, J.; Lee, Y.; Koo, K. Effect of dementia on postoperative mortality in elderly patients with hip fracture. *J. Korean Med. Sci.* **2021**, *36*, e238. [CrossRef] [PubMed]
5. Sim, J.H.; Lee, S.H.; Kim, J.W.; Koh, W.U.; Kim, H.T.; Ro, Y.J.; Kim, H.J. Low psoas lumbar vertebral index is associated with mortality after hip fracture surgery in elderly patients: A retrospective analysis. *J. Pers. Med.* **2021**, *11*, 673. [CrossRef] [PubMed]
6. Koizia, L.; Naik, M.; Peck, G.; Mikhail, G.W.; Sen, S.; Malik, I.S.; Ariff, B.; Fertleman, M.B. The utility of psoas muscle assessment in predicting frailty in patients undergoing transcatheter aortic valve replacement. *Curr. Gerontol. Geriatr. Res.* **2020**, *2020*, 5783107. [CrossRef] [PubMed]

7. Rangel, E.L.; Rios-Diaz, A.J.; Uyeda, J.W.; Castillo-Angeles, M.; Cooper, Z.; Olufajo, O.A.; Salim, A.; Sodickson, A.D. Sarcopenia increases risk of long-term mortality in elderly patients undergoing emergency abdominal surgery. *J. Trauma Acute Care Surg.* **2017**, *83*, 1179–1186. [CrossRef]
8. Ebbeling, L.; Grabo, D.J.; Shashaty, M.; Dua, R.; Sonnad, S.S.; Sims, C.A.; Pascual, J.L.; Schwab, C.W.; Holena, D.N. Psoas: Lumbar vertebra index: Central sarcopenia independently predicts morbidity in elderly trauma patients. *Eur. J. Trauma Emerg. Surg.* **2014**, *40*, 57–65. [CrossRef]
9. Clegg, A.; Young, J.; Iliffe, S.; Rikkert, M.O.; Rockwood, K. Frailty in elderly people. *Lancet* **2013**, *381*, 752–762. [CrossRef]
10. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyere, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. *Age Ageing* **2019**, *48*, 601. [CrossRef]
11. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M156. [CrossRef] [PubMed]
12. Rolfson, D.B.; Majumdar, S.R.; Tsuyuki, R.T.; Tahir, A.; Rockwood, K. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* **2006**, *35*, 526–529. [CrossRef] [PubMed]
13. Tsiouris, A.; Hammoud, Z.T.; Velanovich, V.; Hodari, A.; Borgi, J.; Rubinfeld, I. A modified frailty index to assess morbidity and mortality after lobectomy. *J. Surg. Res.* **2013**, *183*, 40–46. [CrossRef] [PubMed]
14. Canales, C.; Mazor, E.; Coy, H.; Grogan, T.R.; Duval, V.; Raman, S.; Cannesson, M.; Singh, S.P. Preoperative point-of-care ultrasound to identify frailty and predict postoperative outcomes: A diagnostic accuracy study. *Anesthesiology* **2022**, *136*, 268–278. [CrossRef] [PubMed]
15. Balsam, L.B. Psoas muscle area: A new standard for frailty assessment in cardiac surgery? *J. Thorac. Dis.* **2018**, *10* (Suppl. 33), S3846–S3849. [CrossRef] [PubMed]
16. Bentov, I.; Kaplan, S.J.; Pham, T.N.; Reed, M.J. Frailty assessment: From clinical to radiological tools. *Br. J. Anaesth.* **2019**, *123*, 37–50. [CrossRef]
17. Sun, L.Y.; Wijeysundera, D.N.; Tait, G.A.; Beattie, W.S. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* **2015**, *123*, 515–523. [CrossRef]
18. Salmasi, V.; Maheshwari, K.; Yang, D.; Mascha, E.J.; Singh, A.; Sessler, D.I.; Kurz, A. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. *Anesthesiology* **2017**, *126*, 47–65. [CrossRef]
19. Bijker, J.B.; Persoon, S.; Peelen, L.M.; Moons, K.G.; Kalkman, C.J.; Kappelle, L.J.; van Klei, W.A. Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. *Anesthesiology* **2012**, *116*, 658–664. [CrossRef]
20. Droguett, V.S.; Santos Ada, C.; de Medeiros, C.E.; Marques, D.P.; do Nascimento, L.S.; Brasileiro-Santos Mdo, S. Cardiac autonomic modulation in healthy elderly after different intensities of dynamic exercise. *Clin. Interv. Aging* **2015**, *10*, 203–208.
21. Ackland, G.L.; Abbott, T.E.F. Hypotension as a marker or mediator of perioperative organ injury: A narrative review. *Br. J. Anaesth.* **2022**, *128*, 915–930. [CrossRef] [PubMed]
22. Bae, S.J.; Lee, S.H. Computed tomographic measurements of the psoas muscle as a predictor of mortality in hip fracture patients: Muscle attenuation helps predict mortality in hip fracture patients. *Injury* **2021**, *52*, 1456–1461. [CrossRef] [PubMed]
23. Rockwood, K.; Song, X.; Mitnitski, A. Changes in relative fitness and frailty across the adult lifespan: Evidence from the Canadian National Population Health Survey. *CMAJ* **2011**, *183*, E487–E494. [CrossRef]
24. Choi, M.H.; Chae, J.S.; Lee, H.J.; Woo, J.H. Pre-anaesthesia ultrasonography of the subclavian/infraclavicular axillary vein for predicting hypotension after inducing general anaesthesia: A prospective observational study. *Eur. J. Anaesthesiol.* **2020**, *37*, 474–481. [CrossRef]
25. Griffiths, R.; White, S.M.; Moppett, I.K.; Parker, M.J.; Chesser, T.J.; Costa, M.L.; Johansen, A.; Wilson, H.; Timperley, A.J. Safety guideline: Reducing the risk from cemented hemiarthroplasty for hip fracture 2015: Association of Anaesthetists of Great Britain and Ireland British Orthopaedic Association British Geriatric Society. *Anaesthesia* **2015**, *70*, 623–626.
26. Griffiths, R.; Babu, S.; Dixon, P.; Freeman, N.; Hurford, D.; Kelleher, E.; Moppett, I.; Ray, D.; Sahota, O.; Shields, M.; et al. Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists. *Anaesthesia* **2021**, *76*, 225–237. [CrossRef]
27. Lee, T.C.; Ho, P.S.; Lin, H.T.; Ho, M.L.; Huang, H.T.; Chang, J.K. One-year readmission risk and mortality after hip fracture surgery: A National Population-Based Study in Taiwan. *Aging Dis.* **2017**, *8*, 402–409. [CrossRef]
28. Sudfeld, S.; Brechnitz, S.; Wagner, J.Y.; Reese, P.C.; Pinnschmidt, H.O.; Reuter, D.A.; Saugel, B. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br. J. Anaesth.* **2017**, *119*, 57–64. [CrossRef]
29. Nicholas, C.C.; Viandsa, S.S.; Giovanini, T.; Friedo, W.D.; Edouard, L.F.; Carmine, Z. An introduction to inverse probability of treatment weighting in observational research. *Clin. Kidney J.* **2022**, *15*, 14–20.
30. Soysal, P.; Kocyigit, S.E.; Dokuzlar, O.; Ates Bulut, E.; Smith, L.; Isik, A.T. Relationship between sarcopenia and orthostatic hypotension. *Age Ageing* **2020**, *49*, 959–965. [CrossRef] [PubMed]
31. Chow, W.B.; Rosenthal, R.A.; Merkow, R.P.; Ko, C.Y.; Esnaola, N.F. Optimal preoperative assessment of the geriatric surgical patient: A best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J. Am. Coll. Surg.* **2012**, *215*, 453–466. [CrossRef] [PubMed]
32. Beggs, T.; Sepehri, A.; Szwajcer, A.; Tangri, N.; Arora, R.C. Frailty and perioperative outcomes: A narrative review. *Can. J. Anaesth.* **2015**, *62*, 143–157. [CrossRef] [PubMed]

33. Landi, F.; Liperoti, R.; Russo, A.; Giovannini, S.; Tosato, M.; Capoluongo, E.; Bernabei, R.; Onder, G. Sarcopenia as a risk factor for falls in elderly individuals: Results from the ilSIRENTE study. *Clin. Nutr.* **2012**, *31*, 652–658. [CrossRef] [PubMed]
34. Landi, F.; Calvani, R.; Ortolani, E.; Salini, S.; Martone, A.M.; Antoro, L.; Antoliquido, A.; Isto, A.; Picca, A.; Marzetti, E. The association between sarcopenia and functional outcomes among older patients with hip fracture undergoing in-hospital rehabilitation. *Osteoporos. Int.* **2017**, *28*, 1569–1576. [CrossRef]
35. Robinson, B.J.; Ebert, T.J.; O'Brien, T.J.; Colinco, M.D.; Muzi, M. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? *Anesthesiology* **1997**, *86*, 64–72. [CrossRef]
36. Romero-Ortuno, R.; Cogan, L.; O'Shea, D.; Lawlor, B.A.; Kenny, R.A. Orthostatic haemodynamics may be impaired in frailty. *Age Ageing* **2011**, *40*, 576–583. [CrossRef]
37. Belton, P.S.; Packer, K.J. Pulsed NMR studies of water in striated muscle. 3. The effects of water content. *Biochim. Biophys. Acta* **1974**, *354*, 305–314. [CrossRef]
38. Son, H.E.; Ryu, J.Y.; Lee, K.; Choi, Y.I.; Kim, M.S.; Park, I.; Shin, G.T.; Kim, H.; Ahn, C.; Kim, S.; et al. The importance of muscle mass in predicting intradialytic hypotension in patients undergoing maintenance hemodialysis. *Korean J. Nephrol.* **2022**, *41*, 611–622. [CrossRef]
39. Jor, O.; Maca, J.; Koutna, J.; Gemrotova, M.; Vymazal, T.; Litschmannova, M.; Sevcik, P.; Reimer, P.; Mikulova, V.; Trlicova, M.; et al. Hypotension after induction of general anesthesia: Occurrence, risk factors, and therapy. A prospective multicentre observational study. *J. Anesth.* **2018**, *32*, 673–680. [CrossRef]

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Infant Perioperative Risk Factors and Adverse Brain Findings Following Long-Gap Esophageal Atresia Repair

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Abstract: Recent findings implicate brain vulnerability following long-gap esophageal atresia (LGEA) repair. We explored the relationship between easily quantifiable clinical measures and previously reported brain findings in a pilot cohort of infants following LGEA repair. MRI measures (number of qualitative brain findings; normalized brain and corpus callosum volumes) were previously reported in term-born and early-to-late premature infants (n = 13/group) <1 year following LGEA repair with the Foker process. The severity of underlying disease was classified by an (1) American Society of Anesthesiologist (ASA) physical status and (2) Pediatric Risk Assessment (PRAm) scores. Additional clinical end-point measures included: anesthesia exposure (number of events; cumulative **m**inimal **a**lveolar **c**oncentration (MAC) exposure in hours), length (in days) of postoperative intubated sedation, paralysis, antibiotic, steroid, and total parenteral nutrition (TPN) treatment. Associations between clinical end-point measures and brain MRI data were tested using Spearman rho and multivariable linear regression. Premature infants were more critically ill per ASA scores, which showed a positive association with the number of cranial MRI findings. Clinical end-point measures *together* significantly predicted the number of cranial MRI findings for both term-born and premature infant groups, but none of the individual clinical measures did on their own. Listed easily quantifiable clinical end-point measures could be used *together* as indirect markers in assessing the risk of brain abnormalities following LGEA repair.

Keywords: association analysis; critical care; correlations; LGEA; MRI; neurology; pediatrics

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1. Introduction

Esophageal atresia, although a rare congenital anomaly with a stable prevalence around the world [1], is one of the most common gastrointestinal birth defects, with a reported incidence of 1 in 2500 to 1 in 4500 live births [2,3]. Compared to short-gap esophageal atresia, long-gap esophageal atresia (LGEA) is more likely to be an isolated defect and associated with Trisomy 21 [4], but is less commonly associated with other anomalies (viz. VACTERL or CHARGE syndromes) [4,5]. Unlike short-gap defects that can be repaired by direct anastomosis (requiring one major surgery and postoperative pain treatment within 5 days) [6], long disconnects (>3 cm) found in LGEA [4] require more complex treatment. At our institution, infants born with LGEA undergo tension-induced esophageal growth as part of the Foker process repair [7–9]. The Foker process allows for growth and lengthening of infant's existing esophageal pouches, spanning a period of weeks [10,11], but requires at least two separate thoracotomies/thoracoscopies [12] before direct anastomosis is achieved. The unique aspect of such complex repair involves not

only repeated anesthesia exposure, but prolonged sedation of ≥5 days that is known to be associated with the development of tolerance and physical dependence to the drugs of sedation [13–15].

The impact of complex perioperative care with the Foker process on neurobehavioral outcomes in infants born with LGEA represents a major gap in our knowledge. Recent reports indicate that infants undergoing neonatal surgery for noncardiac congenital anomalies, including those with esophageal atresia, are at risk of brain injury [10,16], potentially accounting for the neurodevelopmental delay observed in populations of infants with gastrointestinal anomalies [17]. Our recent pilot studies using brain magnetic resonance imaging (MRI) [10,11,18–20] have provoked concerns over the impact of complex perioperative critical care with the Foker process on brain findings and brain growth in infants born with LGEA [10,18,20,21].

Therefore, the main objective in this novel report was to analyze associations between easily quantifiable clinical measures and previously reported brain findings in a pilot cohort of infants that underwent research brain MRI following Foker process repair for LGEA [10,19,20]. In this study, we hypothesized that either higher clinical severity scores (viz. American Society of Anesthesiologist (ASA) [22] and recently introduced Pediatric Risk Assessment measure (PRAm) [23]), or longer exposure to anesthesia and drug treatment (viz. length of postoperative intubated sedation, muscle relaxants, antibiotics, steroids), and/or TPN administration, would be (1) positively associated with the number of incidental brain MRI findings (novel data) and (2) negatively associated with previously published normative total brain [10,20] and corpus callosum volumes [19]. Since our pilot cohort included infants that underwent research brain MRI in the first year of life following repair of LGEA, our secondary objective was to demonstrate association trends with age.

2. Methods

2.1. Study Design and Participants

This work builds on our previous work (2015–2018) of brain measure quantification using structural magnetic resonance imaging (MRI) [10,19,20] and was approved by the Institutional Review Board as a 'no more than minimal risk' study (IRB-P000007855). Informed written parental consent was obtained prior to subject participation, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. We previously described a detailed methodological approach for (1) recruitment criteria and (2) scanning process for research brain MRI [10].

In this cross-sectional pilot study, infants' eligibility criteria included term-born (37 to 42 weeks gestational age at birth) and early-to-late premature infants <1 year gestation-corrected age (n = 13/group) following LGEA repair with Foker process [7–9], who developed dependency to drugs of sedation (e.g., opioids and benzodiazepines) [15]. The preterm group included only very preterm (28 to <32 weeks GA) and moderate-to-late preterm infants (32 to <37 weeks GA), as defined by *The World Health Organization* [24]. All infants underwent *external* traction as part of the Foker process that requires infants to stay intubated, muscle relaxed, and sedated postoperatively [25,26]. We did not analyze: (i) post-operative drug sedation management, as such treatment is not protocolized at our institution, or (ii) potential symptoms of withdrawal (see [27] for review on weaning). Instead, we confirmed that weaning management to drugs of sedation occurred as per primary team and/or pain service notes. Exclusion criteria were: (1) extreme prematurity (<28 weeks GA); (2) diagnosis of small for gestational age and/or intrauterine growth restriction (SGA/IUGR) [28,29]; (3) history of cardiac arrest and/or major cardiovascular resuscitation; (4) extracorporeal membrane oxygenation exposure; (5) status post tracheostomy; (6) clinically indicated cranial ultrasound findings (e.g., ventricular enlargement with or without intraparenchymal and/or intraventricular hemorrhage); (7) neurological disease as documented in clinical record (e.g., seizures, craniosynostosis requiring surgical repair); (8) chromosomal abnormalities (e.g., Down's syndrome); (9) prenatal drug exposure to either drugs of abuse or prescription medications; and/or (10) MRI-incompatible

implants. Our pilot cohort [30] included infants with isolated LGEA and LGEA with tracheo-esophageal fistula (TEF), while a few patients had other non-cardiac congenital anomaly diagnoses that included LGEA as part of VACTERL association (without a cardiac component). None of the cohort infants had cardiac anomalies requiring surgery, nor exposure to extracorporeal membrane oxygenation, and had no clinical evidence of neurological problems at the time of recruitment, as per detailed chart review and/or cranial ultrasound findings when available (n = 13/group) [30].

2.2. Brain MRI Acquisition and Structural Analyses

Structural research brain MRI was obtained under natural sleep according to the 'feed and wrap' approach. All infants were scanned either just before hospital discharge following Foker process [7–9] (including completion of weaning) or during subsequent admissions for follow-up management in the 1st year of life. Thus, subjects were scanned at different times during gestation-corrected first year of life in relation to the completion of treatment, depending on the time of recruitment. Structural T1- and T2-weighted MRI data were successfully collected for all subjects, allowing for detailed qualitative and quantitative data analysis for term-born and premature groups (n = 13/group). A pediatric neuroradiologist on call reviewed MRI scans for any findings of clinical significance. Additionally, a pediatric neurologist blindly evaluated the same (DBP). Clinically relevant MRI findings included those related to extra-cranial (e.g., abnormal head shape) and intra-cranial findings (e.g., increased extra-axial space, ventriculomegaly, thinning of corpus callosum, subdural hematoma, stroke, etc. [10,18,19]). This qualitative evaluation was summed as the individual total number of cranial MRI findings (novel data). Please refer to our previous reports for detailed description of protocols for (i) preparation and supervision of infants undergoing non-sedated brain MRI [10], (ii) details of structural scanning parameters [10,20], (iii) quantitative T2-weighted brain segmentation [10,20] using Morphologically Adaptive Neonatal Tissue Segmentation (MANTiS) toolbox [31], as well as (iv) quantitative T1-weighted brain and corpus callosum [19,30] volume estimation, since it is beyond the scope of this manuscript. As previously published, we reported normalized volumes of the brain as % of intracranial volume [10,21], and that of corpus callosum as % of total forebrain volume [19].

2.3. Underlying Disease Severity Scores and Clinical Parameter Acquisition

In addition to demographic information (see Table 1 in [30]), several clinical endpoint measures were obtained from the electronic medical records (PowerChart®, Cerner, London, UK) and digital anesthesia records (AIMS Charts, 2019 Citrix Receiver Application, v. 19.3.0.21) for each patient.

2.3.1. Disease Severity Scores

We collected 2 underlying disease severity scores used in clinical practice to assess underlying disease complexity: (1) American Society of Anesthesiologists (ASA) physical status classifications score [22], and (2) Pediatric Risk Assessment (PRAm) score [23]. According to the ASA physical status classification, infants are rated on a scale of I (healthy) to VI (braindead). We collected the highest individual ASA score value, as documented by anesthesia charts at the time of initial esophageal repair surgery (Foker I).

In contrast to ASA, PRAm score was most recently introduced as a novel score to predict perioperative mortality in children undergoing noncardiac surgery [23]. Thus, our research team calculated PRAm scores for infants recruited before 2017. Scoring of PRAm involves the following: urgency of surgical procedure (+1), presence of at least one comorbidity (+2), presence of at least one indication of critical illness (+3), age < 12 months at surgery (+3), and co-existing malignancy (+4) for a range of scores from 0 to 13, with 0 representing the least threat to life and 13 representing the greatest threat to life. Since all infants in this pilot cohort were younger than 12 months, and had no co-existing malignancy, PRAm scores ranged from score 3 to 9.

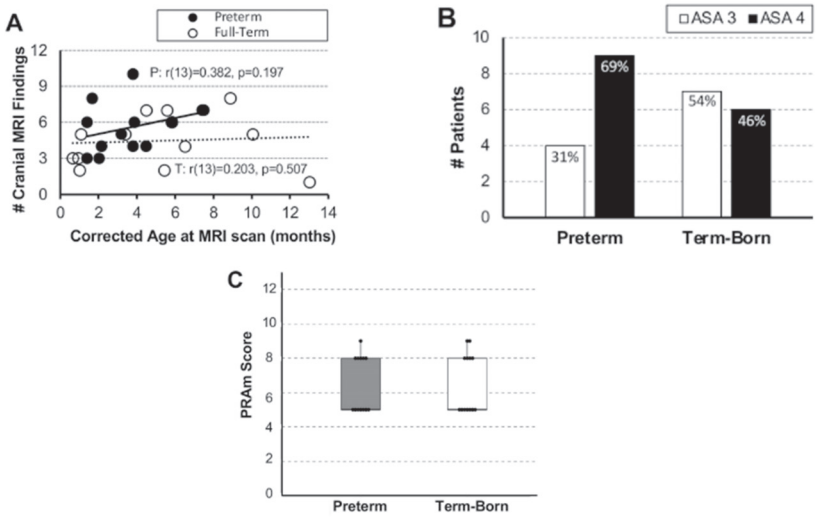

Figure 1. Incidence of Qualitative Brain Findings per Patient and Underlying Disease Severity Scores. Panel (**A**) graph shows no significant associations between individual number of cranial MRI findings and age at the time of research brain MRI scan for early-to-late preterm (n = 13; black circles, solid trend line) and term-born infants (n = 13; open circles, dashed trend line) who underwent Foker process [7] for long-gap esophageal atresia (LGEA) repair. Panels (**B**,**C**) show distribution of American Society of Anesthesiologist (ASA) classification and Pediatric Risk Assessment (PRAm) scores, respectively. The percent (%) of infants per gestational age group for ASA score is shown for each bar (Panel (**B**)). In contrast, PRAm scoring is rated on a wider scale of 0–13, representing the least and the greatest threat to life, respectively. Dots in Panel (**C**) represent individual scores, boxes span the interquartile range (IQR) (first and third quartile), and whiskers represent maximum and minimum values. *Abbreviations*: **#**, number; P, premature; T, term-born.

2.3.2. Clinical Care Measures

We collected 7 easily quantifiable clinical end-point measures from medical records: (1) number of anesthesia events, and (2) cumulative anesthesia exposure as total minimal alveolar concentration (MAC)-equivalent anesthesia hours up to the time of the research brain MRI. All infants received inhalational agents for maintenance of anesthesia during all procedures. None of the infants underwent total intravenous anesthesia (TIVA) for any procedure. Details of anesthesia management (e.g., administration of inhalational agents with/without peripheral nerve block and/or intravenous pain management) are beyond the subject of this manuscript. We also quantified duration of postoperative treatment (in days) of (3) mechanical ventilation and (4) muscle relaxation (as indirect measures of sedation), as well as (5) antibiotics, (6) steroids, and (7) total parenteral nutrition (TPN) with fat emulsion as an indirect measure of complexity of postoperative care (e.g., surgical complications). All listed data metrics were collected from the perioperative period up until the time of research brain MRI scan. Sedation and weaning management were administered as infusions with boluses. It included combination of opioid (e.g., morphine), benzodiazepine (e.g., midazolam), hypnotic (e.g., ketamine), and/or alpha2-agonist (e.g., dexmedetomidine). Neither sedation nor post-operative muscle relaxation was protocolized. For the few infants that underwent minor procedures at other institutions prior to transfer to our institution for esophageal repair, duration of anesthesia events was estimated (i.e., endotracheal intubation = 0.25 h; placement of central access line = 0.5 h; laparoscopic gastrostomy placement = 1 h), likely resulting in the underestimation of total anesthesia exposure. Due to incomplete availability of outside hospital documentation,

comprehensive postoperative intubated sedation/muscle relaxation data were compiled for n = 11/13 term-born infants and n = 10/13 premature infants. Additionally, antibiotic, steroid, and TPN exposure data were only available for n = 12/13 infants per either group. We eliminated only one term-born data point at 12 months of age from correlation analysis as it was considered an aberrant point. This subject underwent extraordinarily long TPN and antibiotic administration that artificially diverted the statistics.

Table 1. Qualitative MRI findings.

Qualitative MRI Findings	# PRETERM (n = 13)	# TERM-BORN (n = 13)	Total # Anomalies
Brain Abnormalities			
Increased extra-axial space	11	7	18
Widened sylvian fissures	5	5	10
Enlarged/Prominent Ventricles	11	9	20
Low cerebellar volume	0	0	0
Low brainstem volume	0	0	0
Chronic blood products (e.g., hemosiderin)	0	2	2
Mass or cyst	1	2	3
Narrowing of cerebral aqueduct	1	0	1
Incomplete rotation of hippocampi	2	0	2
White Matter Abnormalities			
Low cerebral white matter volume	1	0	1
Abnormal signal in white matter	2	4	6
Corpus callosum abnormalities	12	10	22
Grey Matter Abnormalities			
Low cerebral grey matter volume	0	1	1
Abnormal signal in grey matter	0	0	0
Vasculature Abnormalities/Hemorrhage			
Intraventricular Hemorrhage	1	0	1
Subdural hemorrhage	3	0	3
Subdural effusion/collection	1	2	3
Arterial ischemic/hemorrhagic stroke	1	0	1
Venous hemorrhagic stroke	0	1	1
Cerebellar hemorrhage (arterial or venous) stroke	0	1	1
Vascular anomaly	1	0	1
Possible parturitional hemorrhage	0	1	1
Cranial Abnormalities			
Abnormal head shape (e.g., plagiocelphaly)	3	2	5
Non-CNS cranial anomaly	3	2	5

Table 1 summarizes the type and incidence of clinically relevant cranial MRI findings in the cohort of early-to-late premature and term-born infant patients (n = 13/group). The number (#) of each qualitative MRI finding is totaled in the right column. Individual infants had more than one finding listed. For the individual number of cranial MRI findings/patient, refer to Figure 1A. *Abbreviations:* CNS, central nervous system.

2.4. Statistical Analysis

As this was a pilot MRI study [10] and no prior information was available regarding brain volumes in the selected cohort of infants with LGEA, a convenience sample size of 13 infants/group was chosen, based on the anticipated number of eligible infants at our institution and an estimated 50% enrollment rate. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, v.23.0; IBM Corporation, Armonk, NY, USA).

2.4.1. Correlation Analysis

The Shapiro–Wilk test was used to assess for normality of data, while associations were determined by nonparametric Spearman Rho (r) test, which is resistant to the effects of outliers [32]. Strength of correlation was described as: weak ($r < 0.4$), moderate ($r \geq 0.4$ to <0.7), and strong ($r \geq 0.7$) [33]. We used more stringent Bonferroni criteria for $p < 0.01$ as

statistically significant as to protect against false-positive results due to the multitude of testing [34].

2.4.2. Multivariable Linear Regression

A multivariable linear regression model was used to identify independent predictors of adverse neurological data, as quantified by research brain MRI. After testing for multicollinearity using variance inflation factor (VIF) measures, the following 6 variables were included in the final model: (1) group status, (2) cumulative MAC-equivalent hours of anesthesia exposure, and length of (3) postoperative mechanical ventilation, (4) postoperative muscle relaxation, (5) antibiotic, and (6) steroid administration. TPN was excluded from the final model due to its correlation with the other clinical variables. Multivariable linear regression results are presented as *B* coefficients with 95% confidence intervals and *p* values. A two-tailed *a* level of <0.05 was used to assess for statistical significance.

3. Results

3.1. Brain MRI Measures

In this report, we summed qualitative cranial and brain findings of clinical significance that included findings of the gray and white brain matter, as well as vascular abnormalities. Irrespective of the gestation age groups, the most frequent qualitative brain findings (Table 1) were: (1) abnormalities of corpus callosum (viz. shape, size, and hypomyelination), (2) enlarged/prominent ventricles, and (3) increased extra-axial fluid. We report no significant association between the individual number of cranial MRI findings and age (Figure 1A).

3.2. Underlying Disease Severity: American Society of Anesthesiology (ASA) Classification System and Pediatric Risk Assessment (PRAm) Scoring

3.2.1. Disease Severity Score Distribution

We summarize disease severity scores (ASA physical status classification and PRAm scoring) of the pilot cohort based on the gestation age. As expected, prematurity is associated with higher ASA score of IV (9/13; 69%), while term-born infants have an equal distribution between ASA scores of III and IV (Figure 1B). Despite wider scoring range for PRAm (3–9), cohort patients had a similar distribution across a 5–9 score range, irrespective of the gestational age group (Figure 1C).

3.2.2. Associations between Disease Severity Scores and Brain MRI Data

Despite moderate associations between ASA scores and brain MRI metrics in early-to-late preterm infants, we did not show any significant relationship in either preterm or term-born infant patients (Figure 2A–C). Similarly, there is no association between PRAm scores and cranial MRI findings, irrespective of the gestational age group (Figure 2A′–C′).

3.3. Quantification of Clinical Measures of Care

We quantified seven clinical endpoint measures, which included (I) measures of anesthesia exposure (number of anesthesia events and MAC-equivalent cumulative anesthesia hours), (II) indirect measures of postoperative sedation (viz. length of postoperative mechanical ventilation and muscle relaxation in days), as well as (III) indirect measures of postoperative surgical complications and care (viz. length of antibiotics, steroids, and TPN administration in days) up to the time-point of research brain MRI.

3.3.1. Associations between Clinical Measures and Age

Since our pilot cohort included infants that underwent research brain MRI in the first year of life following repair of LGEA with the Foker process, we investigated the relationship between each clinical parameter with age at the time of brain MRI scan. We report a positive association between all clinical measures with age (Figure 3). Specifically, anesthesia exposure (viz. number of anesthesia events and cumulative MAC hours)

shows significant positive associations in both premature (# anesthesia events: r(13) = 0.827, $p < 0.001$; cumulative MAC hours: r(13) = 0.878, $p < 0.001$), and term-born infants (# anesthesia events: r(13) = 0.817, $p = 0.001$; cumulative MAC hours: r(13) = 0.709, $p = 0.007$) with age (Figure 3A,B). This reflects repeated anesthesia exposure in infancy (e.g., revisions or follow-up esophagoduodenoscopies). We also report a significant positive association only in premature infants for length of postoperative mechanical ventilation with age (r(10) = 0.821, $p = 0.004$), while other clinical measures did not show any significant associations with age (Figure 3D–G).

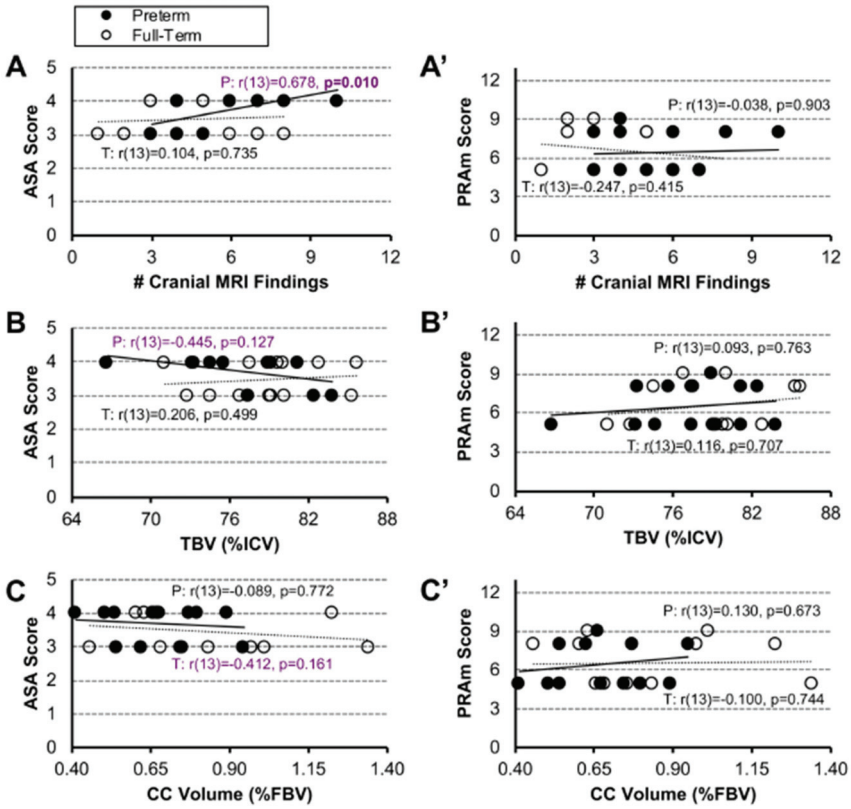

Figure 2. Association Between Disease Severity Scores and Brain MRI Metrics. Associations between an American Society of Anesthesiologist (ASA) classification (**A**–**C**) or Pediatric Risk Assessment (PRAm) scores (**A′**–**C′**) with 3 different brain MRI metrics for early-to-late preterm (n = 10–13; black circles, solid trend line) and term-born infants (n = 11–13; open circles, dashed trend line) following long-gap esophageal atresia (LGEA) repair. Neither group showed significant associations. All correlations were assessed by nonparametric Spearman Rho tests, which are resistant to the effects of outliers. Strength of correlation is described as weak (r < 0.4; black), moderate (r ≥ 0.4 to <0.7; purple), or strong, (r ≥ 0.7; red) with statistical significance as $p < 0.01$ (2-tailed). *Abbreviations*: #, number; %, percent; CC, corpus callosum; FBV, forebrain volume; ICV, intracranial volume; P, premature; T, term-born; TBV, total brain volume.

3.3.2. Associations between Clinical Measures and Disease Severity Scores

In the selected cohort of early-to-late premature and term-born infants following LGEA repair with the Foker process (n = 13/group), we did not find any significant associations between any of the clinical end-point measures with either ASA or PRAm scores, irrespective of the gestational age.

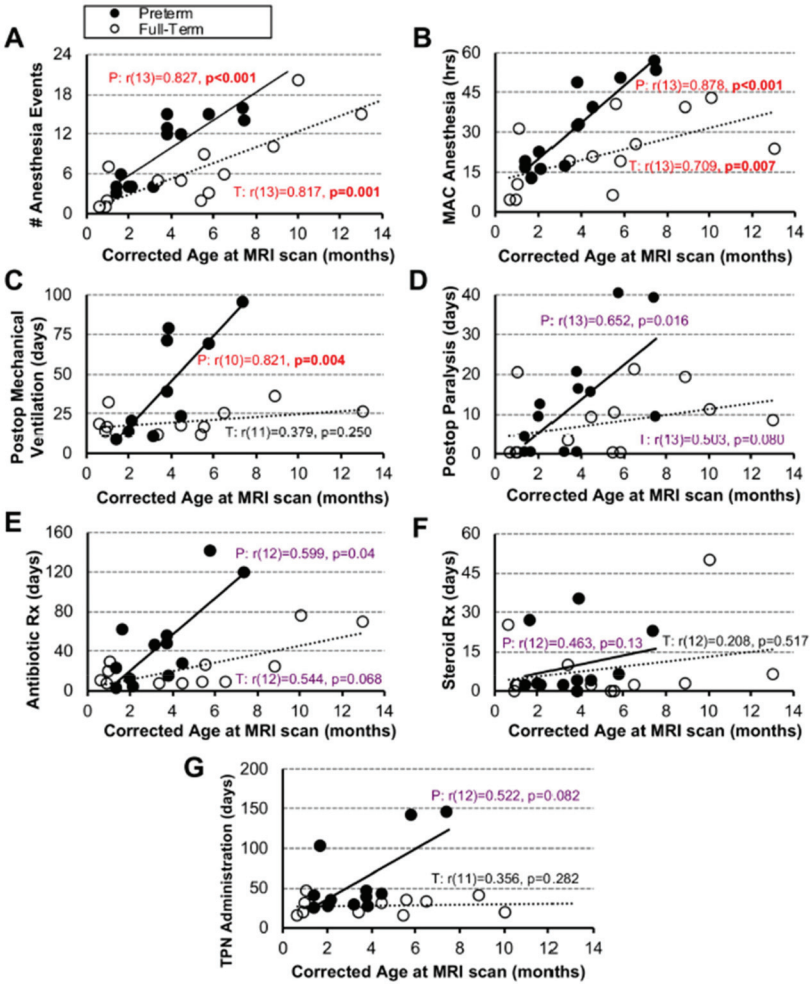

Figure 3. Association Between Clinical Measures and Age. Panels (**A**–**G**) show associations between 7 different clinical care measures and age for early-to-late preterm (n = 10–13; black circles, solid trend line) and term-born infants (n = 11–13; open circles, dashed trend line) following long-gap esophageal atresia (LGEA) repair. All correlations were assessed by nonparametric Spearman Rho tests, which are resistant to the effects of outliers. Data were non-normally distributed for clinical measures in Panels (**D**–**G**). Strength of correlation is described as weak (r < 0.4; black), moderate (r ≥ 0.4 to <0.7; purple), or strong (r ≥ 0.7; red) with statistical significance as $p < 0.01$ (2-tailed). *Abbreviations*: #, number; MAC, minimal alveolar concentration; P, premature; Postop, post-operative; Rx, treatment; T, term-born; TPN, total parenteral nutrition.

3.3.3. Associations between Clinical Measures and Brain MRI Measures

Number of Cranial MRI Findings. As illustrated in Figure 4, we report a significant positive association only between the length of antibiotic treatment and the number of cranial MRI findings in premature infants (r(12) = 0.718, $p = 0.009$; Figure 4E). We did not find any significant positive association between listed measures for the term-born infants.

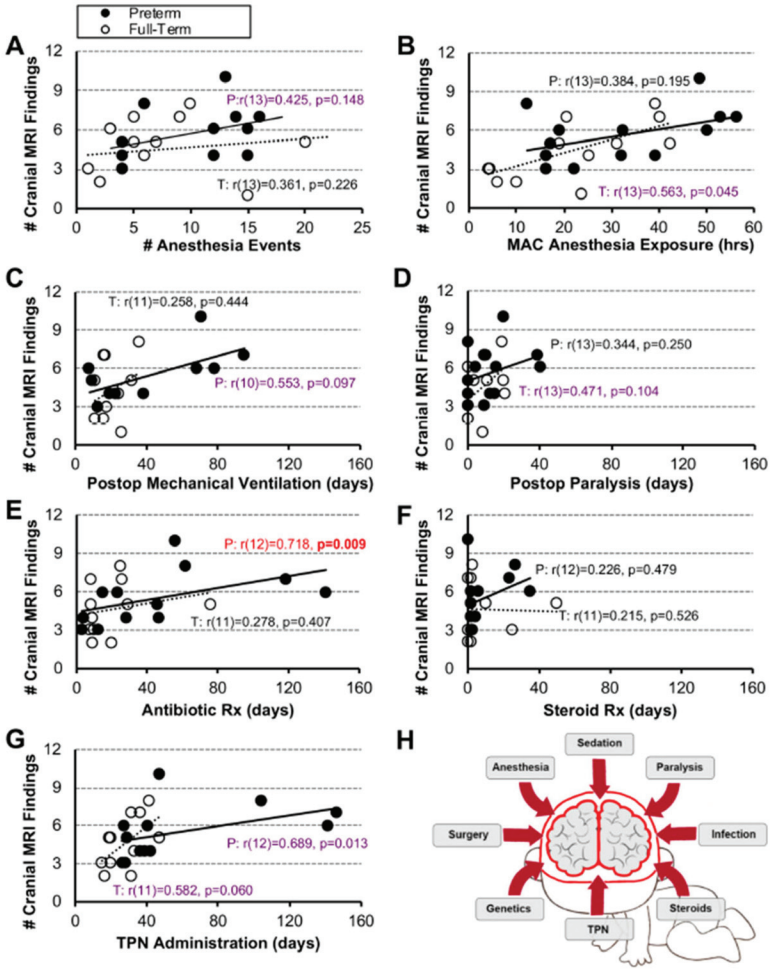

Figure 4. Association Between Clinical Measures and Number of Cranial MRI Findings. Associations between 7 clinical care measures and the number (#) of cranial MRI findings (Panels (**A**–**H**) for early-to-late preterm (n = 10–13; black circles, solid trend line) and term-born infants (n = 11–13; open circles, dashed trend line) following long-gap esophageal atresia (LGEA) repair. All correlations were assessed by nonparametric Spearman Rho tests, which are resistant to the effects of outliers. Data were non-normally distributed for clinical measures in Panels (**D**–**G**). Strength of correlation is described as weak (r < 0.4; black), moderate (r ≥ 0.4 to <0.7; purple), or strong, (r ≥ 0.7; red) with statistical significance as $p < 0.01$ (2-tailed). *Abbreviations*: #, number; MAC, minimal alveolar concentration; P, premature; Postop, post-operative; Rx, treatment; T, term-born; TPN, total parenteral nutrition.

Normalized Brain Volume. Having previously shown smaller absolute and normalized total brain volumes [10,20], and potentially delayed brain growth in infants born with LGEA [10,18,20], we examined the relationship between listed clinical variables and normalized brain size. We report that only in the premature infant group, longer exposure to anesthesia (Figure 5A,B) and duration of postoperative clinical care measures (in days; Figure 5C–G) showed moderate and mild negative associations to brain size, respectively, none of which were significant. For full statistical details, see Figure 5.

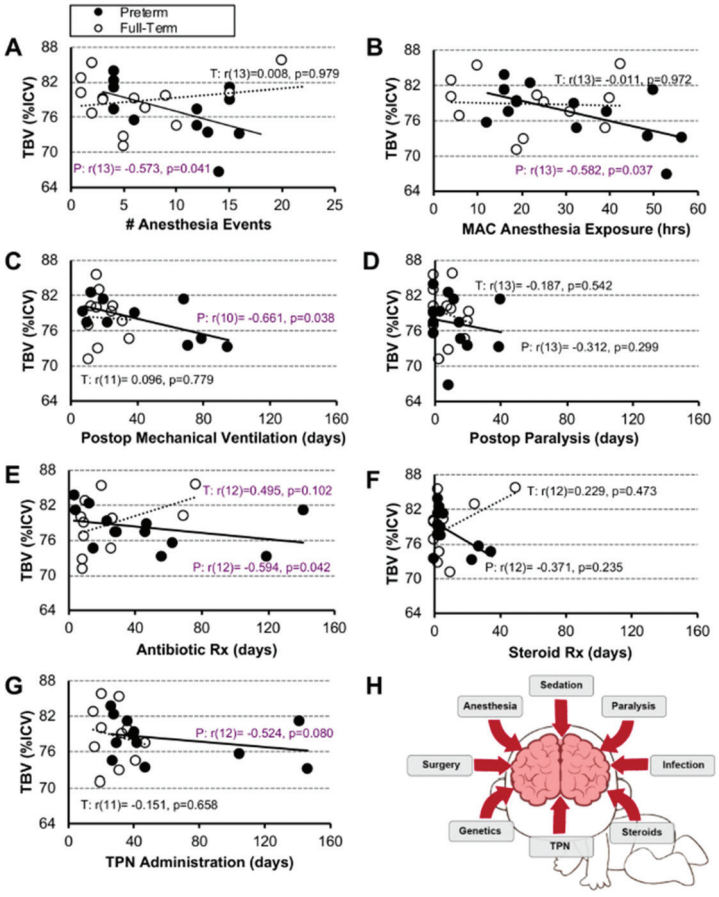

Figure 5. Association Between Clinical Measures and Normalized Total Brain Volume. Panels (**A**–**H**) illustrate associations between 7 clinical care measures and normalized total brain volume (TBV as % intracranial volume (ICV)) for early-to-late preterm (n = 10–13; black circles, solid trend line) and term-born infants (n = 11–13; open circles, dashed trend line) following long-gap esophageal atresia (LGEA) repair. We report no significant associations. All correlations were assessed by nonparametric Spearman Rho tests, which are resistant to the effects of outliers. Data were non-normally distributed for clinical measures in Panels (**D**–**G**). Strength of correlation is described as weak (r < 0.4; black), moderate (r ≥ 0.4 to <0.7; purple), or strong, (r ≥ 0.7) with statistical significance as $p < 0.01$ (2-tailed). *Abbreviations*: **#**, number; MAC, minimal alveolar concentration; P, premature; Postop, post-operative; Rx, treatment; T, term-born; TBV; total brain volume; TPN, total parenteral nutrition.

Normalized Corpus Callosum Volume. We previously reported disproportionally smaller normalized corpus callosum (CC) volumes [19] in a pilot cohort analyzed following complex perioperative critical care with the Foker process for LGEA repair. While one would expect that longer exposure to clinical metrics would be associated with smaller normalized CC volumes, we see the opposite trend. All clinical variables were positively associated with normalized CC volumes, with significant positive association between length of steroid treatment in premature infants (r(12) = 0.760, $p = 0.004$; Figure 6F). This reversal may be due to the cohort's small sample size, the small normalized CC values (in a range within 1% of forebrain volume), and the small scale of group differences, which all

warrant further investigation and should be interpreted with caution. For full statistical details, see Figure 6.

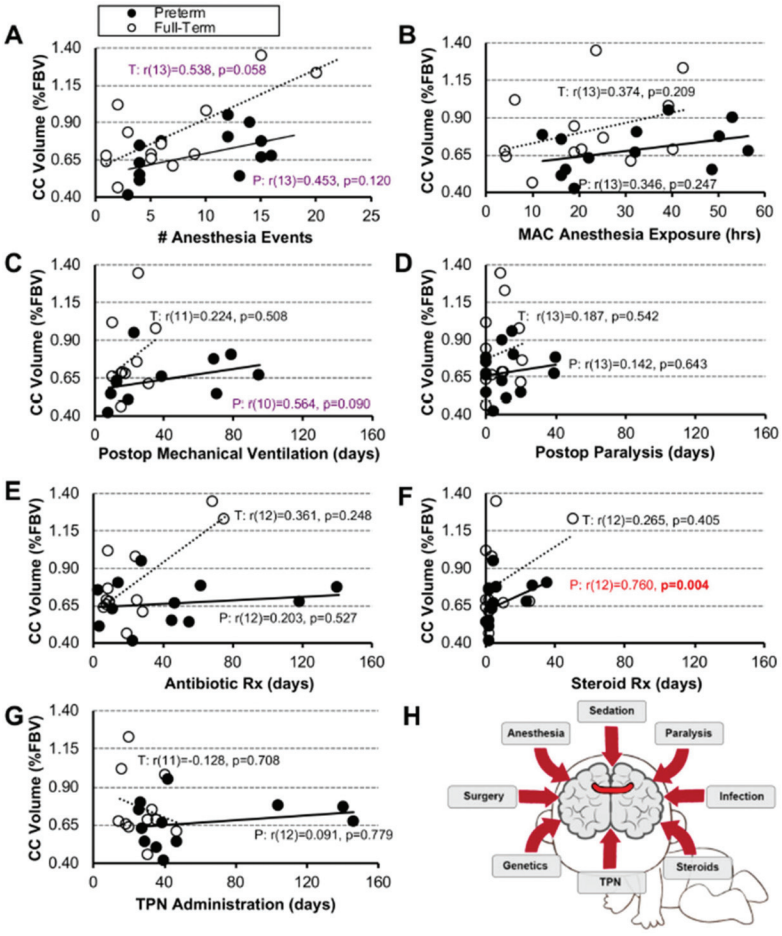

Figure 6. Association Between Clinical Measures and Normalized Corpus Callosum Size. Panels (**A**–**H**) show associations between 7 clinical care measures and normalized corpus callosum (CC) volume (as % forebrain volume (FBV)) for early-to-late preterm (n = 10–13; black circles, solid trend line) and term-born infants (n = 11–13; open circles, dashed trend line) following long-gap esophageal atresia (LGEA) repair. All correlations were assessed by nonparametric Spearman Rho tests, which are resistant to the effects of outliers. Data were non-normally distributed for clinical measures in Panels (**D**–**G**). Strength of correlation is described as weak ($r < 0.4$; black), moderate ($r \geq 0.4$ to <0.7; purple), or strong, ($r \geq 0.7$; red) with statistical significance as $p < 0.01$ (2-tailed). *Abbreviations*: **#**, number; MAC, minimal alveolar concentration; P, premature; Postop, post-operative; Rx, treatment; T, term-born; TPN, total parenteral nutrition.

3.4. Multivariable Linear Regression Models

We performed multivariable regression models that included group status and six clinical end-point measures (Table 2), with length of TPN administration excluded (see Methods section). We report that listed variables *together* significantly predicted the number of cranial MRI findings ($F(6, 14) = 3.12$, $p = 0.037$), but not total brain ($F(6, 14) = 1.11$, $p = 0.405$) or corpus callosum volumes $F(6, 14) = 0.99$, $p = 0.655$) for both term-born and

early-to-late premature patient groups. Interestingly, none of the individual variables studied significantly predicted the number of cranial MRI findings, total brain volume, or total CC volume on their own. For full statistical details, see Table 2.

Table 2. Multivariable model for number of cranial MRI findings: regression analysis.

Clinical Variables	Regression Coefficient	95% CI	*p* Value
1. Group Status (Preterm vs. Term-born)	0.026	−1.881 to 1.932	0.98
2. MAC Anesthesia Exposure (hrs)	0.119	0.002 to 0.237	0.05
3. Intubated Sedation (days)	0.031	−0.05 to 0.113	0.42
4. Postoperative Paralysis (days)	−0.014	−0.157 to 0.128	0.83
5. Antibiotic Rx (days)	−0.029	−0.064 to 0.007	0.11
6. Steroid Rx (days)	−0.039	−0.166 to 0.088	0.52

Multivariable linear regression model showed that listed 6 clinical end-point measures *together* significantly predicted the number of cranial MRI findings for both early-to-late premature and term-born infant infants following long-gap esophageal atresia (LGEA) repair ($F(6, 14) = 3.121$, $p = 0.037$), but none of the *individual* measures did on their own (right column *p* values). *Abbreviations*: hrs, hours; MAC, minimal alveolar concentration; Rx, treatment.

4. Discussion

This report assessed disease severity scores and easily quantifiable clinical measures as potential early markers of qualitative [18] and quantitative [10,20] brain MRI findings in a pilot group of infants following repair of LGEA with the Foker process [7]. Although individual clinical parameters were of limited use in predicting brain findings on their own, *together,* they may serve as an early indirect indicator of possible neurological risk.

4.1. Underlying Disease Severity Scoring Metrics' Validity for Assessing Brain Findings following Long-Gap Esophageal Atresia Repair

Although critical illness in infancy has been known to be associated with neurocognitive morbidities [35], our report represents the first attempt to assess the relationship between ASA classification and PRAm scores with cranial MRI findings. Our study failed to show any association between either ASA or PRAm scores and cranial MRI findings for either term-born or early-to-late preterm infants (Figure 2). Furthermore, our results indicate that PRAm scoring may be of limited use in the selected cohort of infants born with LGEA, despite being introduced as a novel scoring system specifically designed for predicting perioperative risk of mortality in pediatric populations undergoing noncardiac surgery [36]. In contrast, ASA classification supports that premature infants were more critically ill in comparison to term-born infants in our pilot cohort. Indeed, it is widely known that prematurity is a confounding factor in critical illness (with various morbidities) [37], including neurologic and neurocognitive sequelae [38], but future studies are needed to rule out prematurity in relation to brain findings in the context of complex perioperative critical care as part of the Foker process [7–9]. The lack of association between ASA classification and brain findings, despite documented incidental clinically significant MRI findings [10] and smaller brain and CC volumes [10,18,20], probes for (i) a study with larger power and/or (ii) a future new scoring metric in order to expand on previous risk stratification in this unique patient population. Future studies should also explore the usefulness of other scoring tools (viz. pediatric risk of mortality score (PRISM) [39], pediatric logistic organ dysfunction score (PELOD) [40], and pediatric multiple organ dysfunction score (P-MODS) [41] in assessing risk of brain findings.

4.2. Validity of Individual and Combined Clinical Parameters as Predictors of Brain Findings

Most of our *individual* clinical metrics (Figures 4–6) showed no significant associations with brain MRI measures. In contrast, using a multivariable linear regression model, we report that the group status and clinical end-point measures *together* play a role relating to the number of incidental cranial MRI findings (Table 2), irrespective of the gestational age. Similarly, previous studies in premature infants found that a combination of stressful/painful

events during neonatal critical care, as well as the interaction between underlying disease and therapeutic interventions, may, *together*, contribute to an allostatic load [42] and possibly poorer health outcomes [43]. Future studies should attempt to evaluate combined clinical parameters, along with other measures of care, to better understand intrinsic disease and treatment impact for life-saving LGEA repair with the Foker process [7]. Of all the clinical measures, easily quantifiable cumulative MAC anesthesia exposure (hrs) had a $p = 0.05$ value (Table 2), which warrants future studies with larger power before it could be considered a possible early individual indirect marker for risk of brain findings. This implication is in line with previous reports that have established quantification of individual repeated anesthetic exposure in infancy as a possible predictor of neurological outcomes later in childhood [44–46]. Thus, future multicenter studies could help validate the use of anesthesia quantification as a possible early indirect marker of brain vulnerability in the context of complex perioperative critical care in infancy.

4.3. Long-Term Evaluation and Neurodevelopmental Outcomes

There is a gap in our knowledge with respect to long-term neurodevelopmental outcomes of infants born with LGEA that underwent Foker process repair, as most reports focus only on surgical outcomes in the cohort of interest [25,47–49]. Our most recent retrospective analysis [50] showed increased survival of infants born with esophageal atresia when compared to previous decades (using Spits [51] and Waterson's [52] evaluation), highlighting the need for this line of inquiry. The most recent meta-analysis of the literature reported conflicting results regarding the long-term neurodevelopment in children born with esophageal atresia [53]. Only two recent reports implicate neurologic findings and increased risk of brain injuries and long-term neurodevelopmental sequalae in a cohort of infants born with gastrointestinal anomalies that included esophageal atresia (without distinction with respect to surgical type: short-gap vs. long-gap) [16,17].

Two landmark multicenter prospective trials, GAS [54] and RESTORE [55], evaluated long-term neurodevelopmental outcome following anesthesia exposure and prolonged sedation, respectively. However, the GAS study reported no negative neurodevelopmental outcomes in otherwise healthy (ASA I and II) infants following simple hernia repair at 2- [56] or 5-year [54] follow-up. Similarly, results from the RESTORE study [55] do not apply to our cohort of infants born with LGEA exposed to prolonged sedation, since their subjects (i) underwent sedation for treatment of primary respiratory disease in the absence of surgery, and (ii) had a smaller mean length of sedation of 6.5 days.

Very importantly, implication of early illness associated with intraoperative hypotension, hypoxemia, and anemia has been shown to increase the risk of morbidity and mortality early in life, as demonstrated by a recent prospective observational study (NECTARINE trial; [57]). Similarly, perioperative periods of diminished cerebral oxygen delivery are associated with abnormalities in Psychomotor Developmental Index and brain magnetic resonance findings in infants undergoing reparative heart surgery [58]. Although our cohort did not include any LGEA infants undergoing cardiac surgeries, it is well known that about 50% of infants with LGEA have co-existing congenital heart disease [50], and that children supported on extra-corporeal membrane oxygenation (ECMO) for cardiac indications have significant developmental delays and warrant close neurodevelopmental follow-up [59]. Furthermore, early postoperative brain volumes are associated with one-year neurodevelopmental outcome in children with severe congenital heart disease [60]. Long-term health-related quality of life is diminished in children following neonatal surgery for congenital heart abnormalities, with specific deficits in school functioning, intelligence quotients, and neuromotor abilities [61–64]. Moreover, the length of mechanical ventilation and the length of exposure to sedative and analgesic drugs have been negatively associated with quality-of-life findings at 12-month and 4-year follow-up [65–67]. Future studies in infants born with LGEA should also explore the impact of brain perfusion and possible poor tissue oxygenation as additional clinical markers. Our pilot findings call for both

early- and long-term neurobehavioral follow-up after complex perioperative critical care for LGEA repair, both in the absence and presence of congenital heart disease or syndromes.

4.4. Study Limitations

Since the correlation and regression analyses used in this study measure the strength of association between two selected variables without insight into etiology, future studies are needed to elucidate the underlying mechanisms of previously presented brain findings [10,19–21]. Additionally, several study limitations should be noted: *Sex Differences*. Our term-born and premature patient groups had an even sex distribution, which is reflective of the relatively equal sex distribution of LGEA infants, as reported by recent retrospective analysis from *The Esophageal and Airway Treatment Center* at our institution [50]. However, potential sex differences were not analyzed due to lack of power. *Study Size*. Future studies should include at least 16 subjects/sex/gestational group to detect a change of 0.25. These power calculations [68–70] are in accordance with infant studies of volumetric analyses (n = 11–13/group) [71] and long-term neurodevelopmental outcomes (n = 13–16/group) [72]. *Timing of MRI scans.* Scans were collected throughout the 1st year of life, leading to a non-uniform time difference between completion of treatment and research MRI scans, introducing potential bias. Furthermore, MRI scans were not collected prior to Foker process treatment, so it is impossible to assess preexisting differences in brain findings or refute the possibility that detected alterations were associated with prematurity alone and not the caregiving conditions associated with the complex care for LGEA repair. *Estimation of quantification.* Some of the infants were transferred from another institutions, likely resulting in underestimation of anesthesia exposure for procedures performed elsewhere. Future multicenter studies could overcome this limitation. As anesthetic, analgesic, and sedative administration was not protocolized at our institution, each infant received a slightly unique combination of agents that also introduces bias.

5. Conclusions

Reported individual associations do not represent a causative relationship, and prematurity should be considered a confounder, as premature infants are known to be sicker. Gestational age grouping with the easily quantifiable listed clinical end-point measures could be combined for assessing the early impact of allostatic load on brain findings following LGEA repair. The impact of complex perioperative critical care with prolonged sedation in the context of LGEA repair with Foker process calls for future studies of long-term neurodevelopmental outcomes in both early-to-late premature and term-born infants.

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Informed Consent Statement: Informed consent was obtained from all subjects' parents/guardians involved in the study.

Data Availability Statement: The unidentified raw data supporting the conclusions of this article will be made available upon request to the corresponding author.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Data were previously published as an abstract at the 2021 American Society of Anesthesiologists (ASA) Conference.

Abbreviations

ASA	American Society of Anesthesiologists
LGEA	long-gap esophageal atresia
MAC	minimal alveolar concentration
MRI	magnetic resonance imaging
PRAm	Pediatric Risk Assessment
r	Spearman Rho test
SGA/IUGR	small for gestational age/intrauterine growth restriction
TEF	tracheo-esophageal fistula
TIVA	total intravenous anesthesia
TPN	total parenteral nutrition
VIF	variance inflation factor

References

1. Sfeir, R.; Michaud, L.; Salleron, J.; Gottrand, F. Epidemiology of esophageal atresia. *Dis. Esophagus* **2013**, *26*, 354–355. [CrossRef] [PubMed]
2. Moore, K.L.; Persaud, T.V.N.; Torchia, M.G. *The Developing Human, Clinically Oriented Embryology*, 10th ed.; Elsevier: Philadelphia, PA, USA, 2015.
3. Van der Zee, D.C.; van Herwaarden, M.Y.; Tytgat, S.H.; Maffi, M.; Lima, M. Esophageal Atresia and Tracheoesophageal Fistula. In *Neonatal Surgery*; Lima, M., Reinberg, O., Eds.; Springer: Cham, Switzerland, 2019.
4. Bairdain, S.; Zurakowski, D.; Vargas, S.O.; Stenquist, N.; McDonald, M.; Towne, M.C.; Miller, D.T.; Jennings, R.W.; Kantor, D.B.; Agrawal, P.B. Long-Gap Esophageal Atresia Is a Unique Entity within the Esophageal Atresia Defect Spectrum. *Neonatology* **2017**, *111*, 140–144. [CrossRef] [PubMed]
5. Holland, A.J.; Fitzgerald, D.A. Oesophageal atresia and tracheo-oesophageal fistula: Current management strategies and complications. *Paediatr. Respir. Rev.* **2010**, *11*, 100–106. [CrossRef] [PubMed]
6. Hunt, R.W.; Perkins, E.J.; King, S. Peri-operative management of neonates with oesophageal atresia and tracheo-oesophageal fistula. *Paediatr. Respir. Rev.* **2016**, *19*, 3–9. [CrossRef] [PubMed]
7. Foker, J.E.; Kendall Krosch, T.C.; Catton, K.; Munro, F.; Khan, K.M. Long-gap esophageal atresia treated by growth induction: The biological potential and early follow-up results. *Semin. Pediatr. Surg.* **2009**, *18*, 23–29. [CrossRef]
8. Kunisaki, S.M.; Foker, J.E. Surgical advances in the fetus and neonate: Esophageal atresia. *Clin. Perinatol.* **2012**, *39*, 349–361. [CrossRef]
9. Bairdain, S.; Hamilton, T.E.; Smithers, C.J.; Manfredi, M.; Ngo, P.; Gallagher, D.; Zurakowski, D.; Foker, J.E.; Jennings, R.W. Foker process for the correction of long gap esophageal atresia: Primary treatment versus secondary treatment after prior esophageal surgery. *J. Pediatr. Surg.* **2015**, *50*, 933–937. [CrossRef]
10. Mongerson, C.R.L.; Wilcox, S.L.; Goins, S.M.; Pier, D.B.; Zurakowski, D.; Jennings, R.W.; Bajic, D. Infant brain structural MRI analysis in the context of thoracic noncardiac surgery and critical care. *Front. Pediatr.* **2019**, *7*, 315. [CrossRef]
11. Hodkinson, D.J.; Mongerson, C.R.L.; Jennings, R.W.; Bajic, D. Neonatal functional brain maturation in the context of perioperative critical care and pain management: A case report. *Heliyon* **2019**, *5*, e02350. [CrossRef]
12. Liszewski, M.C.; Bairdain, S.; Buonomo, C.; Jennings, R.W.; Taylor, G.A. Imaging of long gap esophageal atresia and the Foker process: Expected findings and complications. *Pediatr. Radiol.* **2014**, *44*, 467–475. [CrossRef]
13. Anand, K.J.; Barton, B.A.; McIntosh, N.; Lagercrantz, H.; Pelausa, E.; Young, T.E.; Vasa, R. Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial. Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch. Pediatr. Adolesc. Med.* **1999**, *153*, 331–338. [CrossRef]

14. Dewey, W.L. Various factors which affect the rate of development of tolerance and physical dependence to abused drugs. *NIDA Res. Monogr.* **1984**, *54*, 39–49.
15. Solodiuk, J.C.; Jennings, R.W.; Bajic, D. Evaluation of Postnatal Sedation in Full-Term Infants. *Brain Sci.* **2019**, *9*, 114. [CrossRef]
16. Stolwijk, L.J.; Keunen, K.; de Vries, L.S.; Groenendaal, F.; van der Zee, D.C.; van Herwaarden, M.Y.A.; Lemmers, P.M.A.; Benders, M. Neonatal Surgery for Noncardiac Congenital Anomalies: Neonates at Risk of Brain Injury. *J. Pediatr.* **2017**, *182*, 335–341. [CrossRef]
17. Stolwijk, L.J.; Lemmers, P.M.; Harmsen, M.; Groenendaal, F.; de Vries, L.S.; van der Zee, D.C.; Benders, M.J.; van Herwaarden-Lindeboom, M.Y. Neurodevelopmental Outcomes After Neonatal Surgery for Major Noncardiac Anomalies. *Pediatrics* **2016**, *137*, e20151728. [CrossRef]
18. Rudisill, S.S.; Wang, J.T.; Jaimes, C.; Mongerson, C.R.L.; Hansen, A.R.; Jennings, R.W.; Bajic, D. Neurologic injury and brain growth in the setting of long-gap esophageal atresia perioperative critical care: A pilot study. *Brain Sci.* **2019**, *9*, 383. [CrossRef]
19. Mongerson, C.R.L.; Jaimes, C.; Zurakowski, D.; Jennings, R.W.; Bajic, D. Infant Corpus Callosum Size After Surgery and Critical Care for Long-Gap Esophageal Atresia: Qualitative and Quantitative MRI. *Sci. Rep.* **2020**, *10*, 6408. [CrossRef]
20. Mongerson, C.R.L.; Jennings, R.W.; Zurakowski, D.; Bajic, D. Quantitative MRI study of infant regional brain size following surgery for long-gap esophageal atresia requiring prolonged critical care. *Int. J. Dev. Neurosci.* **2019**, *79*, 11–20. [CrossRef]
21. Bajic, D.; Rudisill, S.S.; Jennings, R.W. Head circumference in infants undergoing Foker process for long-gap esophageal atresia repair: Call for attention. *J. Pediatr. Surg.* **2021**, *59*, 1564–1569. [CrossRef]
22. Doyle, D.J.; Goyal, A.; Bansal, P.; Garmon, E.H. American Society of Anesthesiologists Classification. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2021.
23. Nasr, V.G.; DiNardo, J.A.; Faraoni, D. Development of a Pediatric Risk Assessment Score to Predict Perioperative Mortality in Children Undergoing Noncardiac Surgery. *Anesth. Analg.* **2017**, *124*, 1514–1519. [CrossRef]
24. Quinn, J.A.; Munoz, F.M.; Gonik, B.; Frau, L.; Cutland, C.; Mallett-Moore, T.; Kissou, A.; Wittke, F.; Das, M.; Nunes, T.; et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine* **2016**, *34*, 6047–6056. [CrossRef] [PubMed]
25. Svetanoff, W.J.; Zendejas, B.; Hernandez, K.; Davidson, K.; Ngo, P.; Manfredi, M.; Hamilton, T.E.; Jennings, R.; Smithers, C.J. Contemporary outcomes of the Foker process and evolution of treatment algorithms for long-gap esophageal atresia. *J. Pediatr. Surg.* **2021**, *56*, 2180–2191. [CrossRef] [PubMed]
26. Kamran, A.; Zendejas, B.; Jennings, R.W. Long-Gap Esophageal Atresia. In *Fundamentals of Pediatric Surgery*; Springer: Cham, Switzerland, 2022; pp. 497–508.
27. Vet, N.J.; Kleiber, N.; Ista, E.; de Hoog, M.; de Wildt, S.N. Sedation in Critically Ill Children with Respiratory Failure. *Front. Pediatr.* **2016**, *4*, 89. [CrossRef] [PubMed]
28. Sharma, D.; Shastri, S.; Farahbakhsh, N.; Sharma, P. Intrauterine growth restriction—Part 1. *J. Matern. Fetal Neonatal. Med.* **2016**, *29*, 3977–3987. [CrossRef] [PubMed]
29. Tsudo, M.; Uchiyama, T.; Takatsuki, K.; Uchino, H.; Yodoi, J. Modulation of Tac antigen on activated human T cells by anti-Tac monoclonal antibody. *J. Immunol.* **1982**, *129*, 592–595. [CrossRef]
30. Kagan, M.S.; Mongerson, C.R.L.; Zurakowski, D.; Bajic, D. Impact of Infant Thoracic Non-cardiac Perioperative Critical Care on Homotopic-Like Corpus Callosum and Forebrain Sub-regional Volumes. *Front. Pain Res.* **2022**, *3*, 788903. [CrossRef]
31. Beare, R.J.; Chen, J.; Kelly, C.E.; Alexopoulos, D.; Smyser, C.D.; Rogers, C.E.; Loh, W.Y.; Matthews, L.G.; Cheong, J.L.; Spittle, A.J.; et al. Neonatal Brain Tissue Classification with Morphological Adaptation and Unified Segmentation. *Front. Neuroinform.* **2016**, *10*, 12. [CrossRef]
32. Schober, P.; Vetter, T.R. Correlation Analysis in Medical Research. *Anesth. Analg.* **2020**, *130*, 332. [CrossRef]
33. Schober, P.; Boer, C.; Schwarte, L.A. Correlation Coefficients: Appropriate Use and Interpretation. *Anesth. Analg.* **2018**, *126*, 1763–1768. [CrossRef]
34. Curtin, F.; Schulz, P. Multiple correlations and Bonferroni's correction. *Biol. Psychiatry* **1998**, *44*, 775–777. [CrossRef]
35. Herrup, E.A.; Wieczorek, B.; Kudchadkar, S.R. Characteristics of postintensive care syndrome in survivors of pediatric critical illness: A systematic review. *World J. Crit. Care Med.* **2017**, *6*, 124–134. [CrossRef]
36. Valencia, E.; Staffa, S.J.; Faraoni, D.; DiNardo, J.A.; Nasr, V.G. Prospective External Validation of the Pediatric Risk Assessment Score in Predicting Perioperative Mortality in Children Undergoing Noncardiac Surgery. *Anesth. Analg.* **2019**, *129*, 1014–1020. [CrossRef]
37. Symington, A.; Pinelli, J. Developmental care for promoting development and preventing morbidity in preterm infants. *Cochrane Database Syst. Rev.* **2003**, *4*, CD001814. [CrossRef]
38. Hickey, L.; Burnett, A.; Spittle, A.J.; Roberts, G.; Anderson, P.; Lee, K.; Doyle, L.W.; Cheong, J.L.Y.; Victorian Infant Collaborative Study, G. Extreme prematurity, growth and neurodevelopment at 8 years: A cohort study. *Arch. Dis. Child.* **2021**, *106*, 160–166. [CrossRef]
39. Pollack, M.M.; Ruttimann, U.E.; Getson, P.R. Pediatric risk of mortality (PRISM) score. *Crit. Care Med.* **1988**, *16*, 1110–1116. [CrossRef]
40. Leteurtre, S.; Duhamel, A.; Salleron, J.; Grandbastien, B.; Lacroix, J.; Leclerc, F.; Groupe Francophone de Reanimation et d'Urgences, P. PELOD-2: An update of the PEdiatric logistic organ dysfunction score. *Crit. Care Med.* **2013**, *41*, 1761–1773. [CrossRef]

41. Graciano, A.L.; Balko, J.A.; Rahn, D.S.; Ahmad, N.; Giroir, B.P. The Pediatric Multiple Organ Dysfunction Score (P-MODS): Development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. *Crit. Care Med.* **2005**, *33*, 1484–1491. [CrossRef]
42. Casavant, S.G.; Cong, X.; Fitch, R.H.; Moore, J.; Rosenkrantz, T.; Starkweather, A. Allostatic Load and Biomarkers of Stress in the Preterm Infant: An Integrative Review. *Biol. Res. Nurs.* **2019**, *21*, 210–223. [CrossRef]
43. Guidi, J.; Lucente, M.; Sonino, N.; Fava, G.A. Allostatic Load and Its Impact on Health: A Systematic Review. *Psychother. Psychosom.* **2021**, *90*, 11–27. [CrossRef]
44. Wilder, R.T.; Flick, R.P.; Sprung, J.; Katusic, S.K.; Barbaresi, W.J.; Mickelson, C.; Gleich, S.J.; Schroeder, D.R.; Weaver, A.L.; Warner, D.O. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* **2009**, *110*, 796–804. [CrossRef]
45. Flick, R.P.; Katusic, S.K.; Colligan, R.C.; Wilder, R.T.; Voigt, R.G.; Olson, M.D.; Sprung, J.; Weaver, A.L.; Schroeder, D.R.; Warner, D.O. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* **2011**, *128*, e1053–e1061. [CrossRef] [PubMed]
46. Ing, C.; DiMaggio, C.; Whitehouse, A.; Hegarty, M.K.; Brady, J.; von Ungern-Sternberg, B.S.; Davidson, A.; Wood, A.J.; Li, G.; Sun, L.S. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* **2012**, *130*, e476–e485. [CrossRef] [PubMed]
47. Oztan, M.O.; Soyer, T.; Oztorun, C.I.; Firinci, B.; Durakbasa, C.U.; Dokumcu, Z.; Gollu, G.; Akkoyun, I.; Demirel, D.; Karaman, A.; et al. Outcome of Very Low and Low Birth Weight Infants with Esophageal Atresia: Results of the Turkish Esophageal Atresia Registry. *Eur. J. Pediatr. Surg.* **2021**, *31*, 226–235. [CrossRef] [PubMed]
48. Van der Zee, D.C.; van Herwaarden, M.Y.A.; Hulsker, C.C.C.; Witvliet, M.J.; Tytgat, S.H.A. Esophageal Atresia and Upper Airway Pathology. *Clin. Perinatol.* **2017**, *44*, 753–762. [CrossRef]
49. Harrington, A.W.; Riebold, J.; Hernandez, K.; Staffa, S.J.; Svetanoff, W.J.; Zurakowski, D.; Hamilton, T.; Jennings, R.; Mehta, N.M.; Zendejas, B. Nutrition delivery and growth outcomes in infants with long-gap esophageal atresia who undergo the Foker process. *J. Pediatr. Surg.* **2021**, *56*, 2133–2139. [CrossRef]
50. Evanovich, D.M.; Wang, J.T.; Zendejas, B.; Jennings, R.W.; Bajic, D. From the Ground Up: Esophageal Atresia Types, Disease Severity Stratification and Survival Rates at a Single Institution. *Front. Surg.* **2022**, *9*, 799052. [CrossRef]
51. Spitz, L.; Kiely, E.M.; Morecroft, J.A.; Drake, D.P. Oesophageal atresia: At-risk groups for the 1990s. *J. Pediatr. Surg.* **1994**, *29*, 723–725. [CrossRef]
52. Waterston, D.J.; Carter, R.E.; Aberdeen, E. Oesophageal atresia: Tracheo-oesophageal fistula. A study of survival in 218 infants. *Lancet* **1962**, *1*, 819–822. [CrossRef]
53. Van Hoorn, C.E.; Ten Kate, C.A.; Rietman, A.B.; Toussaint-Duyster, L.C.C.; Stolker, R.J.; Wijnen, R.M.H.; de Graaff, J.C. Long-term neurodevelopment in children born with esophageal atresia: A systematic review. *Dis. Esophagus* **2021**, *34*, doab054. [CrossRef]
54. McCann, M.E.; de Graaff, J.C.; Dorris, L.; Disma, N.; Withington, D.; Bell, G.; Grobler, A.; Stargatt, R.; Hunt, R.W.; Sheppard, S.J.; et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): An international, multicentre, randomised, controlled equivalence trial. *Lancet* **2019**, *393*, 664–677. [CrossRef]
55. Curley, M.A.; Wypij, D.; Watson, R.S.; Grant, M.J.; Asaro, L.A.; Cheifetz, I.M.; Dodson, B.L.; Franck, L.S.; Gedeit, R.G.; Angus, D.C.; et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. *JAMA* **2015**, *313*, 379–389. [CrossRef]
56. Davidson, A.J.; Disma, N.; de Graaff, J.C.; Withington, D.E.; Dorris, L.; Bell, G.; Stargatt, R.; Bellinger, D.C.; Schuster, T.; Arnup, S.J.; et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): An international multicentre, randomised controlled trial. *Lancet* **2016**, *387*, 239–250. [CrossRef]
57. Disma, N.; Veyckemans, F.; Virag, K.; Hansen, T.G.; Becke, K.; Harlet, P.; Vutskits, L.; Walker, S.M.; de Graaff, J.C.; Zielinska, M.; et al. Morbidity and mortality after anaesthesia in early life: Results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). *Br. J. Anaesth.* **2021**, *126*, 1157–1172. [CrossRef]
58. Kussman, B.D.; Wypij, D.; Laussen, P.C.; Soul, J.S.; Bellinger, D.C.; DiNardo, J.A.; Robertson, R.; Pigula, F.A.; Jonas, R.A.; Newburger, J.W. Relationship of intraoperative cerebral oxygen saturation to neurodevelopmental outcome and brain magnetic resonance imaging at 1 year of age in infants undergoing biventricular repair. *Circulation* **2010**, *122*, 245–254. [CrossRef]
59. Sadhwani, A.; Cheng, H.; Stopp, C.; Rollins, C.K.; Jolley, M.A.; Dunbar-Masterson, C.; Wypij, D.; Newburger, J.; Ware, J.; Thiagarajan, R.R. Early Neurodevelopmental Outcomes in Children Supported with ECMO for Cardiac Indications. *Pediatr. Cardiol.* **2019**, *40*, 1072–1083. [CrossRef]
60. Meuwly, E.; Feldmann, M.; Knirsch, W.; von Rhein, M.; Payette, K.; Dave, H.; Tuura, R.O.G.; Kottke, R.; Hagmann, C.; Latal, B.; et al. Postoperative brain volumes are associated with one-year neurodevelopmental outcome in children with severe congenital heart disease. *Sci. Rep.* **2019**, *9*, 10885. [CrossRef]
61. Garcia Guerra, G.; Robertson, C.M.; Alton, G.Y.; Joffe, A.R.; Dinu, I.A.; Nicholas, D.; Ross, D.B.; Rebeyka, I.M.; Western Canadian Complex Pediatric Therapies Follow-up Group. Quality of life 4 years after complex heart surgery in infancy. *J. Thorac. Cardiovasc. Surg.* **2013**, *145*, 482–488. [CrossRef]
62. Garcia Guerra, G.; Joffe, A.R.; Robertson, C.M.; Atallah, J.; Alton, G.; Sauve, R.S.; Dinu, I.A.; Ross, D.B.; Rebeyka, I.M.; Western Canadian Complex Pediatric Therapies Follow-up Group. Health-related quality of life experienced by children with chromosomal abnormalities and congenital heart defects. *Pediatr. Cardiol.* **2014**, *35*, 536–541. [CrossRef]

63. Ricci, M.F.; Andersen, J.C.; Joffe, A.R.; Watt, M.J.; Moez, E.K.; Dinu, I.A.; Garcia Guerra, G.; Ross, D.B.; Rebeyka, I.M.; Robertson, C.M. Chronic Neuromotor Disability After Complex Cardiac Surgery in Early Life. *Pediatrics* **2015**, *136*, e922–e933. [CrossRef]
64. Garcia Guerra, G.; Zorzela, L.; Robertson, C.M.; Alton, G.Y.; Joffe, A.R.; Moez, E.K.; Dinu, I.A.; Ross, D.B.; Rebeyka, I.M.; Lequier, L.; et al. Survival and neurocognitive outcomes in pediatric extracorporeal-cardiopulmonary resuscitation. *Resuscitation* **2015**, *96*, 208–213. [CrossRef]
65. Andropoulos, D.B.; Ahmad, H.B.; Haq, T.; Brady, K.; Stayer, S.A.; Meador, M.R.; Hunter, J.V.; Rivera, C.; Voigt, R.G.; Turcich, M.; et al. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: A retrospective cohort study. *Paediatr. Anaesth.* **2014**, *24*, 266–274. [CrossRef] [PubMed]
66. Garcia Guerra, G.; Robertson, C.M.; Alton, G.Y.; Joffe, A.R.; Cave, D.A.; Yasmin, F.; Dinu, I.A.; Creighton, D.E.; Ross, D.B.; Rebeyka, I.M.; et al. Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up. *Paediatr. Anaesth.* **2014**, *24*, 257–265. [CrossRef] [PubMed]
67. Kuhn, V.A.; Carpenter, J.L.; Zurakowski, D.; Reitz, J.G.; Tague, L.; Donofrio, M.T.; Murnick, J.; Axt-Fliedner, R.; Limperopoulos, C.; Yerebakan, C. Determinants of neurological outcome in neonates with congenital heart disease following heart surgery. *Pediatr. Res.* **2021**, *89*, 1283–1290. [CrossRef] [PubMed]
68. Morgan, T.M.; Case, L.D. Conservative Sample Size Determination for Repeated Measures Analysis of Covariance. *Ann. Biom. Biostat.* **2013**, *1*, 1002.
69. Staffa, S.J.; Zurakowski, D. Statistical power and sample size calculations: A primer for pediatric surgeons. *J. Pediatr. Surg.* **2019**, *55*, 1173–1179. [CrossRef]
70. Staffa, S.J.; Zurakowski, D. Five Steps to Successfully Implement and Evaluate Propensity Score Matching in Clinical Research Studies. *Anesth. Analg.* **2018**, *127*, 1066–1073. [CrossRef]
71. Zacharia, A.; Zimine, S.; Lovblad, K.O.; Warfield, S.; Thoeny, H.; Ozdoba, C.; Bossi, E.; Kreis, R.; Boesch, C.; Schroth, G.; et al. Early assessment of brain maturation by MR imaging segmentation in neonates and premature infants. *AJNR Am. J. Neuroradiol.* **2006**, *27*, 972–977.
72. Gischler, S.J.; Mazer, P.; Duivenvoorden, H.J.; van Dijk, M.; Bax, N.M.; Hazebroek, F.W.; Tibboel, D. Interdisciplinary structural follow-up of surgical newborns: A prospective evaluation. *J. Pediatr. Surg.* **2009**, *44*, 1382–1389. [CrossRef]

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Brief Report

Lower Patient Height and Weight Are Predisposing Factors for Complex Radial Arterial Catheterization

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Abstract: Background: Radial artery (RA) catheterization for invasive blood pressure monitoring is often performed via palpation, and an ultrasound is used secondarily only in case of multiple unsuccessful attempts. Although more elaborate, it has been shown that primary ultrasound-guided catheterization may be advantageous compared with palpation. The aim of this study was to identify factors associated with difficult RA catheterization. **Methods:** Left RA ultrasound assessments were performed in patients with indicated invasive blood pressure monitoring the day before surgery. RA catheterization was performed by personnel blinded to the ultrasound results. Based on the number of attempts needed for successful catheter placement, the cohort was divided into uncomplicated (group 1) and difficult (more than one attempt, group 2) catheterization cases. Cases subjected to primary ultrasound were excluded from the analysis. **Results:** Body weight, height and surface area (BSA) of patients in group 2 (n = 16) were significantly lower than those of patients in group 1 (n = 25), and internal RA diameters were significantly smaller in group 2 patients. In the whole cohort, BSA was significantly associated with distal and proximal internal RA diameters. In contrast, no differences were observed in the skin-to-artery distance, the longitudinal axis deviation (kinking) or blood flow velocity. Median time to successful catheterization was 77 (47–179) s. Prolonged time needed for cannulation was significantly associated with lower body weight, BMI and BSA, and with reduced distal and proximal internal RA diameter. **Conclusions:** RA catheterization performed through pulse palpation may be difficult, especially in adult patients with lower body weight and height, due to reduced arterial diameters. Initial use of ultrasound in these patients may reduce first-attempt failure, preventing procedural delays and patient discomfort.

Keywords: ultrasound; sonography; arterial catheterization; invasive blood pressure monitoring

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1. Background

Blood pressure monitoring is standard during anesthesia care. While non-invasive assessment based on the Riva-Rocci method is usually assumed to be sufficient for patients presenting with moderate comorbidities and for minor invasive interventions, continuous invasive ("bloody") intra-arterial blood pressure monitoring is recommended for more invasive procedures or for critically ill patients [1]. This requires the insertion of an arterial intravascular catheter, with the radial artery being commonly accessed [2]. Using a fluid-filled pressure conduction line connected to the catheter, beat-to-beat intra-arterial blood pressure can be assessed using a pressure transducer placed outside the patient's body and then displayed on a monitor. The need for higher and frequent arterial blood gas sampling, e.g., during thoracic surgery involving challenging ventilation and oxygenation, is a further indication of the requirement for arterial cannulation [1,3]. Moreover, transradial access has been established as a preferred access for percutaneous coronary catheterization [4].

Radial arterial puncture is usually performed with the index or middle finger of the hand opposite to that palpating the artery. Although it has been shown that primary ultrasound-guided puncture may be advantageous over palpation [5], in clinical practice, vascular sonography followed by secondary ultrasound-guided puncture are utilized only in case of multiple unsuccessful attempts. This results in unwanted delays and may be associated with increased complication rates [5].

Additionally, due to procedural reasons or low availability of ultrasound devices, it is often not possible to perform every arterial catheterization ultrasound-guided. Therefore, the aim of this study was to identify those factors that are associated with difficult puncture or catheterization and that therefore make primary vascular sonography appear reasonable. Surgical patients with a need for invasive blood pressure monitoring were evaluated using vascular ultrasounds the day before their planned catheterization, and the results of the assessments were correlated with punctures performed by an operator blinded to those results.

2. Methods

All analyses were performed in accordance with the Declaration of Helsinki. The local ethics committee (University Hospital Bonn, Germany) considered the study to be compliant with the applicable professional codes and regulations and therefore approved the study protocol (Ethics Committee of the University Hospital Bonn, Germany; protocol number 261/19; date of approval: 28 August 2019). Written informed consent was obtained from all patients before ultrasound examination and catheterization. Elective orthopedic and cardiac surgery patients aged >18 years with indicated invasive blood pressure monitoring were included. Exclusion criteria were emergency surgery and refusal to provide written informed consent.

Radial artery (RA) ultrasound assessment was performed the day before surgery. As per internal standard, arterial catheterization is usually performed on the left side; therefore, left RA ultrasound characteristics were assessed. All assessments were performed by one trained person experienced in anesthesiologic vascular ultrasound using a linear array hockey stick probe (L15-7io) on a Philips CX50 ultrasound machine (Philips GmbH, Hamburg, Germany). The following parameters were obtained:

RA diameter at the level of and 5 cm proximal to the styloid process.
Longitudinal axis deviation over a distance from the level of styloid process to 5 cm proximal to it (kinking of the artery).
Skin-to-artery distance at the level of and 5 cm proximal to the styloid process.
Maximum blood flow velocity (Vmax).
Presence of stenoses and plaques.
RA diameter and axis deviation measured longitudinally (long axis, LA) and cross-sectionally (short axis, SA).

Catheterization of the RA was performed and observed the day following ultrasound examination. The puncture itself was performed either without or primarily or secondarily using ultrasound guidance at the discretion of the operator who was not part of the study personnel and was therefore blinded to the results of the ultrasound assessment. All catheterizations in both groups (see below) were performed uniformly by the same three operators, all of whom were board-certified anesthesiologists with years of experience in performing arterial and venous vascular punctures. In all cases, punctures were performed at the level of the proximal radial artery, approximately 2 cm proximal to the radial styloid (to be differentiated from the recently described distal radial access, which is performed at the level of the snuffbox [6,7]). All catheterizations performed primarily using ultrasounds were excluded from subsequent analyses. Based on the number of attempts needed to successfully place the catheter, the cohort was divided into uncomplicated and difficult (more than one attempt) catheterizations (group 1 or 2, respectively). The following details were recorded:

Number of attempts needed for successful catheter placement.
Time needed for successful catheter placement.
Secondary use of ultrasound.
RA punctures themselves were performed by the same three trained anesthetists according to local hospital standards. Additional data recorded comprised:
Body weight and height.
Heart rate and systolic and diastolic blood pressure during sonography as well as during catheterization.
Pulsatility index obtained from pulse oximetry during catheterization.

Body surface area (BSA) was calculated using the formula by DuBois: BSA (m^2) = body height$^{0.725}$ (cm) × body weight$^{0.425}$ (kg) × 0.007184.

Statistical analyses and visualizations were performed using MS Excel 2019 (Microsoft Corp., Redmond, CA, USA) and GraphPad PRISM 8 (La Jolla, CA, USA). Data are presented as median values with 25th and 75th percentiles or as absolute numbers with percentage values and were analyzed using Mann–Whitney test and Fisher's exact test, respectively, and Spearman's correlation. The alpha level was set to 0.05. All datasets are available from the corresponding author on reasonable request.

3. Results

In total, ultrasound assessments—conducted the day before surgery—and arterial catheterizations were performed in 47 patients. As the anesthetist performing arterial puncture was blinded to the results of the pre-procedural ultrasound assessment and the approach to cannulation was left at their discretion and solely observed, punctures were performed either without or primarily or secondarily (when catheterization appeared difficult) using ultrasound guidance. Only those procedures involving catheterization via palpation were included in the analysis, while those with primary use of sonography (n = 6) were excluded. Difficult cannulation was defined as the need for multiple attempts (more than one) to successfully puncture the artery, and accordingly, the cohort was divided into uncomplicated (group 1, n = 25) and difficult (group 2, n = 16) catheterization. The study included cardiac surgery (n = 36) and orthopedic surgery (n = 5) patients. Median body weight in the whole cohort was 82 (73–90) kg, height was 174 (167–181) cm, BMI was 26.8 (23.8–29.2) kg/m^2 and BSA was 1.96 (1.80–2.12) m^2. In group 1, median body weight was 83 (73–95) kg, height was 178 (170–182) cm, BMI was 27.7 (24.2–29.1) kg/m^2 and BSA was 2.04 (1.83–2.17) m^2. In group 2, median body weight was 75 (65–85) kg, height was 169 (162–178) cm, BMI was 25.9 (22.7–29.3) kg/m^2 and BSA was 1.90 (1.67–1.96) m^2. Body weight (p = 0.046), height (p = 0.011) and BSA (p = 0.011) of patients in group 2 were significantly lower than those of patients in group 1 (Figure 1A). Heart rate and blood pressure showed no significant intergroup differences.

Table 1 provides the results of the preoperative ultrasound assessments for the whole cohort as well as for groups 1 and 2. As shown in Figure 1B, the distal and proximal internal radial artery diameters were significantly smaller in group 2 patients (difficult catheterization) compared with group 1 patients (p = 0.02). In the whole cohort, Spearman's correlation analysis showed that BSA was significantly associated with distal (Spearman's r = 0.48, p = 0.001) as well as proximal internal radial artery diameters (Spearman's r = 0.40, p = 0.009). In contrast, no intergroup differences were observed in the depth of the artery beneath the skin, in the longitudinal axis deviation over a distance of 5 cm or in blood flow velocity. Furthermore, plaques and stenoses had no influence on the difficulties encountered during cannulation.

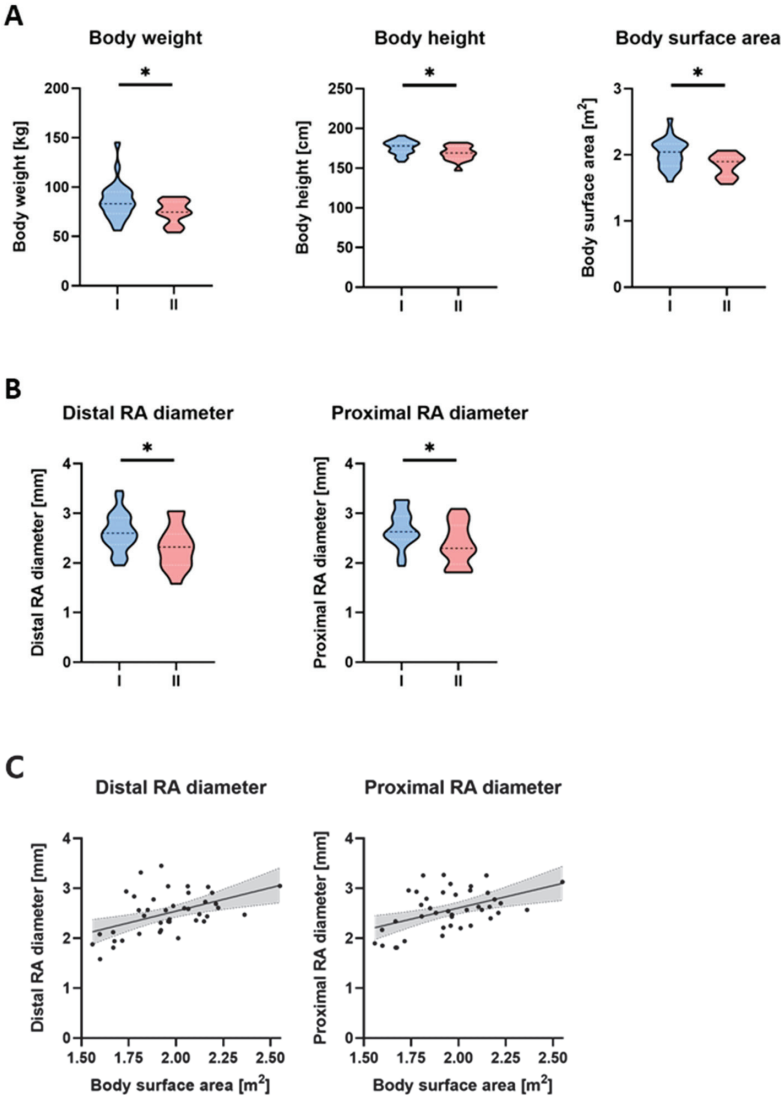

Figure 1. Body metrics and preoperative radial artery ultrasound. Ultrasound assessment of the left radial artery (RA) was performed in all patients the day before surgery using a linear probe. According to the number of attempts needed for successful subsequent RA catheterization, the cohort was divided into un-complicated and difficult (more than one attempt) catheterization (group 1 (n = 25) or 2 (n = 16), respectively). (**A**) Patients in group 2 (difficult catheterization) had lower body weight, height and surface area than those in group 1. (**B**) In group 2 (difficult catheterization), distal (at the level of the styloid process) and 5 cm proximal internal RA diameter was significantly smaller compared to those in group 1. (**C**) In the whole cohort, body surface area was significantly associated with distal as well as proximal internal RA diameter. Data are visualized as violin diagrams with median and interquartile range (25–75), indicated by the dashed lines. Mann-Whitney test and Spearman correlation were used for analysis. * $p < 0.05$.

Table 1. Results of preoperative ultrasound assessment of patients in the whole cohort as well as patients in group 1 (uncomplicated catheterization) and group 2 (difficult catheterization).

	Whole Cohort	Group 1	Group 2	
	***n* = 41**	***n* = 25**	***n* = 16**	***p*-Value**
Basic characteristics:				
Weight (kg)	82 (73–90)	83 (73–95)	75 (65–85)	**0.046**
Height (cm)	174 (167–181)	178 (170–182)	169 (162–178)	**0.011**
Body mass index	26.8 (23.8–29.2)	27.7 (24.2–29.1)	25.9 (22.7–29.3)	0.521
Body surface area (m^2)	1.96 (1.80–2.12)	2.04 (1.83–2.17)	1.90 (1.67–1.96)	**0.011**
Heart rate (bpm)	68 (60–79)	68 (60–81)	66 (60–79)	0.796
Blood pressure sys (mmHg)	125 (110–136)	130 (110–141)	125 (110–134)	0.436
Blood pressure dia (mmHg)	75 (70– 82)	75 (70–85)	75 (70–80)	0.963
Previous arterial puncture (*n*)	31 (76%)	19 (76%)	12 (75%)	0.999
Ultrasound characteristics:				
Dist. int. diameter SA (mm)	2.60 (2.32–2.95)	2.64 (2.38–2.98)	2.41 (1.99–2.60)	**0.039**
Prox. int. diameter SA (mm)	2.61 (2.25–2.91)	2.64 (2.50–3.04)	2.41 (2.04–2.85)	0.058
Dist. int. diameter LA (mm)	2.48 (2.14–2.81)	2.60 (2.37–2.91)	2.32 (1.96–2.58)	**0.018**
Prox. int. diameter LA (mm)	2.57 (2.25–2.93)	2.63 (2.48–2.95)	2.30 (1.98–2.76)	**0.024**
Long axis deviation SA (mm)	4.66 (3.23–6.72)	5.24 (3.15–7.44)	4.31 (3.27–6.13)	0.594
Long axis deviation LA (mm)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.999
Dist. distance skin–artery (mm)	6.43 (5.32–7.21)	6.65 (5.69–8.42)	6.16 (4.42–6.81)	0.084
Prox. distance skin–artery (mm)	7.01 (4.87–8.25)	7.01 (4.70–8.47)	6.96 (4.86–8.29)	0.911
Vmax (cm/s)	80.70 (61.95–99.55)	86.35 (64.53–141.00)	79.15 (55.65–95.83)	0.349
Stenoses, plaques (*n*)	14 (34%)	9 (36%)	5 (31%)	0.999

Data are given as median values with 25th and 75th percentiles or as absolute numbers with percentage values and were compared using the Mann–Whitney test or Fisher's exact test, respectively. *p* values refer to the results of intergroup comparisons (group 1 vs. 2). Significant differences are given in bold values. SA = short axis scan, LA = long axis scan.

Ultrasound assessment of the left radial artery (RA) was performed in all patients the day before surgery using a linear probe. Based on the number of attempts needed for successful subsequent RA catheterization, the cohort was divided into uncomplicated (group 1, $n = 25$) and difficult (more than one attempt, group 2, $n = 16$) catheterization.

Patients in group 2 (difficult catheterization) had lower body weight, height and surface area compared with patients in group 1.

Distal (at the level of the styloid process) and 5 cm proximal internal RA diameters were significantly smaller in group 2 (difficult catheterization) than in group 1.

Body surface area of the whole cohort was significantly associated with distal as well as proximal internal RA diameters.

Data are visualized as violin diagrams with the median and interquartile range (25–75), indicated by the dashed lines. The Mann–Whitney test and Spearman's correlation were used for analysis ($p < 0.05$).

Time needed for successful radial artery (RA) catheterization with lower body weight, height and surface area as well as with smaller distal (at the level of the styloid process) and 5 cm proximal internal RA diameters were measured.

Median time needed for successful catheterization was 77 (47–179) s for the whole cohort. As expected, the need for multiple attempts significantly prolonged the time needed for catheterization in group 2 (181 (155–286) s) compared with group 1 (53 (38–77) s, $p < 0.0001$). Furthermore, difficult arterial puncture with a need for multiple attempts significantly increased secondary ultrasound use in group 2 (50%) compared with group 1 (0%, $p = 0.0001$). Spearman's correlation analysis of the whole cohort showed that the prolonged time needed for cannulation was significantly associated with lower body weight (Spearman's $r = -0.41$, $p = 0.008$), BMI (Spearman's $r = -0.31$, $p = 0.049$) and BSA (Spearman's $r = -0.40$, $p = 0.009$), and with reduced distal (Spearman's $r = -0.38$, $p = 0.014$) and proximal (Spearman's $r = -0.33$, $p = 0.033$) internal radial artery diameters (Figure 2). No intergroup differences were observed in heart rate, systolic and diastolic blood pressure

or pulse perfusion index during catheterization, or in the secondary intraoperative failure of invasive blood pressure monitoring. Results of the catheterization observations in the whole cohort as well as in group 1 and group 2 are given in Table 2.

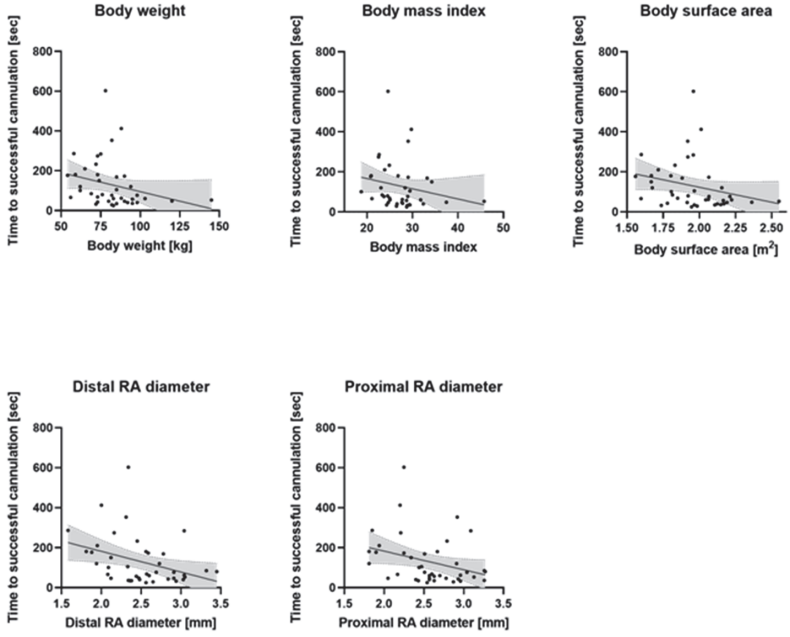

Figure 2. Radial artery catheterization. Time needed for successful radial artery (RA) catheterization with lower body weight, height and surface area as well as with smaller distal (at the level of the styloid process) and 5 cm proximal internal RA diameter. Spearman correlation was used for analysis.

Table 2. Results of radial artery cannulation observations in the whole cohort as well as in group 1 (uncomplicated catheterization) and group 2 (difficult catheterization).

	Whole Cohort	Group 1	Group 2	
	***n* = 41**	***n* = 25**	***n* = 16**	***p*-Value**
Heart rate (bpm)	70 (61–80)	70 (59–80)	70 (63–80)	0.478
Blood pressure sys (mmHg)	141 (125–157)	144 (121–158)	138 (127–156)	0.706
Blood pressure dia (mmHg)	71 (62–83)	73 (61–87)	68 (63–78)	0.520
Pulsatility index	0.80 (0.50–1.80)	0.78 (0.50–1.29)	0.80 (0.50–2.70)	0.536
Number of attempts needed for successful catheter placement (*n*)	1 (1–2)	1 (1–1)	2 (2–3)	**0.0001**
Time needed for successful catheter placement (s)	77 (47–179)	53 (38–77)	181 (155–286)	**0.0001**
Secondary use of ultrasound (*n*)	8 (20%)	0 (0%)	8 (50%)	**0.0001**

Data are given as median values with 25th and 75th percentiles or as absolute numbers with percentage values and were compared using the Mann–Whitney test or Fisher's exact test, respectively. *p*-values refer to the results of intergroup comparisons (group 1 vs. 2). Significant differences are given in bold values.

4. Discussion

Ultrasound guidance can be beneficial during radial artery catheterization. However, the factors that may impede puncture and therefore make primary use of sonography advantageous are still elusive. We demonstrated that difficult radial artery cannulation for invasive blood pressure monitoring resulting in the need for multiple attempts significantly

prolonged the procedural processes. This was associated with reduced proximal as well as distal radial artery diameters and was seen particularly in patients with lower body weight and height. Primary ultrasound use may be advantageous in these patients.

Radial artery catheterization is a common invasive procedure in anesthesia care as it allows for real-time continuous blood pressure monitoring in critically ill patients as well as during more invasive surgical procedures, and for repeated blood sampling, e.g., blood gas analyses [1–3]. Usually, puncture and catheterization of the radial artery are performed using anatomic landmarks and pulse palpation. However, although widely established in daily practice, this technique may fail, especially under circumstances such as arterial hypotension or in small infants [1,2]. The resulting multiple attempts lead to delays in procedural processes and may induce secondary complications such as hematoma or temporary—or even permanent—vascular occlusion with subsequent distal necroses [1,2,8,9]. Ultrasound guidance for vascular access and regional anesthesia allows for direct visualization of targeted vessels and nerval structures and the puncture process and can provide confirmation of the correct guidewire and catheter positioning, and is therefore established in anesthesia and intensive care medicine and recommended in recent guidelines [10–13]. However, in contrast to venous access and nerve blockade, radial artery cannulation is still commonly performed via palpation, and sonography is only used when multiple attempts have failed. In addition to delays and complications, this greatly impairs patient comfort.

In daily practice, operation room workflows may be significantly affected by difficulties encountered while establishing vascular access, greatly impacting cost efficiency [9]. As demonstrated by our results, in case a first attempt performed using palpation fails, the need for further attempts with or without ultrasound obviously delays the whole procedural workflow. A meta-analysis by Gu et al. revealed that radial artery catheterization first-attempt failure was significantly reduced by the use of 2D ultrasound, as were hematoma complications and the mean time needed for successful cannulation [5]. Similar results have been shown for alternative radial access routes such as the distal approach performed at the level of the snuffbox, with ultrasound reducing complications and maximizing technical success, even in small-diameter or pathological arteries [6]. Moreover, the results of the RAUST trial (Radial Artery Access With Ultrasound Trial) demonstrated the advantages of ultrasound use in radial artery cannulation in a randomized multicenter setting [14].

Performing all radial artery catheterization using an ultrasound is possible in centers with high availability of ultrasound machines, but is not possible at our tertiary university medical center. To identify anatomical and physiognomical factors associated with difficult palpational punctures would therefore be of particular interest since this would aid in stratifying patients for primary or secondary ultrasound guidance. Based on our results, reduced distal and proximal radial artery diameters were significantly associated with multiple catheterization attempts and prolonged the time needed for successful catheterization. Since low body weight and height were predisposing factors for reduced arterial diameter, cannulation was difficult in patients with lower body mass index or body surface area. In contrast, skin-surface-to-artery distance or longitudinal axis deviation seemed to have no impact on cannulation success.

Our results are in line with previous reports. Jung Oh et al. report reduced radial artery cross-sectional area as an independent predictor of first-attempt failed catheterization in children even when ultrasound was used [15]. Measures that may increase that diameter and cross-sectional area such as a median nerve block performed prior to radial artery cannulation will help facilitate the puncture [16].

In accordance with our data, the results from Kotowycz et al. revealed that lower patient height, weight, BMI and BSA, together with other physiognomical parameters such as wrist circumference or shoe size, predict reduced radial artery size in patients undergoing cardiac catheterization [17]. Consequently, difficulties encountered during radial cannulation leading to conversion into femoral access were similarly shown to be

associated with reduced patient height and body surface area [18,19]. This is somewhat surprising since radial catheterization is usually thought to be particularly challenging in obese patients [20]. However, it was demonstrated that radial artery diameter is increased in obese patients compared with lean subjects, which possibly explains our finding that difficult cannulation was associated with reduced body mass index [21]. Interestingly, in contrast with our study, results from other studies revealed no association between clinical parameters such as BMI and radial artery diameter [22]. Nevertheless, they similarly stressed the significance of ultrasound in improving radial artery cannulation success.

In our study, plaques and stenoses were equally distributed between the two groups, suggesting that radial artery quality has no impact on catheterization success. In fact, as revealed by a large study by Dehghani et al. involving more than 2000 patients, neither plaques nor stenoses were independently associated with failing transradial cannulation for percutaneous coronary intervention [23]. However, due to the small sample size in our study, an effect may not be excluded with certainty. A recent study by Achim et al. revealed a further interesting aspect, demonstrating that radial artery calcification is correlated with coronary calcification and plaque burden requiring revascularization [24]. This suggests that radial ultrasound may also be useful for preoperatively identifying patients with significant coronary atherosclerosis, underlining the role of the anesthesiologist in screening for relevant comorbidities.

Our study has some limitations, including a small sample size that potentially resulted in underpowered conclusions. Only orthopedic and cardiac surgery patients were evaluated, potentially limiting the application of our results to other surgical patient populations. Last, although performed uniformly in all patients by the same experienced operators, arterial cannulation was not strictly standardized but was left to the discretion of the anesthetist taking care of the patient. Since the classical forearm proximal access was used in all cases, our results cannot be transferred to other approaches such as the distal radial artery access performed at the level of the snuffbox, which has recently been proven to be non-inferior compared with the conventional proximal radial access [6,7].

5. Conclusions

In summary, the results of our observational study revealed that radial artery catheterization performed using pulse palpation may be difficult, especially in adult patients with lower body weight and height, due to their reduced arterial diameters. Initial ultrasound use in these patients may reduce first-attempt failure, preventing procedural delays and patient discomfort.

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References

1. Troianos, C.A.; Hartman, G.S.; Glas, K.E.; Skubas, N.J.; Eberhardt, R.T.; Walker, J.D.; Reeves, S.T. Councils on Intraoperative Echocardiography and Vascular Ultrasound of the American Society of Echocardiography; Society of Cardiovascular Anesthesiologists Special Articles: Guidelines for Performing Ultrasound Guided Vascular Cannulation: Recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *Anesth. Analg.* **2012**, *114*, 46–72. [CrossRef] [PubMed]
2. Brzezinski, M.; Luisetti, T.; London, M.J. Radial Artery Cannulation: A Comprehensive Review of Recent Anatomic and Physiologic Investigations. *Anesth. Analg.* **2009**, *109*, 1763–1781. [CrossRef] [PubMed]
3. Anesthesiology Core Review: Part Two Advanced Exam | AccessAnesthesiology | McGraw Hill Medical. Available online: https://accessanesthesiology.mhmedical.com/book.aspx?bookID=1750 (accessed on 11 September 2022).
4. Dworeck, C.; Redfors, B.; Völz, S.; Haraldsson, I.; Angerås, O.; Råmunddal, T.; Ioanes, D.; Myredal, A.; Odenstedt, J.; Hirlekar, G.; et al. Radial Artery Access Is Associated with Lower Mortality in Patients Undergoing Primary PCI: A Report from the SWEDEHEART Registry. *Eur. Heart J. Acute Cardiovasc. Care* **2020**, *9*, 323–332. [CrossRef]
5. Gu, W.-J.; Wu, X.-D.; Wang, F.; Ma, Z.-L.; Gu, X.-P. Ultrasound Guidance Facilitates Radial Artery Catheterization: A Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials. *Chest* **2016**, *149*, 166–179. [CrossRef] [PubMed]
6. Achim, A.; Péter, O.Á.; Kákonyi, K.; Sasi, V.; Nemes, A.; Homorodean, C.; Stanek, A.; Olinic, D.M.; Ruzsa, Z. The Role of Ultrasound in Accessing the Distal Radial Artery at the Anatomical Snuffbox for Cardiovascular Interventions. *Life* **2023**, *13*, 25. [CrossRef]
7. Xiong, J.; Hui, K.; Xu, M.; Zhou, J.; Zhang, J.; Duan, M. Distal Radial Artery as an Alternative Approach to Forearm Radial Artery for Perioperative Blood Pressure Monitoring: A Randomized, Controlled, Noninferiority Trial. *BMC Anesthesiol.* **2022**, *22*, 67. [CrossRef]
8. Scheer, B.; Perel, A.; Pfeiffer, U.J. Clinical Review: Complications and Risk Factors of Peripheral Arterial Catheters Used for Haemodynamic Monitoring in Anaesthesia and Intensive Care Medicine. *Crit. Care Lond. Engl.* **2002**, *6*, 199–204. [CrossRef]
9. Fatima, H.; Chaudhary, O.; Krumm, S.; Mufarrih, S.H.; Qureshi, N.Q.; Oren-Grinberg, A.; Bose, R.R.; Huang, L.; Mahmood, F.; Matyal, R. Workflow of Ultrasound-Guided Arterial Access. *J. Cardiothorac. Vasc. Anesth.* **2021**, *35*, 1611–1617. [CrossRef] [PubMed]
10. Boselli, E.; Hopkins, P.; Lamperti, M.; Estèbe, J.-P.; Fuzier, R.; Biasucci, D.G.; Disma, N.; Pittiruti, M.; Traškaitė, V.; Macas, A.; et al. European Society of Anaesthesiology and Intensive Care Guidelines on Peri-Operative Use of Ultrasound for Regional Anaesthesia (PERSEUS Regional Anesthesia): Peripheral Nerves Blocks and Neuraxial Anaesthesia. *Eur. J. Anaesthesiol.* **2021**, *38*, 219–250. [CrossRef] [PubMed]
11. Lamperti, M.; Biasucci, D.G.; Disma, N.; Pittiruti, M.; Breschan, C.; Vailati, D.; Subert, M.; Traškaitė, V.; Macas, A.; Estebe, J.-P.; et al. European Society of Anaesthesiology Guidelines on Peri-Operative Use of Ultrasound-Guided for Vascular Access (PERSEUS Vascular Access). *Eur. J. Anaesthesiol.* **2020**, *37*, 344–376. [CrossRef]
12. Baehner, T.; Rohner, M.; Heinze, I.; Schindler, E.; Wittmann, M.; Strassberger-Nerschbach, N.; Kim, S.-C.; Velten, M. Point-of-Care Ultrasound-Guided Protocol to Confirm Central Venous Catheter Placement in Pediatric Patients Undergoing Cardiothoracic Surgery: A Prospective Feasibility Study. *J. Clin. Med.* **2021**, *10*, 5971. [CrossRef] [PubMed]
13. Hilbert, T.; Weber, S.; Knies, R.; Kim, S.-C. Value of Ultrasound with a Single Linear Transducer to Confirm Correct Positioning of Central Venous Catheter in Low Body Weight Neonates. *Eur. J. Anaesthesiol.* **2015**, *32*, 893–894. [CrossRef]
14. Seto, A.H.; Roberts, J.S.; Abu-Fadel, M.S.; Czak, S.J.; Latif, F.; Jain, S.P.; Raza, J.A.; Mangla, A.; Panagopoulos, G.; Patel, P.M.; et al. Real-Time Ultrasound Guidance Facilitates Transradial Access: RAUST (Radial Artery Access with Ultrasound Trial). *JACC Cardiovasc. Interv.* **2015**, *8*, 283–291. [CrossRef]
15. Jung Oh, E.; Jin Min, J.; Su Kim, C.; Yun Hwang, J.; Gook, J.; Lee, J.-H. Evaluation of the Factors Related to Difficult Ultrasound-Guided Radial Artery Catheterization in Small Children: A Prospective Observational Study. *Acta Anaesthesiol. Scand.* **2021**, *65*, 203–212. [CrossRef]
16. Men, X.; Wang, Q.; Hu, W.-S.; Chai, Y.; Ni, T.-T.; Shou, H.-Y.; Zhou, Z.-F. Median Nerve Block Increases the Success Rate of Radial Artery Cannulation in Women with Gestational Hypertension Undergoing Cesarean Section. *BMC Anesthesiol.* **2022**, *22*, 248. [CrossRef]
17. Kotowycz, M.A.; Johnston, K.W.; Ivanov, J.; Asif, N.; Almoghairi, A.M.; Choudhury, A.; Nagy, C.D.; Sibbald, M.; Chan, W.; Seidelin, P.H.; et al. Predictors of Radial Artery Size in Patients Undergoing Cardiac Catheterization: Insights from the Good Radial Artery Size Prediction (GRASP) Study. *Can. J. Cardiol.* **2014**, *30*, 211–216. [CrossRef] [PubMed]
18. Roeschl, T.; Jano, A.M.; Fochler, F.; Grewe, M.M.; Wacker, M.; Meier, K.; Schmidt, C.; Maier, L.; Grewe, P.H. Prevalence and Predictors of Difficult Vascular Anatomy in Forearm Artery Access for Coronary Angiography and PCI. *Sci. Rep.* **2022**, *12*, 13060. [CrossRef] [PubMed]
19. Carvalho, M.S.; Calé, R.; de Gonçalves, P.A.; Vinhas, H.; Raposo, L.; Teles, R.; Martins, C.; Gabriel, H.M.; Pereira, H.; Almeida, M. Predictors of Conversion from Radial into Femoral Access in Cardiac Catheterization. *Arq. Bras. Cardiol.* **2015**, *104*, 401–408. [CrossRef]
20. Zou, Q.; Jiang, J.; Shi, C.; Wu, B.; Gui, B.; Zhou, X. Single and Double Developing Lines Improve Ultrasound-Guided Radial Artery Catheterization in Obese Patients: A Randomized Controlled Trial. *Anaesth. Crit. Care Pain Med.* **2022**, *42*, 101166. [CrossRef]

21. Mangoni, A.A.; Giannattasio, C.; Brunani, A.; Failla, M.; Colombo, M.; Bolla, G.; Cavagnini, F.; Grassi, G.; Mancia, G. Radial Artery Compliance in Young, Obese, Normotensive Subjects. *Hypertension* **1995**, *26*, 984–988. [CrossRef]
22. Roberts, J.S.; Niu, J. An Ultrasound Survey of the Radial and Ulnar Arteries in an American Population: Implications for Transradial Access. *J. Invasive Cardiol.* **2023**, *35*, E143–E150. [PubMed]
23. Dehghani, P.; Mohammad, A.; Bajaj, R.; Hong, T.; Suen, C.M.; Sharieff, W.; Chisholm, R.J.; Kutryk, M.J.B.; Fam, N.P.; Cheema, A.N. Mechanism and Predictors of Failed Transradial Approach for Percutaneous Coronary Interventions. *JACC Cardiovasc. Interv.* **2009**, *2*, 1057–1064. [CrossRef] [PubMed]
24. Achim, A.; Kákonyi, K.; Nagy, F.; Jambrik, Z.; Varga, A.; Nemes, A.; Chan, J.S.K.; Toth, G.G.; Ruzsa, Z. Radial Artery Calcification in Predicting Coronary Calcification and Atherosclerosis Burden. *Cardiol. Res. Pract.* **2022**, *2022*, e5108389. [CrossRef] [PubMed]

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Comparison of Early and Late Surgeries after Coronary Stent Implantation in Patients with Normal Preoperative Troponin Level: A Retrospective Study

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Abstract: Current guidelines recommend delaying noncardiac surgery for 6 months after drug eluting stent implantation. However, this recommendation is largely based on limited evidence and various event definitions. Whether early surgery within 6 months of coronary stent implantation increases myocardial injury in patients with normal preoperative high-sensitivity cardiac troponin I (hs-cTnI) has not yet been investigated. This retrospective study assessed patients who received coronary stent implantation and underwent noncardiac surgery (vascular, abdominal, or thoracic) between 2010 and 2017 with normal preoperative hs-cTnI (n = 186). Patients were divided into early (within 6 months of PCI) and late (after 6 months of PCI) groups. The primary endpoint was the incidence of myocardial injury as diagnosed by hs-cTnI within 3 days post-operation. The secondary outcomes were myocardial infarction, stent thrombosis, emergent coronary revascularization, major bleeding (bleeding requiring transfusion or intracranial bleeding), stroke, renal failure, heart failure, or death within 30 days post-operation. Inverse probability treatment weighting (IPTW) was carried out to adjust for the intergroup baseline differences. Myocardial injury occurred in 28.6% (8/28) and 27.8% (44/158) of the early and late groups, respectively, with no difference between groups (odds ratio [OR] 1.067, 95% confidence interval [CI] 0.404, 2.482; $p = 0.886$). Secondary outcomes did not differ between the groups. IPTW analysis also showed no differences in myocardial injury and secondary outcomes between the groups. In conclusion, early surgery within 6 months after coronary stent implantation did not increase the incidence of myocardial injury in patients with normal preoperative hs-cTnI.

Keywords: coronary stents; noncardiac surgery; troponin I; stent to surgery time interval

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1. Introduction

Now that percutaneous coronary interventions (PCI) are performed worldwide, the incidence of noncardiac surgery (NCS) after coronary stent implantation is 10 to 20% within the second year of stent insertion [1,2].

The proper time interval from "coronary stent to surgery" has been the subject of debate. The interval between "stent to surgery" is determined by risk-benefits that consider the possibility of stent thrombosis associated with premature cessation of antiplatelets, bleeding associated with the continuous use of antiplatelets, and adverse patient outcomes from delayed surgery. Current practice guidelines of the American Society of Anesthesiologists recommend that elective noncardiac surgery be postponed for at least 12 months until endothelization of the drug eluting stent (DES) is completed [3,4]. The 2016 American College of Cardiology and the American Heart Association (ACC/AHA) recommends waiting 6 months in cases of stable coronary artery disease (class of recommendation:

1, level of evidence: B-non-randomized) [5]. With advances in coronary stent techniques and improved patient care, a shorter interval of "stent to surgery" is increasingly recommended by more recent guidelines [5–7]. However, some anesthesiologists may choose to practice more conservatively as these guidelines are based on limited and weak evidences drawn from non-randomized trials [1,8–12].

In previous studies, patients who underwent surgery after PCI were compared to those who received coronary stents but did not undergo surgery [12], or patients who underwent surgery but did not have coronary stents [13–15]. Few studies directly compared those who underwent early or late surgery. In addition, previous studies focused on composite complications of major adverse cardiac events (MACEs) such as myocardial infarction (MI), bleeding, stroke, or death to determine the appropriate timing for noncardiac surgery after PCI [1,2,8,13,16–22], rather than relying on a universal direct marker of cardiac injury.

High-sensitivity cardiac troponin I (hs-cTnI) is used as an objective early marker for postoperative myocardial injury. To the best of our knowledge, there were no studies that compared changes in hs-cTnI between early and late surgeries after PCI, and no information is available on postoperative outcomes in patients who had normal hs-cTnI before surgery.

In this single-center retrospective study, we evaluated whether early surgery (within 6 months of PCI) increases the incidence of myocardial injury, as diagnosed by hs-cTnI level, compared with late surgery (after 6 months of PCI) in coronary stented patients who underwent vascular, abdominal or thoracic surgery with normal preoperative hs-cTnI. Inverse probability treatment weighting (IPTW) was performed to compare early and late groups, as few patients undergo surgery within 6 months of PCI.

2. Materials and Methods

2.1. Patients

All patients (n = 2517) who received PCI and underwent noncardiac surgery (vascular, abdominal or thoracic surgery) between January 2010 and March 2017 at Samsung Medical Center, Seoul, Republic of Korea were assessed. Only the first index surgery within 30 days of a single admission was included. The stent to surgery interval was based on the most recent coronary stent implantation before the surgery if the patient had more than one PCI episode. Patients were divided into early (within 6 months of PCI) or late (after 6 months of PCI) groups.

2.2. Inclusion and Exclusion Criteria

Coronary stented patients with pre- and post-operative hs-cTnI results undergoing the index surgery were included. The exclusion criteria were as follows: (1) no preoperative hs-cTnI test, (2) abnormal preoperative hs-cTnI level, (3) no postoperative hs-cTnI test within 3 days post-operation, (4) previous PCI with balloon angioplasty without stent implantation, (5) operation other than the index surgery, and (6) concomitant coronary artery graft surgery (Figure 1).

2.3. Data Acquisition

Data were collected using our hospital's electronic medical records. Reviewed data include patient characteristics; underlying disease; echocardiographic findings; revised cardiac risk index (RCRI); laboratory data including preoperative N-Terminal-proB-type Natriuretic Peptide (NT-proBNP); surgery type; emergency surgery; estimated blood loss; intraoperative transfusion; surgery duration; cause of coronary stent implantation, coronary stent type, number, and site(s); and discontinued days of antiplatelets before surgery.

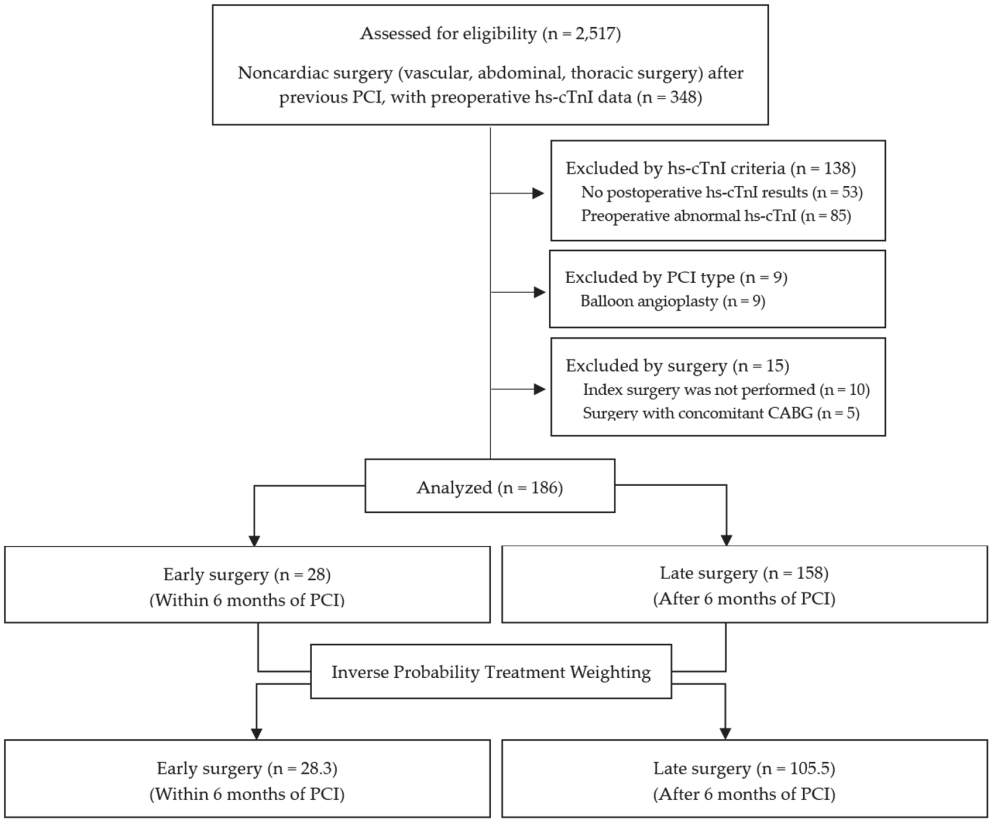

Figure 1. Flow diagram. PCI, percutaneous coronary intervention; Hs-cTnI, high-sensitivity cardiac troponin I; CABG, coronary artery bypass surgery.

2.4. Outcomes and Follow-Up

The primary outcome was myocardial injury, assessed by hs-cTnI within 3 days post-operation. The secondary outcomes were myocardial infarction, stent thrombosis, and the need for emergent coronary revascularization, as well as bleeding requiring transfusion or intracranial bleeding within 30 days post-operation. Other complications such as stroke, renal failure, heart failure, or death within 30 days post-operation were collected. The postoperative duration of the hospital stay was also obtained.

Myocardial injury was defined as any hs-cTnI result exceeding 0.04 ng/mL within 3 days of the operation. The lower detection limit was 0.006 ng/mL, and the normal range was $\leq$0.04 ng/mL according to the 99th percentile reference. Levels were measured using a highly sensitive immunoassay with an automated analyzer (Advia Centaur XP, Siemens Healthcare Diagnostics, Erlangen, Germany). Myocardial infarction was assessed using the third universal definition [23], which is a cardiac biomarker (hs-cTnI) elevation of at least one value above the 99th percentile upper reference limit, in addition to one of the following criteria: symptoms, cardiac echocardiographic diagnosis, or electrocardiogram change indicating myocardial ischemia. Major bleeding was defined as significant bleeding requiring transfusion or an intracranial hemorrhage. Stroke was diagnosed by neurologic symptoms and brain magnetic resonance imaging. Heart failure was defined as dyspnea, pulmonary congestion, and elevated NT-proBNP, or as noted on echocardiography.

2.5. Statistical Analysis

For the comparison of early and late groups in baseline patient characteristics and outcome data, continuous variables were analyzed using the Student's *t*-test or the Mann–Whitney *U* test, according to the normality of data as evaluated with the Shapiro–Wilk test. Data are presented as mean (standard deviation) or median (interquartile range) as appropriate. Categorical variables were analyzed by Chi-square test or Fisher's exact test as appropriate and are described as number (%).

2.6. IPTW

The "stent to surgery" interval may have been affected by several patient characteristics, and the early and late group may show differences in baseline demographics. Thus, IPTW was performed to adjust for these intergroup differences in age, sex, body mass index (BMI), American Society of Anesthesiologist Physical Status (ASA PS; II, III vs. IV), surgery type (major vascular vs. non major vascular), emergency surgery, etiology of stent insertion (acute myocardial infarction vs. angina pectoris), preoperative antiplatelets (or anticoagulant) use, discontinued days (duration) of antiplatelets, and preoperative comorbidity including diabetes mellitus (DM), hypertension (HTN), chronic kidney diseases (CKD), atrial fibrillation, peripheral vascular diseases, and transient ischemic attack (TIA) or stroke. A weight of mean of propensity score (PS)/PS was assigned to the early group and (1-means of PS)/(1-PS) to the late group, with PS being the probability of being assigned to the early group. The ability of the model to balance the cohort characteristics in a pseudo-population was assessed using standardized mean differences. Simple logistic regression was performed for the primary endpoint, and double adjustments using the weighted multiple logistic regression were carried out to adjust for variables with standardized mean difference >0.1 even after IPTW (adjusted odds ratio and 95% confidence interval) [24].

To identify confounding factors for myocardial injury, multiple logistic regression was carried out, with a stepwise selection (likelihood ratio, enter if $p < 0.05$ and remove variable if $p > 0.2$) in the unweighted raw data. Variables assessed for the multiple logistic regression are as follows: the early group vs. the late group was set as a fixed variable, plus age, sex, BMI, surgery type, emergency surgery, ASA PS, etiology of stent insertion, DM, use of DM medications (metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor), HTN, CKD, atrial fibrillation, peripheral vascular disease, stroke including TIA, preoperative antiplatelets, and discontinuation of antiplatelets.

2.7. Sample Size Calculation

We performed a sample size justification for this retrospective analysis. Since there was no report on the incidence of myocardial injury diagnosed by hs-cTnI in coronary stented patients undergoing noncardiac surgery, we based it on the incidence of myocardial injury after noncardiac surgery, which ranged from 5 to 20% in the previous literature [25,26]. On the presumption that the incidence of myocardial injury in the late group was 10% compared to that of 35% in the early group, 25 patients in the early group and 100 patients in the late group would have the power of 83%.

All p values were two-sided, and $p < 0.05$ indicated a significant difference. Rex Excel-based statistical analysis software ver. 3.6.1 (RexSoft, Seoul, Republic of Korea, http://rexsoft.org/, accessed on 1 November 2022) based on R ver. 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS® Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA) were used to conduct all analyses.

3. Results

In this single-center retrospective study, all patients who underwent noncardiac surgery (vascular, abdominal, or thoracic surgery) after PCI between January 2010 and March 2017 were assessed (n = 2517). Among them, those with preoperative hs-cTnI results were selected (n = 348). Patients with no postoperative hs-cTnI results within 3 days post-

operation (n = 53), or with high preoperative hs-cTnI results indicating ongoing cardiac injury (n = 85), or those who underwent balloon angioplasty only for PCI (n = 9), or those who did not receive the index surgery (n = 10), or those who received concomitant coronary artery bypass surgery (n = 5) were all excluded. Finally, 186 patients were analyzed for myocardial injury. Data on primary and secondary outcomes were available in all analyzed patients (Figure 1).

3.1. Demographics Data and Operative Characteristics

In the raw data, the baseline characteristics of patients in the early and late groups did not differ except for preoperative use of dual antiplatelet therapy (96% vs. 38%, $p < 0.001$), which was more common in the early group (Table 1). Most patients received clopidogrel and/or aspirin as antiplatelet therapy. The discontinued days of preoperative antiplatelets (or anticoagulant) were similar between the groups (3.4 vs. 4.4 days, early vs. late group; $p = 0.25$) (Table 1).

Table 1. Patient and operative characteristics between early and late surgery (raw data).

Variables	Early Surgery (n = 28)	Late Surgery (n = 158)	*p*
Age, year	67.3 (8.1)	68.3 (8.3)	0.55
Female	1 (4)	18 (12)	0.32
BMI, kg/m^2	25.0 (2.6)	24.6 (3.2)	0.54
Weight, kg	68.7 (7.4)	67.9 (10.6)	0.71
Height, cm	165.8 (6.2)	165.9 (7.5)	0.91
ASA PS			
II	7 (25)	74 (47)	0.06
III	20 (71)	81 (51)	
IV	1 (4)	3 (2)	
Hypertension	18 (64)	113 (72)	0.44
Diabetes mellitus	11 (39)	62 (39)	>0.99
Metformin	4 (14)	28 (18)	
Sulfonylurea	2 (7)	21 (13)	
Dipeptidyl Peptidase-4 inhibitor	3 (11)	21 (13)	
Insulin	1 (4)	7 (4)	
Alpha glucosidase	0 (0)	2 (1)	
Thiazolidinediones	1 (4)	0 (0)	
No antidiabetic medication	2 (7)	5 (3)	
Stroke or transient ischemia attack	5 (18)	35 (22)	0.61
Chronic kidney disease	1 (4)	18 (11)	0.32
Structural heart disease [a]	3 (11)	21 (13)	>0.99
Left ventricular ejection fraction < 30%	0 (0)	2 (1)	>0.99
Atrial fibrillation	2 (7)	11 (7)	>0.99
Peripheral vascular disease	5 (18)	27 (17)	>0.99
Revised cardiac risk index			
0	2 (7)	9 (6)	0.74
1	14 (55)	91 (60)	
2	9 (32)	49 (31)	
3	3 (11)	9 (6)	
Serum creatinine $\geq$ 2.0 mg/dL	1 (4)	12 (8)	0.70
Hemoglobin, g/dL	12.5 (1.9)	12.7 (2.1)	0.62
CRP, mg/dL [b]	0.13 (0.06, 0.71)	0.25 (0.07,0.88)	0.58
NT-proBNP, ng/dL [c]	88.2 (46.6, 715.0)	148 (67.5, 503.4)	0.75
Albumin, g/dL	4.0 (0.5)	4.0 (0.5)	0.59
Cholesterol	123.9 (37.1)	134.8 (32.1)	0.11
LDL cholesterol [d]	66.5 (25.7)	75.3 (25.3)	0.16
Glucose, mg/dL	136.8 (46.3)	129.7 (53.9)	0.52

Table 1. *Cont.*

Variables	Early Surgery (n = 28)	Late Surgery (n = 158)	*p*
Surgery			
Major vascular	7 (25)	39 (25)	0.74
Non major-vascular (sub-category, below)	21 (75)	119 (75.3)	
Cholecystectomy	2 (7)	16 (10)	
Gastrectomy	5 (18)	10 (7)	
Hepatobiliary	1 (4)	17 (11)	
Colorectal surgery	2 (7)	10 (6)	
Nephrectomy-cystectomy	0 (0)	2 (1)	
Kidney transplantation	0 (0)	2 (1)	
Liver transplantation	0 (0)	5 (3)	
Other abdominal surgery	10 (36)	62 (39)	
Thoracic surgery	5 (18)	21 (13)	
Carotid endarterectomy	6 (21)	36 (23)	
Emergency surgery	3 (11)	13 (8)	0.71
Intraoperative estimated blood loss, ml	125 (80, 450)	200 (100, 700)	0.33
Intraoperative transfusion	4 (14)	43 (27)	0.15
Surgery duration, min	174.5 (117, 206)	192 (122, 262)	0.21
Coronary stent data			
Causes of coronary stent implantation			0.99
Acute Myocardial Injury	9 (32)	52 (33)	
Angina pectoris	17 (61)	94 (60)	
Not known	2 (7)	12 (7)	
Coronary stent type			0.11
DES	16 (57)	65 (41)	
First generation	1 (6)	26 (40)	
Durable polymer coated	11 (69)	29 (45)	
Biodegradable polymer coated	2 (13)	4 (6)	
Polymer free drug coated	1 (6)	0 (0)	
Unknown DES type	1 (6)	6 (9)	
BMS	4 (14)	14 (9)	
Unknown stent type	8 (29)	79 (50)	
Coronary stent number$_b$			0.61
1	17 (63)	76 (67)	
2	7 (26)	30 (27)	
3	3 (11)	7 (6)	
Coronary stent site$_b$			0.10
Left anterior descending	16 (57)	62 (39)	
Antiplatelets (or anticoagulants) use			<0.001
None	0 (0)	3 (2)	
Aspirin only	1 (4)	70 (44)	
Clopidogrel only	0 (0)	22 (14)	
Dual (aspirin + clopidogrel)	27 (96)	60 (38)	
Warfarin	0 (0)	3 (2)	
Discontinued days of any antiplatelets (or anticoagulants)	3.4 (3.1)	4.4 (4.0)	0.25

Values are presented as mean (standard deviation) or median (interquartile range) or number (%). Early vs. Late surgery: surgical time from coronary stent implantation within 6 months vs. after 6 months. BMI, body mass index; ASA PS, American Society of Anesthesiologist Physical Status; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide N-terminal; CRP, C-reactive protein; LDL, low density lipoprotein; DES, drug eluting stent; BMS, bare metal stent.$_a$ Structural heart disease included regional wall motion abnormality or valvular heart disease. $_b$ early surgery n = 28, late surgery n = 138. $_c$ early surgery n = 20, late surgery n = 114. $_d$ early surgery n = 20, late surgery n = 111.

3.2. Myocardial Injury and Postoperative Complications

In the raw data, the incidence of myocardial injury was 28.0% (52/186). There was no difference in myocardial injury between the early and late groups (28.6% [8/28] vs. 27.8% [44/158]; OR 1.067, 95% CI 0.404, 2.482; p= 0.886). Myocardial infarction occurred in nine patients, all in the late group (0% [0/28] vs. 5.7% [9/158]; OR 0.276, 95% CI 0.000,

2.276; $p = 0.398$) Among these patients with myocardial infarction, four showed changes in ST, two of whom required emergent coronary revascularization for non-ST segment elevation myocardial infarction (NSTEMI) (0% [0/28] vs. 1.3% [2/158]; OR 1.098, 95% CI 0.000, 13.648; $p = 0.953$). None of the patients experienced stent thrombosis or restenosis. The incidence of major bleeding was 14.5% (27/186), with no group difference (7.1% [2/28] vs. 15.8% [25/158]; OR 0.494, 95% CI 0.064, 1.645; $p = 0.319$) (Table 2). The composite incidence of either myocardial injury or major bleeding did not differ between the early and late groups (32.1% [9/28] vs. 35.4% [56/158]; $p = 0.690$) (Figure 2).

3.3. IPTW

The IPTW matched cohort is shown in Appendix A Table A1. After IPTW, a pseudo-population was created, and the incidence of myocardial injury was 31.1% (8.8/28.3) vs. 30.8% (32.5/105.5) of patients in the early vs. late group (OR 1.035, 95% CI 0.400, 2.447; $p = 0.939$) (Table 2). Double adjustment results for a standardized mean difference >0.1 after IPTW also showed no significant differences between the early and late groups in myocardial injury (OR 1.125, 95% CI 0.465, 2.723; $p = 0.795$). After IPTW, secondary outcomes did not differ between the groups (Table 2).

Table 2. Myocardial injury and other complications between early and late surgery before and after IPTW.

Variables	Unmatched Cohort				Weighted Cohort after IPTW			
	Early Surgery (n = 28)	Late Surgery (n = 158)	Odds Ratio (95% CI) [a]	*p*	Early Surgery (n = 28.3)	Late Surgery (n = 105.5)	Odds Ratio (95% CI) [b]	*p*
Myocardial injury	8 (28.6)	44 (27.8)	1.067 (0.404, 2.482)	0.886	8.8 (31.1)	32.5 (30.8)	1.035 (0.400, 2.447)	0.939
Myocardial infarction	0 (0)	9 (5.7)	0.276 (0.000, 2.276)	0.398	0.0 (0.0)	6.9 (6.6)	0.232 (0.000, 1.995)	0.330
MACE	3 (10.7)	23 (14.6)	0.791 (0.159, 2.367)	0.707	3.3 (11.8)	17.4 (16.5)	0.748(0.163, 2.251)	0.636
In-stent thrombosis	0	0	NA	NA	0	0	NA	NA
Emergent coronary revascularization	0 (0)	2 (1.3)	1.098 (0.000, 13.648)	0.953	0.0 (0.0)	1.9 (1.8)	0.746 (0.000, 9.460)	0.854
Major bleeding	2 (7.1)	25 (15.8)	0.494 (0.064, 1.645)	0.319	0.8 (3.0)	18.1 (17.1)	0.227 (0.006, 1.014)	0.113
Stroke	0 (0)	3 (1.9)	0.779 (0.000, 8.248)	0.872	0.0 (0.0)	1.9 (1.8)	0.758 (0.000, 9.711)	0.862
Thrombosis	1 (3.6)	4 (2.5)	1.873 (0.072, 10.547)	0.522	0.8 (3.0)	2.8 (2.6)	1.516 (0.038, 10.540)	0.695
Heart failure	2 (7.1)	7 (4.4)	1.906 (0.239, 7.607)	0.403	2.5 (8.8)	5.6 (5.3)	1.892 (0.300, 7.697)	0.394
Newly onset atrial fibrillation or flutter	1 (3.6)	13 (8.2)	0.588 (0.022, 2.566)	0.555	0.8 (3.0)	10.5 (10.0)	0.416 (0.010, 1.973)	0.358
New dialysis	0 (0)	3 (1.9)	0.779 (0.000, 8.248)	0.872	0.0 (0.0)	2.2 (2.1)	0.672 (0.000, 8.063)	0.801
Clavien-Dindo surgical complications ≥ 1	7 (25.0)	58 (36.7)	0.599 (0.215, 1.408)	0.268	5.5 (19.3)	39.7 (37.6)	0.423 (0.132, 1.069)	0.090
Postoperative hospital stay, days	12.5 (17.9)	11.1 (14.7)	1.449 (-4.664, 7.562)	0.642	10.90 (16.68)	10.15 (12.13)	0.750 (-4.813, 6.312)	0.792
In-hospital mortality	0 (0)	1 (0.6)	1.842 (0.000, 58.189)	0.714	0.0 (0.0)	1.0 (1.0)	1.208 (0.000, 32.219)	0.910

Values are mean (standard deviation) or number (%). Early vs. Late surgery: surgical time from coronary stent implantation within 6 months vs. after 6 months. IPTW, inverse probability treatment weighting; MACE, major adverse cardiovascular event; OR, odds ratio; CI, confidence interval. [a] Logistic regression with Firth's penalized maximum likelihood estimator (MLE). [b] Weighted logistic regression.

In the raw data, the differences in other major complications including heart failure, stroke, renal failure, Clavien–Dindo surgical complications, postoperative hospital stays, and in-hospital mortality were not significant statistically. One patient in the late group died due to cerebral infarction and subsequent heart failure (Table 2).

Table 3 shows the simple logistic regression and multiple logistic regression of raw data to identify contributing factors to myocardial injury. Early or late surgery was not associated with myocardial injury. Major vascular surgery was the only variable that increased the odds of myocardial injury significantly (adjusted OR 5.060, 95% CI 2.407, 10.635; $p < 0.001$).

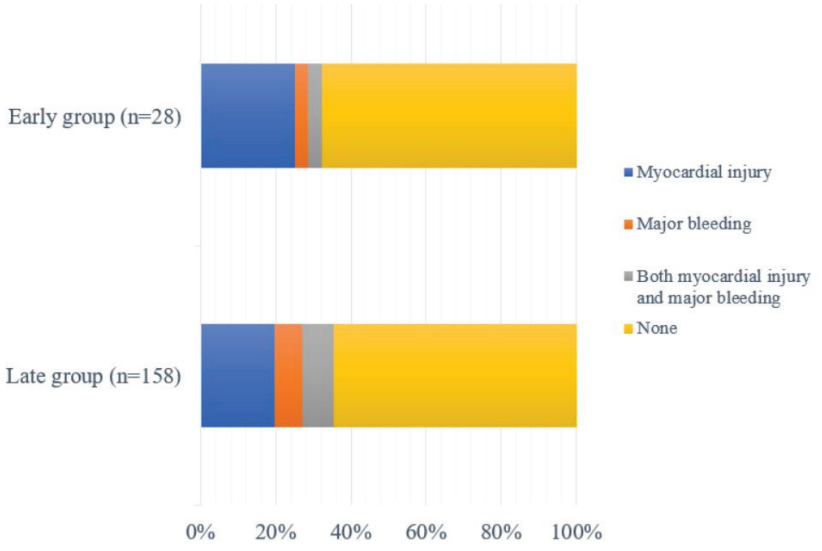

Figure 2. Incidence of composite events (myocardial injury or major bleeding) between early (9/28 [32.2%]) and late groups (56/158 [35.4%]) were not different (p = 0.690). Major bleeding included bleeding requiring transfusion or intracranial hemorrhage within 30 days post-operation.

Table 3. Multiple logistic regression for myocardial injury (raw data).

			Univariable Analysis		Multiple Logistic Regression	
	Myocardial Injury (n = 52)	**No Myocardial Injury (n = 134)**	**OR, 95% CI**	***p* Value**	**aOR, 95% CI**	***p* Value**
Early surgery	8 (15.4)	20 (14.9)	1.034 (0.418, 2.558)	0.937	1.249 (0.478, 3.262)	0.65
Age, year	70.0 (9.5)	67.4 (7.7)	1.045 (1.004, 1.089)	0.033		
BMI, kg/m^2	24.9 (3.5)	24.6 (3.0)	1.032 (0.926, 1.150)	0.568		
Female	9 (17.3)	11 (8.2)	2.595 (0.964, 6.985)	0.059	2.749 (0.969, 7.795)	0.057
Surgery type Major vascular surgery	25 (48.1)	21 (15.7)	5.010 (2.399, 10.464)	<0.001	5.060 (2.407, 10.635)	<0.001
Emergency surgery	4 (7.7)	12 (9.0)	0.919 (0.274, 3.079)	0.891		
ASA PS						
II	21 (40.4)	60 (44.8)	(ref)			
III	30 (57.7)	71 (53.0)	1.100 (0.562, 2.154)	0.780		
IV	1 (1.9)	3 (2.2)	0.810 (0.080, 8.234)	0.858		
Etiology of stent insertion						
AMI	16 (31.4)	45 (37.2)	(ref)			
Angina pectoris	35 (68.6)	76 (62.8)	1.301 (0.646, 2.618)	0.461		
Unknown	1 (1.0)	13 (1.0)	NA			
DM	15 (28.8)	58 (43.3)	0.529 (0.262, 1.069)	0.076		
Metformin	5 (9.6)	28 (20.9)	0.403 (0.146, 1.108)	0.078		
Sulfonylurea	3 (5.8)	21 (15.7)	0.330 (0.094, 1.156)	0.083		
DPP-4-inhibitor	4 (7.7)	20 (14.9)	0.475 (0.154, 1.464)	0.195		
HTN	35 (67.3)	96 (71.6)	0.777 (0.383, 1.575)	0.483		
CKD	10 (19.2)	9 (6.7)	3.398 (1.190, 9.706)	0.022	2.583 (0.893, 7.468)	0.08
Atrial fibrillation	4 (7.7)	9 (6.7)	1.170 (0.336, 4.076)	0.805		
Peripheral vascular diseases	10 (19.2)	22 (16.4)	0.990 (0.418, 2.341)	0.981		

Table 3. *Cont.*

			Univariable Analysis		Multiple Logistic Regression	
	Myocardial Injury (n = 52)	No Myocardial Injury (n = 134)	OR, 95% CI	*p* Value	aOR, 95% CI	*p* Value
Any stroke or TIA	7 (13.5)	33 (24.6)	0.409 (0.158, 1.057)	0.065		
Preoperative antiplatelets						
None	1 (1.9)	2 (1.5)	(ref)			
Dual antiplatelets	26 (50.0)	61 (46.5)	<0.001 (0, Infinite)	0.981		
Single antiplatelet	25 (48.1)	71 (53.0)	<0.001 (0, Infinite)	0.986		
Discontinued days of antiplatelets	4 (1,5)	4 (1,5)	0.931 (0.839, 1.034)	0.182		

Values are presented as mean (standard deviation) or median (interquartile range), or number (%). Early vs. Late surgery: surgical time from coronary stent implantation within 6 months vs. after 6 months; OR odds ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; ASA PS, American Society of Anesthesiologist Physical Status; AMI, acute myocardial infarction; DM, diabetes mellitus; DPP-4-inhibitor, dipeptidyl peptidase-4 inhibitor; HTN, hypertension; CKD, chronic kidney diseases; TIA, transient ischemic attacks.

4. Discussion

Using a definition of myocardial injury as elevated hs-cTnI, early noncardiac surgery within 6 months of coronary stent implantation did not increase the incidence of myocardial injury in patients with normal preoperative hs-cTnI. The incidence of major bleeding also did not differ between the groups.

In our study, the incidence of myocardial injury based on hs-cTnI was 28.6% and 27.8% in the early and late groups, respectively. This is higher than that of the Godet et al.'s study, where the incidence was 12% in 96 consecutive patients who underwent noncardiac surgery after PCI [27]. This difference may be attributable to our use of a high sensitivity troponin assay, hs-cTnI, which may be a more accurate marker for myocardial injury than the troponin used in Godet et al. [27].

Previous studies focused on a wide range of composite outcomes of MACEs. However, MACE may not be directly related to coronary stent in surgical population. Our one heart failure case was due primarily to massive bleeding from surgical complications and our mortality case was due to cerebral infraction and subsequent heart failure, neither of which was accompanied by elevated hs-cTnI. If the rationale for delaying surgery is to wait for stent endothelization and safe cessation of dual antiplatelet therapy, it appears to be more appropriate to focus on the measurement of hs-cTnI (primary outcome) and the occurrence of myocardial injury or infarction and stent thrombosis/revascularization (secondary outcomes) to determine "stent to surgery" time [5,27].

It is not clear why the rate of myocardial injuries did not differ between the two groups. First, this study included patients with normal preoperative hs-cTnI. According to previous studies, noncardiac surgery after acute coronary syndrome has a high risk of MACE or myocardial infarction, but stable coronary artery diseases have a low risk of MACE regardless of the timing of the surgery [5,10]. Second, another possible explanation involves the type 2 mechanism of myocardial injury in surgical patients [28]. During the perioperative period, myocardial supply-demand mismatch (type 2) is more common than stent thrombosis (type 1) [29,30], which may be treated conservatively and not require coronary artery intervention. In our study, no patients who manifested myocardial injury required coronary artery intervention, and all were treated conservatively, except for two patients in the late group, who had to be referred to cardiologists for emergency revascularization. If the type 2 mechanism is the major contributor of myocardial injury, delaying surgery would not reduce it. Third, coronary stent type may also have contributed to the lack of difference between the two groups. Recent generation DESs were designed using thinner stent platforms and thrombo-resistant, bioabsorbable, or biocompatible polymers [31]. These newer polymers minimize inflammation [32,33] and result in lower rates of stent thrombosis [33–35]. Stent

thrombosis occurred in only 1.5% of patients over a 3-year follow up [36]. Emerging data suggest that it may be safe to discontinue dual antiplatelet therapy as early as 3 months after implantation of a new generation stent [33–35]. Because of the retrospective nature of the study, we were unable to identify the generation of stents used in some patients. However, the early surgery group received a new generation DES more frequently than did the late group, despite the missing data. Lastly, some antidiabetics such as metformin [37], glucagon-like peptide 1 (GLP-1; incretins) analogs [38,39], or SGLT2 (Sodium-glucose cotransporter 2) inhibitors [40,41] are known to have a favorable effect against myocardial infarction. Patients in our study were not receiving GLP-1 analogs and/or SGLT2 inhibitors, but some were taking DPP-4-inhibitors, which indirectly increase GLP-1. In our study, patients who were taking metformin (14% vs. 18%; early vs. late group) and DPP-4-inhibitor (11% and 13%; early vs. late group) were not different between the groups. These drugs may have affected the result of no difference in the rate of myocardial injury.

In our study, preoperative use of dual antiplatelet therapy was more common in the early group than the late group (96% vs. 38%, $p < 0.001$ in unweighted cohort data), but the duration of preoperative antiplatelet discontinuation was similar between the groups (3.4 days and 4.4 days; $p = 0.25$ in unweighted cohort data). The risk of stopping antiplatelet therapy is not consistent among previous studies. The RECO study found an increased incidence of MACE with a complete cessation of antiplatelets after noncardiac surgery [8], but other studies reported no differences between the stop and the continued use [2,9,42]. Some studies reported even higher incidences of MACE in patients with greater platelet inhibition [19,29] and those with continuous antiplatelet medication [20]. In our multiple logistic regression (Table 3), types and discontinued duration of antiplatelets were not contributing variables for the occurrence of myocardial injury. Antiplatelet therapy should be tailored to the patient depending on the cause of PCI, inherent surgical risk of bleeding, and type of stent [1,18,20], and the consensus decision should be based on the opinions of the cardiologist, surgeon, and anesthesiologist [5–7,43].

Our study has several limitations. First, the small number of patients in this study limits generalizability and makes it difficult to draw a concrete conclusion. However, inclusion of minor or outpatient surgery is likely to produce more favorable outcomes for early surgery [12]. A large cohort study is required in future. Second, the retrospective nature of this study has resulted in a lack of information on the type of coronary stent and the etiology of stent implantation in some patients. Third, our cohort is Asian. East-Asians are reportedly to show a decreased thrombotic risk compared to other ethnicities [44]. Fourth, as a retrospective study, perioperative management was not controlled, especially in relation to restarting antiplatelets or postoperative thromboprophylaxis. However, if clinically acceptable, antiplatelet therapy was routinely resumed on the first postoperative day as an institutional protocol.

5. Conclusions

In conclusion, early surgery within 6 months of coronary stent implantation may not increase the incidence of myocardial injury in patients with normal preoperative hs-cTnI. The decision on the timing of surgery may be tailored for each patient by the consensus of surgeons, cardiologists, and anesthesiologists rather than by a strict adherence to the guidelines.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Baseline Patient and Operative Characteristics after IPTW.

	Weighted Cohort after IPTW			
	Early Surgery (n = 28.3)	**Late Surgery (n = 105.5)**	***p*-Value**	**Test SMD**
Age, year	66.91 (8.29)	68.11 (8.25)	0.533	0.145
Female	2.6 (9.3)	5.4 (5.1)	0.56	0.162
BMI, kg/m^2	25.10 (2.68)	24.78 (3.18)	0.637	0.112
ASA PS $\geq$ IV	28.3 (100.0)	105.5 (100.0)	NA	<0.001
Nonvascular surgery	21.6 (76.3)	82.0 (77.7)	0.884	0.034
Emergency surgery	3.3 (11.6)	6.4 (6.1)	0.514	0.196
Etiology of stent insertion, angina pectoris	18.1 (63.7)	70.3 (66.6)	0.805	0.061
Use of any antiplatelets	28.3 (100.0)	105.5 (100.0)	NA	<0.001
Discontinued days of antiplatelets	4.97 (3.74)	3.70 (2.29)	0.214	0.409
Comorbidity				
Diabetus Melitus	11.4 (40.1)	40.9 (38.8)	0.917	0.026
Hypertension	22.3 (78.7)	71.0 (67.3)	0.26	0.258
Chronic kidney diseases	1.3 (4.5)	8.1 (7.6)	0.605	0.131
Preoperative atrial fibrillation	1.3 (4.5)	6.9 (6.5)	0.728	0.087
Peripheral vascular diseases	4.6 (16.4)	18.5 (17.5)	0.899	0.030
Stroke or TIA	4.4 (15.4)	18.9 (17.9)	0.775	0.068

Values are presented as mean (standard deviation) or number (%). Early vs. Late surgery: surgical time from coronary stent implantation within 6 months vs. after 6 months. IPTW, inverse probability treatment weighting; SMD, standardized mean difference; BMI, body mass index; ASA PS, American Society of Anesthesiologist Physical Status; TIA, transient ischemic event.

References

1. Berger, P.B.; Kleiman, N.S.; Pencina, M.J.; Hsieh, W.H.; Steinhubl, S.R.; Jeremias, A.; Sonel, A.; Browne, K.; Barseness, G.; Cohen, D.J.; et al. Frequency of major noncardiac surgery and subsequent adverse events in the year after drug-eluting stent placement results from the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) Registry. *JACC Cardiovasc. Interv.* **2010**, *3*, 920–927. [CrossRef] [PubMed]
2. Hawn, M.T.; Graham, L.A.; Richman, J.S.; Itani, K.M.; Henderson, W.G.; Maddox, T.M. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA* **2013**, *310*, 1462–1472. [CrossRef] [PubMed]
3. Caplan, R.A.; Connis, R.T.; Nickinovich, D.G.; Riedel, B.J.; Fleisher, L.A.; Joshi, G.P. Practice alert for the perioperative management of patients with coronary artery stents: A report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* **2009**, *110*, 22–23. [CrossRef]
4. Vetter, T.R.; Short, R.T., 3rd; Hawn, M.T.; Marques, M.B. Perioperative management of the patient with a coronary artery stent. *Anesthesiology* **2014**, *121*, 1093–1098. [CrossRef] [PubMed]
5. Levine, G.N.; Bates, E.R.; Bittl, J.A.; Brindis, R.G.; Fihn, S.D.; Fleisher, L.A.; Granger, C.B.; Lange, R.A.; Mack, M.J.; Mauri, L.; et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2016**, *68*, 1082–1115. [CrossRef]

6. Valgimigli, M.; Bueno, H.; Byrne, R.A.; Collet, J.P.; Costa, F.; Jeppsson, A.; Juni, P.; Kastrati, A.; Kolh, P.; Mauri, L.; et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **2018**, *39*, 213–260. [CrossRef]
7. Mehta, S.R.; Bainey, K.R.; Cantor, W.J.; Lordkipanidze, M.; Marquis-Gravel, G.; Robinson, S.D.; Sibbald, M.; So, D.Y.; Wong, G.C.; Abunassar, J.G.; et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. *Can. J. Cardiol.* **2018**, *34*, 214–233. [CrossRef]
8. Albaladejo, P.; Marret, E.; Samama, C.M.; Collet, J.P.; Abhay, K.; Loutrel, O.; Charbonneau, H.; Jaber, S.; Thoret, S.; Bosson, J.L.; et al. Non-cardiac surgery in patients with coronary stents: The RECO study. *Heart* **2011**, *97*, 1566–1572. [CrossRef]
9. Hollis, R.H.; Graham, L.A.; Richman, J.S.; Deierhoi, R.J.; Hawn, M.T. Adverse cardiac events in patients with coronary stents undergoing noncardiac surgery: A systematic review. *Am. J. Surg.* **2012**, *204*, 494–501. [CrossRef]
10. Cruden, N.L.; Harding, S.A.; Flapan, A.D.; Graham, C.; Wild, S.H.; Slack, R.; Pell, J.P.; Newby, D.E.; Scottish Coronary Revascularisation Register Steering, C. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. *Circ. Cardiovasc. Interv.* **2010**, *3*, 236–242. [CrossRef]
11. Rabbitts, J.A.; Nuttall, G.A.; Brown, M.J.; Hanson, A.C.; Oliver, W.C.; Holmes, D.R.; Rihal, C.S. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. *Anesthesiology* **2008**, *109*, 596–604. [CrossRef]
12. Holcomb, C.N.; Graham, L.A.; Richman, J.S.; Rhyne, R.R.; Itani, K.M.; Maddox, T.M.; Hawn, M.T. The incremental risk of noncardiac surgery on adverse cardiac events following coronary stenting. *J. Am. Coll. Cardiol.* **2014**, *64*, 2730–2739. [CrossRef]
13. Wijeysundera, D.N.; Wijeysundera, H.C.; Yun, L.; Wasowicz, M.; Beattie, W.S.; Velianou, J.L.; Ko, D.T. Risk of elective major noncardiac surgery after coronary stent insertion: A population-based study. *Circulation* **2012**, *126*, 1355–1362. [CrossRef]
14. Egholm, G.; Kristensen, S.D.; Thim, T.; Olesen, K.K.; Madsen, M.; Jensen, S.E.; Jensen, L.O.; Sorensen, H.T.; Botker, H.E.; Maeng, M. Risk Associated With Surgery Within 12 Months After Coronary Drug-Eluting Stent Implantation. *J. Am. Coll. Cardiol.* **2016**, *68*, 2622–2632. [CrossRef]
15. Thim, T.; Egholm, G.; Kristensen, S.D.; Olesen, K.K.W.; Madsen, M.; Jensen, S.E.; Jensen, L.O.; Sørensen, H.T.; Bøtker, H.E.; Maeng, M. Risk of Myocardial Infarction and Death After Noncardiac Surgery Performed Within the First Year After Coronary Drug-Eluting Stent Implantation for Acute Coronary Syndrome or Stable Angina Pectoris. *Am. J. Cardiol.* **2021**, *160*, 14–20. [CrossRef]
16. Kaluza, G.L.; Joseph, J.; Lee, J.R.; Raizner, M.E.; Raizner, A.E. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J. Am. Coll. Cardiol.* **2000**, *35*, 1288–1294. [CrossRef]
17. Wilson, S.H.; Fasseas, P.; Orford, J.L.; Lennon, R.J.; Horlocker, T.; Charnoff, N.E.; Melby, S.; Berger, P.B. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J. Am. Coll. Cardiol.* **2003**, *42*, 234–240. [CrossRef]
18. Schouten, O.; van Domburg, R.T.; Bax, J.J.; de Jaegere, P.J.; Dunkelgrun, M.; Feringa, H.H.; Hoeks, S.E.; Poldermans, D. Noncardiac surgery after coronary stenting: Early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. *J. Am. Coll. Cardiol.* **2007**, *49*, 122–124. [CrossRef]
19. van Kuijk, J.P.; Flu, W.J.; Schouten, O.; Hoeks, S.E.; Schenkeveld, L.; de Jaegere, P.P.; Bax, J.J.; van Domburg, R.T.; Serruys, P.W.; Poldermans, D. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am. J. Cardiol.* **2009**, *104*, 1229–1234. [CrossRef] [PubMed]
20. Vicenzi, M.N.; Meislitzer, T.; Heitzinger, B.; Halaj, M.; Fleisher, L.A.; Metzler, H. Coronary artery stenting and non-cardiac surgery–a prospective outcome study. *Br. J. Anaesth.* **2006**, *96*, 686–693. [CrossRef]
21. Grines, C.L.; Bonow, R.O.; Casey, D.E., Jr.; Gardner, T.J.; Lockhart, P.B.; Moliterno, D.J.; O'Gara, P.; Whitlow, P. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: A science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation* **2007**, *115*, 813–818. [CrossRef] [PubMed]
22. Anwaruddin, S.; Askari, A.T.; Saudye, H.; Batizy, L.; Houghtaling, P.L.; Alamoudi, M.; Militello, M.; Muhammad, K.; Kapadia, S.; Ellis, S.G. Characterization of post-operative risk associated with prior drug-eluting stent use. *JACC Cardiovasc. Interv.* **2009**, *2*, 542–549. [CrossRef] [PubMed]
23. Thygesen, K.; Alpert, J.S.; Jaffe, A.S.; Simoons, M.L.; Chaitman, B.R.; White, H.D. Third universal definition of myocardial infarction. *Circulation* **2012**, *126*, 2020–2035. [CrossRef] [PubMed]
24. Nguyen, T.L.; Collins, G.S.; Spence, J.; Daurès, J.P.; Devereaux, P.J.; Landais, P.; Le Manach, Y. Double-adjustment in propensity score matching analysis: Choosing a threshold for considering residual imbalance. *BMC Med. Res. Methodol.* **2017**, *17*, 78. [CrossRef] [PubMed]
25. van Waes, J.A.; Nathoe, H.M.; de Graaff, J.C.; Kemperman, H.; de Borst, G.J.; Peelen, L.M.; van Klei, W.A. Myocardial injury after noncardiac surgery and its association with short-term mortality. *Circulation* **2013**, *127*, 2264–2271. [CrossRef]
26. Ruetzler, K.; Smilowitz, N.R.; Berger, J.S.; Devereaux, P.J.; Maron, B.A.; Newby, L.K.; de Jesus Perez, V.; Sessler, D.I.; Wijeysundera, D.N. Diagnosis and Management of Patients With Myocardial Injury After Noncardiac Surgery: A Scientific Statement From the American Heart Association. *Circulation* **2021**, *144*, e287–e305. [CrossRef]

27. Godet, G.; Le Manach, Y.; Lesache, F.; Perbet, S.; Coriat, P. Drug-eluting stent thrombosis in patients undergoing non-cardiac surgery: Is it always a problem? *Br. J. Anaesth.* **2008**, *100*, 472–477. [CrossRef]
28. Helwani, M.A.; Amin, A.; Lavigne, P.; Rao, S.; Oesterreich, S.; Samaha, E.; Brown, J.C.; Nagele, P. Etiology of Acute Coronary Syndrome after Noncardiac Surgery. *Anesthesiology* **2018**, *128*, 1084–1091. [CrossRef]
29. Wasowicz, M.; Syed, S.; Wijeysundera, D.N.; Starzyk, L.; Grewal, D.; Ragoonanan, T.; Harsha, P.; Travis, G.; Carroll, J.; Karkouti, K.; et al. Effectiveness of platelet inhibition on major adverse cardiac events in non-cardiac surgery after percutaneous coronary intervention: A prospective cohort study. *Br. J. Anaesth.* **2016**, *116*, 493–500. [CrossRef]
30. Verbree-Willemsen, L.; Grobben, R.B.; van Waes, J.A.; Peelen, L.M.; Nathoe, H.M.; van Klei, W.A.; Grobbee, D.E. Causes and prevention of postoperative myocardial injury. *Eur. J. Prev. Cardiol.* **2019**, *26*, 59–67. [CrossRef]
31. Chin-Quee, S.L.; Hsu, S.H.; Nguyen-Ehrenreich, K.L.; Tai, J.T.; Abraham, G.M.; Pacetti, S.D.; Chan, Y.F.; Nakazawa, G.; Kolodgie, F.D.; Virmani, R.; et al. Endothelial cell recovery, acute thrombogenicity, and monocyte adhesion and activation on fluorinated copolymer and phosphorylcholine polymer stent coatings. *Biomaterials* **2010**, *31*, 648–657. [CrossRef]
32. Lee, D.H.; de la Torre Hernandez, J.M. The Newest Generation of Drug-eluting Stents and Beyond. *Eur. Cardiol.* **2018**, *13*, 54–59. [CrossRef]
33. Otsuka, F.; Vorpahl, M.; Nakano, M.; Foerst, J.; Newell, J.B.; Sakakura, K.; Kutys, R.; Ladich, E.; Finn, A.V.; Kolodgie, F.D.; et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation* **2014**, *129*, 211–223. [CrossRef]
34. Palmerini, T.; Biondi-Zoccai, G.; Della Riva, D.; Mariani, A.; Genereux, P.; Branzi, A.; Stone, G.W. Stent thrombosis with drug-eluting stents: Is the paradigm shifting? *J. Am. Coll. Cardiol.* **2013**, *62*, 1915–1921. [CrossRef]
35. Kedhi, E.; Stone, G.W.; Kereiakes, D.J.; Serruys, P.W.; Parise, H.; Fahy, M.; Simonton, C.A.; Sudhir, K.; Sood, P.; Smits, P.C. Stent thrombosis: Insights on outcomes, predictors and impact of dual antiplatelet therapy interruption from the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials. *EuroIntervention* **2012**, *8*, 599–606. [CrossRef]
36. Cornelissen, A.; Vogt, F.J. The effects of stenting on coronary endothelium from a molecular biological view: Time for improvement? *J. Cell. Mol. Med.* **2019**, *23*, 39–46. [CrossRef]
37. Sardu, C.; Paolisso, P.; Sacra, C.; Mauro, C.; Minicucci, F.; Portoghese, M.; Rizzo, M.R.; Barbieri, M.; Sasso, F.C.; D'Onofrio, N.; et al. Effects of Metformin Therapy on Coronary Endothelial Dysfunction in Patients With Prediabetes With Stable Angina and Nonobstructive Coronary Artery Stenosis: The CODYCE Multicenter Prospective Study. *Diabetes Care* **2019**, *42*, 1946–1955. [CrossRef]
38. Marfella, R.; Sardu, C.; Balestrieri, M.L.; Siniscalchi, M.; Minicucci, F.; Signoriello, G.; Calabrò, P.; Mauro, C.; Pieretti, G.; Coppola, A.; et al. Effects of incretin treatment on cardiovascular outcomes in diabetic STEMI-patients with culprit obstructive and multivessel non obstructive-coronary-stenosis. *Diabetol. Metab. Syndr.* **2018**, *10*, 1–11. [CrossRef]
39. Marfella, R.; Sardu, C.; Calabrò, P.; Siniscalchi, M.; Minicucci, F.; Signoriello, G.; Balestrieri, M.L.; Mauro, C.; Rizzo, M.R.; Paolisso, G.; et al. Non-ST-elevation myocardial infarction outcomes in patients with type 2 diabetes with non-obstructive coronary artery stenosis: Effects of incretin treatment. *Diabetes Obes. Metab.* **2018**, *20*, 723–729. [CrossRef]
40. Paolisso, P.; Bergamaschi, L.; Gragnano, F.; Gallinoro, E.; Cesaro, A.; Sardu, C.; Mileva, N.; Foà, A.; Armillotta, M.; Sansonetti, A.; et al. Outcomes in diabetic patients treated with SGLT2-Inhibitors with acute myocardial infarction undergoing PCI: The SGLT2-I AMI PROTECT Registry. *Pharmacol. Res.* **2023**, *187*, 106597. [CrossRef]
41. Paolisso, P.; Bergamaschi, L.; Santulli, G.; Gallinoro, E.; Cesaro, A.; Gragnano, F.; Sardu, C.; Mileva, N.; Foà, A.; Armillotta, M.; et al. Infarct size, inflammatory burden, and admission hyperglycemia in diabetic patients with acute myocardial infarction treated with SGLT2-inhibitors: A multicenter international registry. *Cardiovasc. Diabetol.* **2022**, *21*, 77. [CrossRef] [PubMed]
42. Tokushige, A.; Shiomi, H.; Morimoto, T.; Furukawa, Y.; Nakagawa, Y.; Kadota, K.; Iwabuchi, M.; Shizuta, S.; Tada, T.; Tazaki, J.; et al. Incidence and outcome of surgical procedures after coronary bare-metal and drug-eluting stent implantation: A report from the CREDO-Kyoto PCI/CABG registry cohort-2. *Circ. Cardiovasc. Interv.* **2012**, *5*, 237–246. [CrossRef] [PubMed]
43. Rossini, R.; Tarantini, G.; Musumeci, G.; Masiero, G.; Barbato, E.; Calabro, P.; Capodanno, D.; Leonardi, S.; Lettino, M.; Limbruno, U.; et al. A Multidisciplinary Approach on the Perioperative Antithrombotic Management of Patients With Coronary Stents Undergoing Surgery: Surgery After Stenting 2. *JACC Cardiovasc. Interv.* **2018**, *11*, 417–434. [CrossRef] [PubMed]
44. Kim, H.K.; Tantry, U.S.; Park, H.W.; Shin, E.S.; Geisler, T.; Gorog, D.A.; Gurbel, P.A.; Jeong, Y.H. Ethnic Difference of Thrombogenicity in Patients with Cardiovascular Disease: A Pandora Box to Explain Prognostic Differences. *Korean Circ. J.* **2021**, *51*, 202–221. [CrossRef]

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Reversing Neuromuscular Blockade without Nerve Stimulator Guidance in a Postsurgical ICU—An Observational Study

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Abstract: We aimed to determine if not using residual neuromuscular blockade (RNB) analysis to guide neuromuscular blockade reversal administration in the postsurgical ICU resulted in consequences related to residual weakness. This single-center, prospective study evaluated 104 patients arriving in a postcardiac surgical ICU. After demonstrating spontaneous movement and T > 35.5 °C, all patients underwent RNB evaluation, and neostigmine/glycopyrrolate was then administered. When patients later demonstrated an adequate Rapid Shallow Breathing Index, negative inspiratory force generation, and arterial blood gas values with minimal mechanical ventilatory support, RNB evaluation was repeated in 94 of the 104 patients, and all patients were extubated. Though RNB evaluation was performed, patients were extubated without considering these results. Eleven of one hundred four patients had not achieved a Train-of-Four (TOF) count of four prior to receiving neostigmine. Twenty of ninety-four patients demonstrated a TOF ratio $\leq$ 90% prior to extubation. Three patients received unplanned postextubation adjunct respiratory support—one for obvious respiratory weakness, one for pain-related splinting compounding baseline disordered breathing but without obvious benefit from BiPAP, and one for a new issue requiring surgery. Residual neuromuscular weakness may have been unrecognized before extubation in 1 of 104 patients administered neostigmine without RNB analysis. ICU-level care may mitigate consequences in such cases.

Keywords: Neuromuscular blockade reversals; neostigmine; residual neuromuscular blockade

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1. Introduction

Standard anesthesiology teaching is to utilize residual neuromuscular blockade (RNB) analysis at two points to guide the appropriate administration of agents to reverse neuromuscular blockades given intraoperatively. First, utilize it before administering reversal agents to assure adequate spontaneous resolution of the blockade. Second, utilize it after administering reversal agents to assure the blockade is sufficiently resolved before extubating. Though this is not universally the standard practice before extubating patients in the intensive care unit (ICU), patient safety implications of postoperative residual weakness following neuromuscular blocking agent administration [1] are leading many to urge broader incorporation of such standards [2]. This is based on observed consequences associated with a lack of verifying chemical neuromuscular agent reversal prior to extubation in the operating room [3].

The purpose of this study was to evaluate the effectiveness at preventing weakness-induced complications of utilizing neostigmine/glycopyrrolate without RNB analysis to reverse chemical neuromuscular blockades in a surgical ICU.

2. Methods

2.1. Study Participants

The study was a prospective, single-center, observational study conducted at an academic hospital 18-bed cardiac surgical ICU. The study was designed to incorporate 100 patients over two years as part of a quality improvement initiative, but the enrollment period was extended due to COVID-19. Patients were eligible August 2017–February 2021 if they were admitted intubated to the ICU directly following sternotomy and heart surgery, insertion of mechanical ventricular support, or heart transplantation, and had received rocuronium and/or vecuronium and had not yet received chemical neuromuscular blocking reversal agents. The ICU is administratively run by the Cardiac Surgical Department but staffed by intensivists from the Departments of Cardiac Surgery, Anesthesiology and Pulmonary Medicine. By practice, some intensivists prefer acetylcholinesterase inhibitors nearly exclusively, while others prefer cyclodextrins to reverse chemical neuromuscular blocking agents. Only patients receiving acetylcholinesterase inhibitors were eligible for this study.

2.2. Baseline Characteristics and Follow-Up

All data except TOF information were extracted from the medical records. Difficult laryngoscopy was defined by Cormack–Lehane Classification [4] >3 by direct laryngoscopy or requirement for adjuvant instrumentation (e.g., bougie, indirect laryngoscopy). Renal dysfunction was considered as baseline creatinine > 2.0. Patients at risk for hepatic dysfunction were considered those with a history of significant ETOH or illicit drug use, known hepatitis of nonalcoholic fatty liver, chronic highly active antiretroviral therapy (HAART), or increased likelihood of embolic disease from endocarditis. Postextubation respiratory adjuncts were considered to be a use of simple nasal cannula oxygen > 6 L/min, simple face mask oxygen > 6 L/min, high-flow nasal cannula, or noninvasive or invasive mechanical support. Such adjuvant therapy was deemed to not be treating muscular weakness if it was administered (1) as HFNC in order to supply epoprostenol for RV support; (2) as HFNC for hypoxia in the setting of pH $\geq$ 7.35; (3) for a diagnosis of hypervolemia; (4) as planned continuation of patient's home OSA therapy; (5) in a patient who is able to stand. RNB data were recorded separately as part of a quality improvement initiative.

2.3. Intraoperative and Perioperative Anesthesia

An opioid-sparing anesthetic plan was employed intraoperatively, as previously [5,6]. In short, this involved preinduction administration of acetaminophen (1000 mg) and gabapentin (300–600 mg), intraoperative administration of ketamine (0.2–0.3 mg/kg/h) and/or dexmetetomidine (0.2–1.5 mcg/kg/h, titrated to hemodynamic and sedation goals), and rare use of regional nerve block (Serratus Anterior Plane block). ICU sedation was based predominantly on dexmetetomidine (0.2–1.5 mcg/kg/h) and/or propofol (10–50 mcg/kg/min). Narcotic supplementation per provider choice included fentanyl ($\leq$250 mcg) or hydromophone ($\leq$2 mg) intraoperatively and fentanyl ($\leq$200 mcg) or hydromorphone ($\leq$1 mg) postoperatively prior to extubation. The postoperative sedation target was typically to maintain hemodynamics but minimize spontaneous movement until chest tube bleeding < 150 mL/h was achieved. At this point, sedation was lightened to achieve calm response to commands. After neostigmine administration (see below), sedation was severely limited or completely stopped in an effort to promote awakening and evaluation of extubation readiness.

Intraoperative muscle relaxant was administered per provider discretion but rarely guided by quantitative RNB evaluation. Intraoperative temperature control typically involves "drifting" and active cooling rarely to a low of $\geq$33 °C during cardiopulmonary

bypass. After cardiopulmonary bypass, patients were actively warmed to 35 °C (bladder temperature) before separating cardiopulmonary bypass. They continued active warming to 36.5 °C in the operating room and in the ICU and did not receive neostigmine/glycopyrrolate until a bladder temperature of 36 °C was achieved.

2.4. Neostigmine Administration

Midlevel providers (nurse practitioners and physician assistants) dosed neuromuscular reversal agents when hemodynamic lability and bleeding were resolved (<150 mL/h), the patient has achieved T $\geq$ 35.5 °C, and has demonstrated some spontaneous movement (eg. extremity movement, respiratory effort). The typical reversal dose is 0.05–0.07 mg/kg neostigmine and 0.01–0.015 mg/kg glycopyrrolate.

2.5. Residual Neuromuscular Blockade Assessment

RNB was objectively assessed using STIMPOD NMS450 acceleromyograph, with leads over the ulnar nerve at the wrist and an accelerometer on the thumb, with the observer placing three of his/her fingers between the thumb and index finger of the patient to apply a mild "stretch". A Train-of-Four (TOF) stimulation with 60 mV at a 2 Hz frequency was delivered, with each twitch corresponding to a bar on the monitor display. For those achieving a Train-of-Four Count (TOFC) of 4, relative acceleration of 4th vs. 1st twitch (displayed in percentage) was indicated and used as Train-of-Four ratio (TOFR). Assessment was at two time points—once immediately before the delivery of chemical reversal agents for neuromuscular blockers and once before extubation. The second assessment ideally occurred as close to the point of extubation as comfortably possible for the patient (i.e., before propofol, dexmetetomidine, fentanyl, and/or hydromorphone was completely removed) but at least 25 min after delivering the reversal agent. Residual blockade assessment was performed by midlevel providers who were unfamiliar with their interpretation or significance. These providers were nurse practitioners with a master's or doctorate degree in nursing. Each demonstrated proficiency at the time of accelerometer use instruction, was intermittently reminded of proper use, and could refer to pictures on the accelerometer storage case for proper use.

2.6. Extubation Timing

Extubation timing was determined by demonstration of acceptable arterial blood gas values (pH > 7.30, PaCO2 mmHg < 50, PaO2 > 70 mmHg, HCO3 > 17 meq/L) and Rapid Shallow Breathing Index (RSBI) $\leq$ 80, NIF more negative than $-$20 cm H_2O, and FVC 8–10 mL/kg [7] after the patient had been on a pressure support of 5 cm H_2O, positive end-expiratory pressure of 5 cm H_2O, and FiO2 0.4 for $\geq$30 min. The results of the RNB evaluation did not inform the decision to extubate.

3. Results

Patient Population: 104 intubated patients (30 Female and 74 male, 63.3 $\pm$ 11.7 years old) admitted directly to the ICU following sternotomy and cardiac surgery having not received reversal agents for neuromuscular blockade were admitted to the study (Table 1). Ninety-four patients underwent RNB evaluation both pre-neostigmine administration and pre-extubation. One of these patients had a pre-neostigmine TOFR of 73% and a pre-extubation TOFC 4 recorded, but the post TOFR was not recorded. In an additional 10 patients, providers failed to perform RNB at the post-neostigmine administration time point. No patient required active intraoperative cooling below 33 °C (e.g., circulatory arrest).

Table 1. Surgical Procedures: *CAB* Coronary Artery Bypass, *Valve* aortic valve, mitral valve and/or tricuspid valve procedure, *AoV* Aortic Valve, *MV* Mitral Valve, *TV* Tricuspid Valve, *AscAo/AoRoot* Ascending Aorta and/or Aortic Root, and *Arch* Aortic Arch.

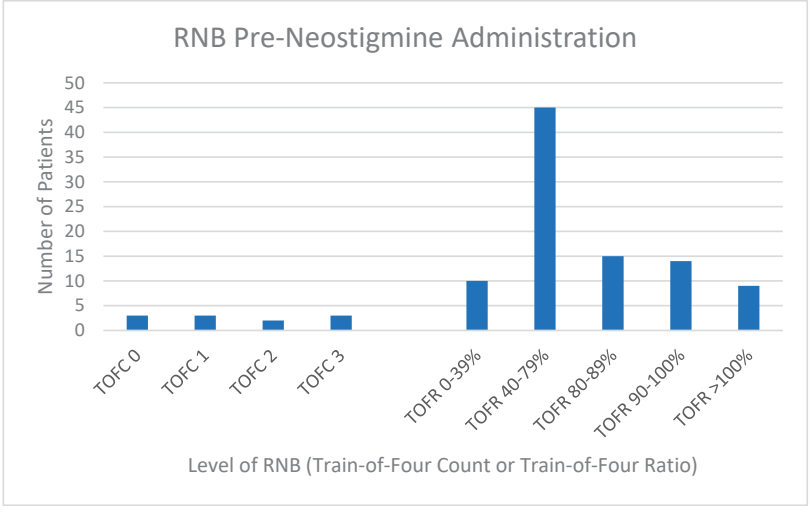
CAB	CAB/Valve	AoV	MV	TV	AscAo/AoRoot	Arch	Other
58	3	13	13	3	6	2	6 *

* MV/TV × 1, MV/AoV × 1, ASD × 1, LVAD × 2, Ht Transplant × 1.

Patient Characteristics: Of the 104 patients, 96 received only rocuronium, 7 received only vecuronium, and 1 received both rocuronium and vecuronium. The timing and quantity of rocuronium dosing and neostigmine dosing, as well as the timing of RNB evaluation, are shown in Table 2. At RNB evaluation prior to neostigmine/glycopyrrolate administration, 93 of 104 patients demonstrated TOFC 4 and generated a TOFR by acceleromyography. Of the remaining 11 patients, 6 demonstrated TOFC < 2 and 5 demonstrate TOFC 2 or 3 (Figure 1a).

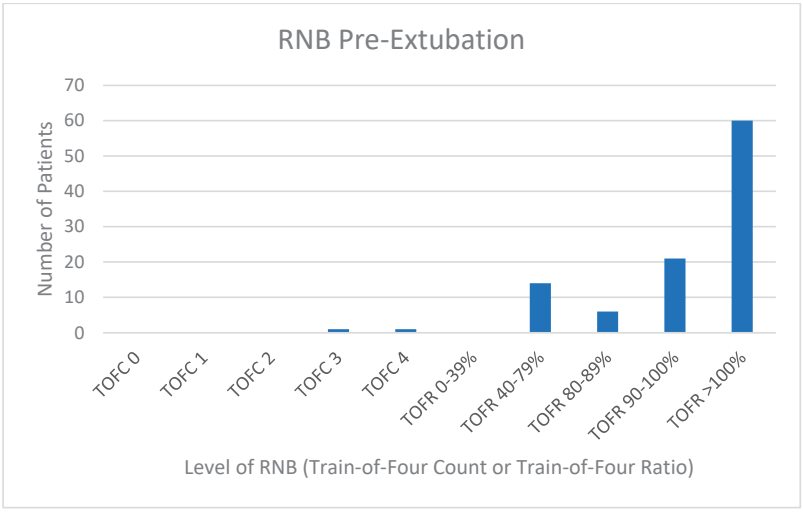
Table 2. Dosing Rocuronium and Timing of RNB Evaluation, *IQR* Interquartile Range, *NMBA* Neuromuscular Blocking Agent, *RNB* residual neuromuscular blockade.

	Rocuronium (mg/kg)	Final NMBA Dose-1st TOF Interval (h)	Neostimine (mg/kg)	Final RNB Evaluation—Extubation Interval (h)
	1.6	5.1	0.045	1.5
IQR	0.6–1.9	3.25–6.75	0.037–0.051	0.12–1.5



(**a**)

Figure 1. *Cont.*



(**b**)

Figure 1. (**a**)—RNB pre-neostigmine administration—histogram indicating number of patients at each Train-of-Four Count (TOFC) or Train-of-Four Ratio (TOFR) as their level of residual neuromuscular blockade (RNB) when analyzed at the preneostigmine administration time point. Total number of patients evaluated = 104. (**b**)—RNB pre-extubation—histogram indicating number of patients at each Train-of-Four Count (TOFC) or Train-of-Four Ratio (TOFR) as their level of residual neuromuscular blockade (RNB) when analyzed at the pre-extubation time point. Total number of patients evaluated = 94.

Of the 104 patients, 94 underwent RNB evaluation prior to extubation (Figure 1b). Two of these patients had only qualitative (i.e., TOFC) RNB data recorded—one because the pre-extubation TOFC < 4 prohibited acceleromyography and one with a pre-extubation TOFC 4 but no acceleromyography data recorded. Figure 2 shows the relationship between RNB preneostigmine and RNB pre-extubation in 93 of the 94 patients, with evaluations recorded at both time points. (The patient with a pre-extubation TOFC 4 but no recorded TOFR was excluded.) Of the 93 patients, 10 had pre-neostigmine TOFC < 4 and only qualitative NMB analysis, while 83 had pre-neostigmine TOFC 4 and could therefore have quantitative NMB analysis (i.e., acceleromyography) pre-neostigmine administration. Six of the ten patients (60%) with pre-neostigmine TOFC < 4 failed to achieve TOFR $\geq$ 90% prior to extubation. Fifteen of the eighty-two patients (18%) with TOFC 4 and acceleromyography on pre-neostigmine evaluation failed to achieve TOFR $\geq$ 90% prior to extubation.

The prevalence of patient factors that may compromise post-extubation respiratory mechanics (limited mobility/high inotrope requirement/IABP/OSA) are also listed (Supplemental Information).

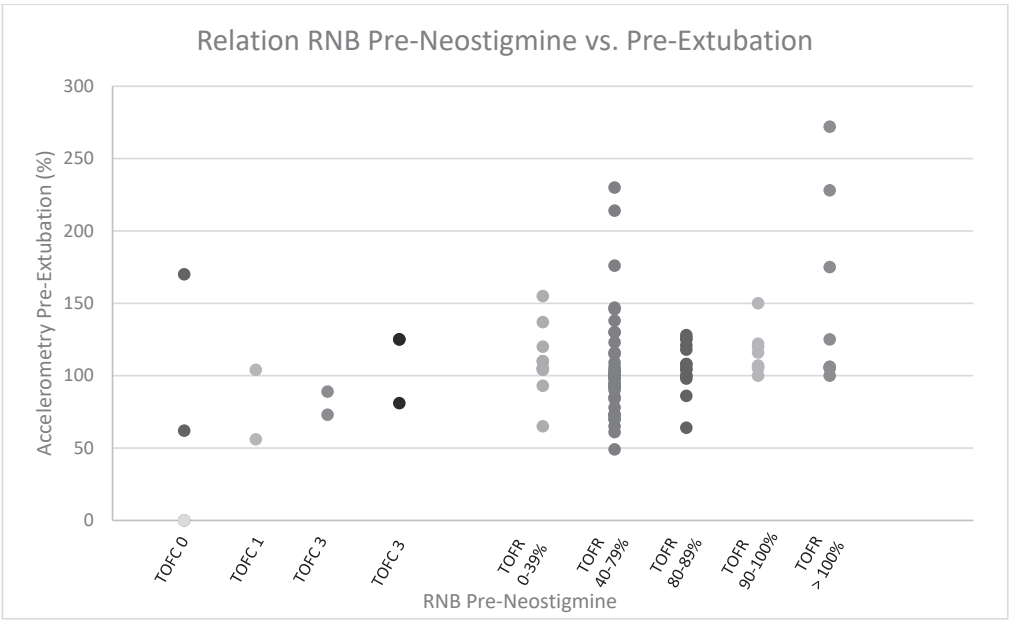


Figure 2. Relation of RNB pre-neostigmine vs. pre-extubation—dot plot indicating the pre-extubation accelerometry level achieved as a function of the level of residual neuromuscular blockade (RNB) present at the time of neostigmine administration. *X*-axis indicates the patients achieving various levels of Train-of-Four Count (TOFC) or Train-of-Four Ratio (TOFR) at the pre-neostigmine administration time point. *Y*-axis indicates the accelerometry level achieved at the pre-extubation time point for individual patients within each pre-neostigmine level of TOFC or TOFR. Accelerometry level of "0" indicates patients whose pre-extubation RNB was less than TOFC 4 and therefore could not be quantified by acceleromyograhphy. Ninety-three of ninety-four patients had RNB values obtained at both pre-neostigmine and pre-extubation time points. One excluded patient had post-extubation TOFC 4 but no indication of TOFR associated with this.

3.1. Patients Receiving Unplanned Postextubation Pulmonary Adjunct Support

Three patients received unplanned mechanical ventilatory adjunct support (noninvasive and/or invasive) following extubation. One patient received an unplanned postop regimen of BiPAP alternating with 6l n/c without obvious benefit that began after a planned nighttime BiPAP trial was poorly tolerated. This patient had a BMI of 36.7 and was noncompliant with home BiPAP for known paradoxical breathing. The patient demonstrated a pre-neostigmine TOFR of 68% prior to receiving 0.05 mg/kg neostigmine/0.01 mg/kg glycopyrrolate. Pre-extubation RNB evaluation was TOFR 70%. The patient was extubated 7.17 h following neostigmine administration with NIF −28 cm H_2O, a vital capacity of 0.63 L, 7.32/45 mmHg/82 mmHg/23 meq/L, and a positive cuff leak but no RSBI recorded on minimal ventilator support.

An arterial blood gas 75 min post-extubation showed 7.33/45 mmHg/90 mmHg/23 meq/L. A planned trial of BiPAP for sleep began 5.5 h following extubation, but patient intolerance and a satisfactory blood gas prior to initiating the trial (7.30/48 mmHg/82 mmHg/23) led to aborting this plan. Unfortunately, the patient's respiratory acidosis progressed, and the patient began intermittent BiPAP (IPAP 10 cm H_2O/EPAP 5 cm H_2O, FiO_2 0.4; 2–3 h periods of BiPAP interrupted by 2–3 h periods of 6l n/c) beginning ~12 h following initial intubation. Poor tolerance of BiPAP resulted in a lack of perceived effect (typical ABG off/on BiPAP was similar at ~7.26/52 mmHg/94 mmHg/23 meq/L), in spite of gradually increasing support intensity during the periods it was being applied (IPAP

16 cm H_2O/EPAP 5 cm H_2O). All attempts at daytime BiPAP, as well as any blood gas analysis, ended ~60 h following initial extubation. At this point, empiric nighttime BiPAP was utilized without evaluation as to its effectiveness.

A second patient who received unplanned post-extubation BiPAP had undergone ascending aortic aneurysm repair and left atrial appendage closure, with TEE showing an LVEF of 35–40% on epinephrine 0.05 mcg/kg/min/norepinephrine 0.05 mcg/kg/min following CPB. This patient had a pre-neostigmine TOFR of 61% prior to receiving 0.04 mg/kg neostigmine/0.01 mg/kg glycopyrrolate. No pre-extubation RNB evaluation was performed. The patient was extubated 3.17 h following neostigmine administration with NIF 36 cm H_2O, RSBI 48 br/min/L), vital capacity of 1.25 L, and 7.35/58 mmHg/134 mmHg/31 meq/L on minimal ventilator support.

A venous gas 2 h post-extubation showed pH 7.27/70 mmHg/50 mmHg/31 meq/L on 6 l n/c, resp. rate of ~20–22 persistently postop, GCS of 10 persistently postop, and no narcotics other than 50 mcg fentanyl on arrival. At 5 h following extubation, the patient was placed on BiPAP (iPAP 10 cm H_2O/EPAP 5 cm H_2O) after arterial 7.24/76 mmHg/160 mmHg/32 meq/L. On BiPAP, ABG recovered to 7.36/54 mmHg/109 mmHg/30 meq/L.

A third patient was reintubated. This patient had a history of bilateral iliac stenting, left carotid-subclavian bypass, and right femoral->axillary bypass. The present surgery was aortic arch repair with aortic debranching (aorta to right carotid, aorta to left carotid, and aorta to left subclavian) and CAB (LIMA->LAD). This patient had a TOFR of 88% prior to administration of 0.05 mg/kg neostigmine/0.01 mg/kg glycopyrrolate. No pre-extubation RNB evaluation was performed. However, the patient demonstrated a NIF of −40 cm H_2O, a Rapid Shallow Breathing Index of 48 br/min/L, a spontaneous respiratory rate of 18, a vital capacity of 0.73 L, positive cuff leak, and a blood gas of 7.44/41 mmHg/97 mmHg/27 meq/L on PS 5 cm H_2O, PEEP 5 cm H_2O, and FiO_2 0.4 at 30 min prior to extubation. She was, unfortunately, in the early stages of developing a fever when extubated (temp 38 °C, up 0.4 °C from 15 min earlier) and deteriorated 110 min after extubation to BiPAP support for fever (38.8 °C), respiratory failure (7.24/63 mmHg/72 mmHg/25 meq/L), and eventual intubation 11 h after extubation to return to the operating room for RLE occlusive thrombus.

No patient receiving unplanned supplemental respiratory care had suspected renal or hepatic dysfunction. Two patients had creatinine > 2.0. One, with cr 2.4, had a pre-extubation TOF4 of 110%. One, with cr 3.4, had a pre-extubation TOFr of 155%. One, with cr 2.7, had a pre-neostigmine TOF4 of 97%. None had post-extubation issue.

3.2. Patients Receiving Planned Postextubation Pulmonary Adjunct Support

Of the 94 patients having documented RNB evaluations both pre-neostigmine and pre-extubation, 10 received post-extubation adjunct pulmonary care as part of a care plan prepared prior to extubation (Supplemental Information). The reasons included (1) HFNC as part of a protocol to deliver epoprostenol for right ventricular afterload (n = 3); (2) HFNC in a patient with arterial pH > 7.35 (n = 3); (3) HFNC felt due to hypervolemia (n = 2); and (4) extubation on the patient's home CPAP/BiPAP settings as part of pre-ordained plan (n = 2). Only 1 of the 10 demonstrated a pre-extubation RNB < TOFR of 90%. Their pre-extubation RNB was a TOFR of 56%. They underwent planned extubation to epoprostenol via high-flow nasal cannula to reduce afterload on a dysfunctional right ventricle.

4. Discussion

Our study was designed to determine whether not using RNB analysis to guide administration of chemical neuromuscular blockade reversal in a postsurgical ICU resulted in consequences related to residual weakness. Of the 104 patients evaluated, 3 patients received unplanned adjunct respiratory care. In at least one of these cases, this unplanned respiratory care (BiPAP) likely reversed progressive respiratory decline related to weakness and possibly prevented reintubation.

Using observed spontaneous patient movement as the trigger to administer acetylcholinesterase inhibitor to reverse chemical neuromuscular blockade, we failed to recognize that ~12% of patients demonstrated a TOFC < 4, and an additional ~11% of patients demonstrated a TOFR < 40% prior to neostigmine administration. A TOFR of 40% is the minimum level of spontaneous recovery acceptable for antagonism with neostigmine [8–11]. Furthermore, subjective evaluation failed to recognize that 6% of patients had not yet spontaneously recovered to a TOFC $\geq$ 2 and that 3% had not yet even recovered to a TOFC $\geq$ 1. The 2 mg/kg sugammadex dose is Food and Drug Administration (FDA)-approved to antagonize residual rocuronium or vecuronium blockade of TOFC $\geq$ 2. For TOFC 1 or TOFC 0, sugammadex dosing of 4 mg/kg or 16 mg/kg is FDA-recommended. Neglecting to quantify RNB prior to administering reversal therefore risks not only the inappropriate use of neostigmine but also the inappropriate dosing of sugammadex.

The observed 11% TOFC < 4 at the time of pre-neostigmine dosing was surprising in that the time from the most recent neuromuscular blockade dosing was long (5.1, IQR 3.1–6.4 h), and the rocuronium dosing was not excessive (1.6, IQR 0.6–1.9 mg/kg). Though renal and hepatic functions are critical to the metabolism of rocuronium and vecuronium, renal failure was uncommon, and hepatic failure was nonexistent in our patients preoperatively. Hypothermia can decrease neostigmine efficacy [12], increase rocuronium effectiveness [13], and prolong the metabolism of nondepolarizing neuromuscular blocking agents [14,15]. Though our patients were warmed to $\geq$36 °C before neostigmine administration, most were <34 °C for at least 35% of their intraoperative course. Improper accelerometer utilization is possible, though the providers utilizing them had been individually trained and demonstrated proficiency before unsupervised use.

Although 23% of our patients demonstrated RNB above the level recommended before extubation (i.e., TOFR 90%), only 1 of our patients received unplanned pulmonary adjunct care for what was likely RNB. This could, in part, be due to ICU protocols that may help identify those whose RNB is truly dangerous, delaying extubation until RNB is resolved, or even treating patients for RNB. These protocols include evaluating spontaneous breathing patterns and verifying adequate gas exchange with minimal mechanical ventilator support prior to extubation [16], patient positioning, and aggressive pulmonary toilet following extubation, as well as deliberate down-titration of supplemental oxygen support. Compared with many intraoperative scenarios, ICU providers may feel less compelled to urgently extubate patients. This can result in more time being taken to assure RNB resolution prior to extubating patients whose capacity for pulmonary toileting may be limited by positioning restrictions or for whom reintubation is anticipated to be challenging. In our group, 8 patients arrived in the ICU with IABP, and 6 additional patients had known or suspected difficult airways. Furthermore, adjunct respiratory support for purposes other than recognized RNB may simultaneously avoid weakness-related decompensation. One of the ten patients receiving planned adjunct respiratory care in our study demonstrated a pre-extubation TOFR of 56%. The epoprostenol they received via high-flow nasal cannula as part of a planned intervention to reduce right heart afterload may simultaneously have protected against hypoxemia from unrecognized RNB. Finally, ICU-level surveillance identified the need for adjunct mechanical support in at least three patients with unanticipated progressive post-extubation respiratory acidosis.

Some use post-extubation hypoxemia as a marker of residual neuromuscular blockade [17,18]. Given the multiple potential causes of post-extubation residual A-a gradient in the early post-CPB period, such as hypervolemia [19], systemic inflammatory response [20], and infection [21], hypoxemia in patients capable of standing was considered unrelated to neuromuscular weakness. Nevertheless, the expectation of post-extubation A-a gradient may actually increase the importance of achieving full reversal of chemical neuromuscular blockades. Neuromuscular blocking agents blunt the hypoxic drive in animals [22] and in humans [23]. This attenuated drive is not immediately normalized with complete reversal of chemical neuromuscular blocking agents achieved with either neostigmine or

sugammadex [24]. It is tempting to speculate, however, that an earlier return baseline neuromuscular junction activity would hasten normalization of this chemoreflex.

Quantification of RNB is neither fool-proof nor cost-free. We chose an acceleromyograph with objective quantification of twitch ratio because it is more sensitive than subjective evaluation in detecting postoperative RNB [3,25]. However, RNB evaluation requires repetitive evaluation [26,27], assurance of adequate preload [25], and utilization in a sleeping patient [26] for optimized sensitivity and specificity. Of the 93 patients having pre-extubation NRB evaluation that included documented acceleromyography when appropriate, 7 had pre-extubation RNB evaluation performed within 10 min of extubation (i.e., patient likely awake) (data not shown). Even with attention to these performance measures, acceleromyography may overestimate neuromuscular recovery [28,29]. Furthermore, subjective distress can precede objective decline [30], and subtle risks to airway integrity may be an inherent risk to administration of neuromuscular blocking agents in that they persist even if extubated at a TOFR of $\geq$90% [31]. Additionally, a simple TOF nerve stimulator costs ~USD 350, while the acceleromyograph used in our study costs ~USD 2450.

Our study was small and did not address the newly appreciated potential for long-term consequences of residual neuromuscular blockades in susceptible patients such as the elderly [32]. Importantly, our study was carried out by the bedside providers rather than a separate study team. Providers were unaware of the significance of RNB evaluation. Providers found it cumbersome to locate equipment and perform pre-extubation RNB evaluation at a time close enough to the time of extubation to represent recovery, yet while the patient was still receiving adequate sedation and assuring free movement of the hand and fingers. Easily available RNB evaluation equipment, utilizing equipment with repeated reminders of appropriate technique, and provider understanding of its importance will facilitate provider adoption of RNB evaluation, albeit balanced by equipment cost.

5. Conclusions

In 104 post-cardiac-surgery ICU patients, RNB was reversed with neostigmine/glycopyrrolate administered after patients achieved T > 35.5 °C and were observed making spontaneous respiratory and/or extremity movement efforts. Residual neuromuscular weakness may have been unrecognized before extubation in at least 1 patient, but ICU-level care likely mitigated the consequences.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12093253/s1, Supplemental Information.

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Abbreviations

ICU	Intensive Care Unit
TOFC	Train-of-Four Count
TOFR	Train-of-Four Ratio
RV	Right Ventricle
HFNC	High-Flow Nasal Canula
CPAP	Continuous Positive Airway Pressure
BiPAP	Bilevel Positive Airway Pressure
OSA	Obstructive Sleep Apnea
CAB	Coronary Artery Bypass
MV	Mitral Valve
TV	Tricuspid Valve
LVAD	Left Ventricular Assist Device
ASD	Atrial Septal Defect
AscAo	Ascending Aorta
AoRoot	Aortic Root
IABP	Intra-aortic Balloon Pump
OR	Operating Room
RSBI	Rapid Shallow Breathing Index
BMI	Body Mass Index
SD	Standard Deviation

References

1. Stoelting, R.K. Monitoring of Neuromuscular Blockade: What Would You Expect If You Were the Patient? *APSF Newsl.* **2016**, *30*, 45–47.
2. Brull, S.J.; Kopman, A.F. Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities. *Anesthesiology* **2017**, *126*, 173–190. [CrossRef] [PubMed]
3. Murphy, G.S.; Szokol, J.W.; Marymont, J.H.; Greenberg, S.B.; Avram, M.J.; Vender, J.S. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth. Analg.* **2008**, *107*, 130–137. [CrossRef] [PubMed]
4. Cormack, R.S.; Lehane, J. Difficult tracheal intubation in obstetrics. *Anaesthesia* **1984**, *39*, 1105–1111. [CrossRef] [PubMed]
5. Grant, M.C.; Isada, T.; Ruzankin, P.; Gottschalk, A.; Whitman, G.; Lawton, J.S.; Dodd, O.J.; Barodka, V. Opioid-Sparing Cardiac Anesthesia: Secondary Analysis of an Enhanced Recovery Program for Cardiac Surgery. *Anesth. Analg.* **2020**, *131*, 1852–1861. [CrossRef] [PubMed]
6. Grant, M.C.; Isada, T.; Ruzankin, P.; Whitman, G.; Lawton, J.S.; Dodd, O.J.; Barodka, V.; Johns Hopkins Enhanced Recovery Program for the Cardiac Surgery Working Group. Results from an enhanced recovery program for cardiac surgery. *J. Thorac. Cardiovasc. Surg.* **2020**, *159*, 1393–1402.e1397. [CrossRef]
7. Yang, K.L.; Tobin, M.J. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *New Engl. J. Med.* **1991**, *324*, 1445–1450. [CrossRef]
8. Klein, A.A.; Meek, T.; Allcock, E.; Cook, T.M.; Mincher, N.; Morris, C.; Nimmo, A.F.; Pandit, J.J.; Pawa, A.; Rodney, G.; et al. Recommendations for standards of monitoring during anaesthesia and recovery 2021: Guideline from the Association of Anaesthetists. *Anaesthesia* **2021**, *76*, 1212–1223. [CrossRef]
9. Naguib, M.; Brull, S.J.; Kopman, A.F.; Hunter, J.M.; Fulesdi, B.; Arkes, H.R.; Elstein, A.; Todd, M.M.; Johnson, K.B. Consensus Statement on Perioperative Use of Neuromuscular Monitoring. *Anesth. Analg.* **2018**, *127*, 71–80. [CrossRef]
10. Plaud, B.; Baillard, C.; Bourgain, J.L.; Bouroche, G.; Desplanque, L.; Devys, J.M.; Fletcher, D.; Fuchs-Buder, T.; Lebuffe, G.; Meistelman, C.; et al. Guidelines on muscle relaxants and reversal in anaesthesia. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 125–142. [CrossRef]
11. Thilen, S.R.; Weigel, W.A.; Todd, M.M.; Dutton, R.P.; Lien, C.A.; Grant, S.A.; Szokol, J.W.; Eriksson, L.I.; Yaster, M.; Grant, M.D.; et al. 2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade. *Anesthesiology* **2023**, *138*, 13–41. [CrossRef] [PubMed]
12. Heier, T.; Caldwell, J.E.; Sessler, D.I.; Miller, R.D. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology* **1991**, *74*, 815–819. [CrossRef] [PubMed]
13. Kim, J.S.; Kim, Y.M.; Kim, H.J.; Choi, J.M.; Kim, Y.B.; Song, J.S.; Yang, H.S. Effects of hyperthermia on the effective concentration of rocuronium and sugammadex-mediated reversal in isolated phrenic nerve hemidiaphragm preparations of rats. *BMC Anesthesiol.* **2020**, *20*, 194. [CrossRef] [PubMed]

14. Beaufort, A.M.; Wierda, J.M.; Belopavlovic, M.; Nederveen, P.J.; Kleef, U.W.; Agoston, S. The influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans. *Eur. J. Anaesthesiol. Suppl.* **1995**, *11*, 95–106.
15. Caldwell, J.E.; Heier, T.; Wright, P.M.; Lin, S.; McCarthy, G.; Szenohradszky, J.; Sharma, M.L.; Hing, J.P.; Schroeder, M.; Sessler, D.I. Temperature-dependent pharmacokinetics and pharmacodynamics of vecuronium. *Anesthesiology* **2000**, *92*, 84–93. [CrossRef]
16. Frutos-Vivar, F.; Ferguson, N.D.; Esteban, A.; Epstein, S.K.; Arabi, Y.; Apezteguia, C.; Gonzalez, M.; Hill, N.S.; Nava, S.; D'Empaire, G.; et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest* **2006**, *130*, 1664–1671. [CrossRef]
17. Berg, H.; Roed, J.; Viby-Mogensen, J.; Mortensen, C.R.; Engbaek, J.; Skovgaard, L.T.; Krintel, J.J. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol. Scand.* **1997**, *41*, 1095–1103. [CrossRef]
18. Bissinger, U.; Schimek, F.; Lenz, G. Postoperative residual paralysis and respiratory status: A comparative study of pancuronium and vecuronium. *Physiol. Res.* **2000**, *49*, 455–462.
19. Morin, J.F.; Mistry, B.; Langlois, Y.; Ma, F.; Chamoun, P.; Holcroft, C. Fluid Overload after Coronary Artery Bypass Grafting Surgery Increases the Incidence of Post-Operative Complications. *World J. Cardiovasc. Surg.* **2011**, *1*, 18–23. [CrossRef]
20. Rubenfeld, G.D.; Caldwell, E.; Peabody, E.; Weaver, J.; Martin, D.P.; Neff, M.; Stern, E.J.; Hudson, L.D. Incidence and outcomes of acute lung injury. *N. Engl. J. Med.* **2005**, *353*, 1685–1693. [CrossRef]
21. Pasquina, P.; Tramer, M.R.; Walder, B. Prophylactic respiratory physiotherapy after cardiac surgery: Systematic review. *BMJ* **2003**, *327*, 1379. [CrossRef]
22. Jonsson, M.; Wyon, N.; Lindahl, S.G.; Fredholm, B.B.; Eriksson, L.I. Neuromuscular blocking agents block carotid body neuronal nicotinic acetylcholine receptors. *Eur. J. Pharmacol.* **2004**, *497*, 173–180. [CrossRef] [PubMed]
23. Eriksson, L.I.; Lennmarken, C.; Wyon, N.; Johnson, A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. *Acta Anaesthesiol. Scand.* **1992**, *36*, 710–715. [CrossRef] [PubMed]
24. Broens, S.J.L.; Boon, M.; Martini, C.H.; Niesters, M.; van Velzen, M.; Aarts, L.; Dahan, A. Reversal of Partial Neuromuscular Block and the Ventilatory Response to Hypoxia: A Randomized Controlled Trial in Healthy Volunteers. *Anesthesiology* **2019**, *131*, 467–476. [CrossRef] [PubMed]
25. Claudius, C.; Skovgaard, L.T.; Viby-Mogensen, J. Is the performance of acceleromyography improved with preload and normalization? A comparison with mechanomyography. *Anesthesiology* **2009**, *110*, 1261–1270. [CrossRef] [PubMed]
26. Baillard, C.; Bourdiau, S.; Le Toumelin, P.; Ait Kaci, F.; Riou, B.; Cupa, M.; Samama, C.M. Assessing residual neuromuscular blockade using acceleromyography can be deceptive in postoperative awake patients. *Anesth. Analg.* **2004**, *98*, 854–857, table of contents. [CrossRef] [PubMed]
27. Samet, A.; Capron, F.; Alla, F.; Meistelman, C.; Fuchs-Buder, T. Single acceleromyographic train-of-four, 100-Hertz tetanus or double-burst stimulation: Which test performs better to detect residual paralysis? *Anesthesiology* **2005**, *102*, 51–56. [CrossRef]
28. Bowdle, A.; Bussey, L.; Michaelsen, K.; Jelacic, S.; Nair, B.; Togashi, K.; Hulvershorn, J. A comparison of a prototype electromyograph vs. a mechanomyograph and an acceleromyograph for assessment of neuromuscular blockade. *Anaesthesia* **2020**, *75*, 187–195. [CrossRef] [PubMed]
29. Capron, F.; Alla, F.; Hottier, C.; Meistelman, C.; Fuchs-Buder, T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. *Anesthesiology* **2004**, *100*, 1119–1124. [CrossRef] [PubMed]
30. Eikermann, M.; Groeben, H.; Husing, J.; Peters, J. Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. *Anesthesiology* **2003**, *98*, 1333–1337. [CrossRef]
31. Kirmeier, E.; Eriksson, L.I.; Lewald, H.; Jonsson Fagerlund, M.; Hoeft, A.; Hollmann, M.; Meistelman, C.; Hunter, J.M.; Ulm, K.; Blobner, M.; et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): A multicentre, prospective observational study. *Lancet Respir. Med.* **2019**, *7*, 129–140. [CrossRef] [PubMed]
32. Tan, Z.; He, Q.; Liu, Y. Residual neuromuscular block: Beware of long-term adverse respiratory outcomes after departure from postanesthesia care unit (PACU). *Asian J. Surg.* **2022**. [CrossRef] [PubMed]

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Review

Anesthesia and Perioperative Management for Surgical Correction of Neuromuscular Scoliosis in Children: A Narrative Review

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Abstract: Scoliosis is the most frequent spinal deformity in children. It is defined as a spine deviation of more than 10° in the frontal plane. Neuromuscular scoliosis is associated with a heterogeneous spectrum of muscular or neurological symptoms. Anesthesia and surgery for neuromuscular scoliosis have a higher risk of perioperative complications than for idiopathic scoliosis. However, patients and their relatives report improved quality of life after the surgery. The challenges for the anesthetic team result from the specifics of the anesthesia, the scoliosis surgery itself, or factors associated with neuromuscular disorders. This article includes details of preanesthetic evaluation, intraoperative management, and postoperative care in the intensive care unit from an anesthetic view. In summary, adequate care for patients who have neuromuscular scoliosis requires interdisciplinary cooperation. This comprehensive review covers information about the perioperative management of neuromuscular scoliosis for all healthcare providers who take care of these patients during the perioperative period, with an emphasis on anesthesia management.

Keywords: neuromuscular scoliosis; anesthesia; total intravenous anesthesia; children; spondylosurgery; spine

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1. Introduction

Scoliosis is the most common spinal deformity in children. It is an abnormal lateral deviation of the spine, greater than 10° in the frontal plane. The lateral curvature is typically in combination with deviation in the sagittal plane (hyper/hypokyphosis or hyper/hypolordosis) and vertebral rotation [1,2]. The pathophysiological effect of scoliosis is complex and multiorgan. Besides musculoskeletal disturbances, cardiovascular, pulmonary, or psychosocial effects are described [1–4]. Scoliosis is categorized according to the etiology. The most frequent types include idiopathic (80%), congenital, and neuromuscular scoliosis [1,3]. Neuromuscular scoliosis, scoliosis associated with any neuromuscular syndrome, can be followed by alterations of vital functions by underlying diseases. Patients are at higher risk of curve progression to a significant deviation, which can lead to ventilation/perfusion (V/Q) mismatching, respiratory failure, and cor pulmonale [3,5–7]. The surgical correction of any scoliosis is indicated to prevent curve progression or the progression of restrictive lung disease. Other indications, especially in neuromuscular scoliosis, include improving posture and nursing care. Although there is a higher rate of perioperative complications in neuromuscular scoliosis surgery, patients and their relatives report improvements in quality of life after the surgery [7–9].

Scoliosis surgery is a major surgery associated with a high possibility of serious complications, particularly in patients with neuromuscular scoliosis. According to our experience, the management of patients undergoing surgery for idiopathic scoliosis is well described in many articles. This narrative review is focused on the differences and specifics of pediatric patients with neuromuscular scoliosis. Our goal is to bring relevant and comprehensive information to all perioperative team members, such as anesthesiologists, pediatricians, surgeons, or neurophysiologists, since interdisciplinary cooperation could be crucial for the patient outcome. We highlight the challenges both in the perioperative management of scoliosis surgery itself and in high-risk anesthesia for patients with neuromuscular disease [9–11].

2. Methods

The main limitation for the research was the diversity and rareness of some neuromuscular syndromes and the fact that neuromuscular scoliosis correction is a serious surgery but also a marginal topic requiring specialized care. For this reason, we choose an extended time frame of 1995–2022. The Google Scholar (https://scholar.google.com, Access time: 1–31 August 2022) [12], PubMed (https://pubmed.ncbi.nlm.nih.gov/, Access time: 1–31 August 2022) [13], Embase (https://www.embase.com/, Access time: 1–31 August 2022 [14] and Web of Science databases (https://www.webofscience.com/wos/author/search, Access time: 1–31 August 2022) [15] were used to search the literature. The aim was to map the whole perioperative process (preanesthetic assessment, anesthesia, and postoperative care).

We used a combination of terms, such as "anesthesia", "anesthetic management", "neuromuscular disease", neuromuscular disorders", "neuromuscular scoliosis", "pediatric". Besides this, we focus on specific issues in each section of this article.

Preanesthetic assessment Medical Subject Headings (MeSH) terms: "airway management", "respiratory functions examination", "cardiovascular examination", "neurological examination", invasive access", "nutrition", "prehabilitation".

Anesthesia and intraoperative MeSH terms: "air embolism", "blood management", "intraoperative neurophysiological monitoring", "malignant hyperthermia", "orphananesthesia", "perioperative monitoring", "prone position", "rhabdomyolysis", "temperature management", "total intravenous anesthesia", "vital functions monitoring".

Postoperative care MeSH terms: "intensive care unit", "postoperative care", "respiratory insufficiency", "ventilator weaning", "hemodynamic monitoring", "emergence delirium", "pain management", "postoperative pain", "fluid therapy", "acute kidney injury", "nutritional support", "postoperative hemorrhage", "postoperative complication", "postoperative wound infection", "rehabilitation".

3. Results

3.1. Preanesthetic Assessment

The preanesthetic evaluation requires a multidisciplinary approach. An integral part of this assessment is the identification of decompensated functions or organ reserves that could bring possible perioperative complications and its maximal preoperative optimization [9,10]. Anesthesiologists should individually consider the extent of preoperative testing according to the risks and benefits, scoliotic curvature severity, mental state or physical status with comorbidities, and type of planned surgical technique. The administration of pharmaceutical premedication has to be considered individually in patients with neuromuscular disorders. There are no precise data about dose restriction; it should be decided with respect to the neurological status and other associated aspects, such as the vagus stimulator, Lioresal pump, or severity of lung disease [10,16–18]. We list the specifics of preanesthetic assessment divided according to the ABCDE approach. This represents a widely respected approach to seriously ill patients, including the pediatric population. This approach could be used to anticipate and systematically prevent life-threatening complications [19].

3.1.1. Airways

Difficult airway management should be expected with a higher rate in patients with neuromuscular disorders as some syndromes are associated with facial dysmorphism, abnormal habitus, or limited mobility, especially limited neck mobility [17,19]. Anesthesiologists should search for risk factors for difficult airway management during the preanesthesia visit and prepare for airway securing, including advanced airway techniques such as video laryngoscopy or awake fiber optic intubation [20–22].

3.1.2. Breathing

The evaluation of respiratory function should be extended to chest X-radiation (X-ray), peripheral capillary oxygen saturation (SpO_2) measurement, and pulmonary function tests such as spirometry. Chest X-ray can provide information about airway deviations or signs of recurrent gastric content aspiration [10,18]. Spirometry quantifies the type and severity of lung dysfunction, typically restrictive lung disease. However, a development delay may impair the feasibility of spirometry. Severe restrictive lung disease (forced vital capacity <50% of normal values in patients with muscle weakness and symptoms of hypoventilation, or forced vital capacity <30% of normal values without muscle weakness) predicts a higher risk of respiratory complications such as pneumonia or prolonged weaning from ventilatory support [10,23]. Another method to determine high-risk patients (when spirometry is not available) is carbon dioxide monitoring during sleeping. However, this method is unreliable to detect hypoventilation and it is not preferred nowadays. Non-invasive bioelectrical impedance is available for clinicians. These monitors measure the tidal volume, minute ventilation, or respiratory rate to detect hypoventilation. It is essential to reduce the risk of perioperative complications and respiratory failure by optimizing respiratory function. Prehabilitation in cooperation with physiotherapists and pneumologists can improve patients' outcomes. This prehabilitation includes preoperative training in non-invasive ventilation or assisted coughing [23–25].

3.1.3. Circulation

Electrocardiography (ECG) is a standard part of preoperative assessment that can detect arrhythmias potentially associated with autonomic dysfunction [9–11]. Careful cardiologist examination with echocardiography is recommended in patients with myocardial dysfunction, because many neuromuscular syndromes are associated with heart disease, such as cardiomyopathy, valve disease, congenital heart disease, or limited stress tolerance. Preoperative cardiologic evaluation should be suggested in patients without myocardial dysfunction if pulmonary hypertension is suspected [10,20,26,27].

3.1.4. Disability (Neurology)

The neurological examination must provide a precise diagnosis with the known pathophysiology of a neuromuscular disorder. It helps with individualized anesthesia planning, which should reduce the risk of many anesthetic complications (see below). Exact neurological status description is suitable for juridical reasons, in case of postoperative neurological deficit development [27]. In addition, neurological deficit description helps with physiotherapy planning [26,27]. Epilepsy is diagnosed more frequently in patients with neuromuscular disorders [28]. Actual electroencephalography (EEG) should be considered, and perioperative antiepileptic drug administration must respect neurologist recommendations, taking into account possible interactions with anesthetic drugs [26,27].

3.1.5. Exposure (Environment)

Signs of difficult invasive access and suitable places for cannulation should be actively searched for. The signs of difficult access include muscle contractures or abnormal body proportions [27]. Other specific examinations should be indicated individually, e.g., nutritionists' recommendations in patients with signs of malnutrition [9,29]. Except for standard blood tests, plasma levels of myoglobin or creatine kinase should be obtained. These

markers are often altered in patients with neuromuscular disease. However, plasma levels before surgery are helpful to determine the baseline and monitor these levels' dynamics after surgery when suspecting rhabdomyolysis development [27,30,31].

3.2. Anesthesia and Intraoperative Management

Anesthesia for neuromuscular scoliosis is a challenge for the anesthetic team. Intraoperative management is specific and unique due to neuromuscular disease in children with its possible associated complications, such as intraoperative neurophysiological monitoring (IONM), high blood loss, patient positioning—typically pronation—fluid shift, long surgical times, and body temperature loss [10,27,31].

3.2.1. Anesthetic Management

Anesthesia and the choice of anesthetic drugs have to respect the pathophysiological category of the syndrome. Data on orphan syndromes are scarce. However, anesthesiologists can obtain information about the syndromes and anesthetic management from internet sources, e.g., published unique case reports, Orphananesthesia [32]. Total intravenous anesthesia (TIVA), most often the combination of propofol and remifentanil, is the most suitable and safe method, especially in the case of IONM. It requires a sufficient intravenous (IV) line. However, cannulation can be difficult due the joint contractures or abnormal habitus [33,34]. The indication of a central venous catheter should be considered individually according to the comorbidities and expectation of the need for vasopressors [10,27]. Ultrasound-guided cannulation can reduce the incidence of unsuccessful attempts and also increases the safety of the procedure [10,20]. Depth of anesthesia monitoring is recommended for TIVA to prevent overdosing and shorten the time of awakening after the surgery [10,18,27].

Non-depolarizing muscle relaxants can be administered safely. The effect of these drugs is variable, typically prolonged in patients suffering from neuromuscular disorders. Therefore, any administration of neuromuscular blocking agents should be followed by monitoring of the depth of neuromuscular blockade [26,27,32]. Rocuronium with available antagonist sugammadex represents a safe combination to provide complete recovery after the blockade and allow reliable IONM [35].

Anesthesia and vital functions should be managed individually with consideration of the age and comorbidities of each patient. The aim of ventilation and oxygenation is normoxia and normocapnia [9,10]. Anesthesiologists can manage perioperative vital functions according to vital function levels mentioned in the European Pediatric Advanced Life Support (EPALS) Guidelines 2021 [36]. The target blood pressure is not strongly recommended in children during scoliosis surgery. However, some data recommend maintaining a mean arterial blood pressure (MAP) near 65 mmHg, but approximately the fifth percentile of the mean and systolic arterial blood pressure for the relevant age group can be used safely. Transesophageal echocardiography should be considered in high-risk patients, e.g., patients with myocardial dysfunction or pulmonary hypertension. In addition, intraoperative transesophageal echocardiography helps to evaluate the volume status and manage goal-directed fluid therapy [10,33,37].

3.2.2. Neuromuscular Disease and Associated Complications—Malignant Hyperthermia and Rhabdomyolysis

Perioperative complications in patients with neuromuscular syndrome are observed at a higher rate compared to patients without neuromuscular disorders [9]. The most severe complications are malignant hyperthermia (MH) and rhabdomyolysis. Their development depends on the pathophysiology category of concrete neuromuscular disease, e.g., myopathies represent a high risk for MH or rhabdomyolysis [38].

MH is a syndrome caused by the hypermetabolic response with increased carbon dioxide production to suxamethonium or volatile anesthetics exposure. Early diagnosis and treatment with cooling of the patient are essential. It is recommended to use local pro-

tocols (personalized guidelines with particular locations of, e.g., dantrolene and emergency numbers) for the treatment of malignant hyperthermia. These protocols should be available in the operation room, where surgeries for high-risk patients are performed. To manage the crisis, the elimination of triggers (mentioned anesthetic drugs), hyperventilation with 100% oxygen, treatment of hyperkalemia (calcium administration for membrane stabilization, salbutamol, and insulin/glucose administration for kalemia reduction) are necessary. Dantrolene administration and symptomatic therapy, such as arrhythmia treatment, should be managed according to the actual guidelines [38–40].

Rhabdomyolysis is a condition associated with muscle damage. Myoglobin, potassium, and creatine kinase are released from the intracellular space [41]. Rhabdomyolysis was described after succinylcholine or volatile anesthetics exposure as anesthesia-induced rhabdomyolysis. Moreover, it was reported after muscle injury during a long surgery with inadequate patient positioning [38,42]. The differential diagnosis of MH can be complicated, and both syndromes can initially present with similar clinical signs. Rhabdomyolysis is typical of hyperkalemia, creatine kinase elevation, or myoglobinuria with "cola-colored urine". Myoglobinuria can be monitored postoperatively. Therapy has to focus on hyperkalemia treatment, hyperventilation with 100% oxygen, the prevention of acute kidney injury development, volume therapy, and the elimination of triggers [38,41,42].

3.2.3. Intraoperative Neurophysiological Monitoring

IONM represents an important and, in recent years, rising method for neural structure injury monitoring. Anesthetic management, including oxygenation, ventilation, massive blood loss, or hypotension, can influence the IONM reproducibility. IONM reproducibility can be limited in patients with neuromuscular disorders. The anesthetic team has to create the best conditions for IONM. The most common anesthetic technique is TIVA, typically in a combination of propofol and remifentanil. This combination is suitable for patients with neuromuscular disorders and allows early awakening from anesthesia if surgeons require the wake-up test. Other intravenous agents can be applied considering their adverse effect profiles and contraindications. Modern trends show the use of ketamine in combination as a co-analgesic, which reduces the total dose of propofol and remifentanil. All neuromuscular relaxants interfere with motor evoked potential (MEP) monitoring. They are administered in the phase of induction to the anesthesia to facilitate airway securing. Other anesthesiological aspects include maintaining normoxia with normocapnia, preventing severe hypothermia (more than 2.5 °C from the baseline), and ensuring adequate blood flow to the spinal cord. This means maintaining normotension during surgery (see above), namely increasing MAP above 85 mmHg when MEP is decreased. Anesthesiologists must consider the transfusion trigger to ensure adequate perfusion and oxygenation (see below) [43,44].

3.2.4. Positioning and Associated Complications

The prone position is the most frequent position for scoliosis surgery to facilitate access to the spine. This position is associated with several complications caused by raised intra-abdominal or thoracic pressure. In addition, prone positioning is associated with a higher risk of postoperative visual loss [45–48].

Patients with neuromuscular disorders can suffer from joint and muscle contractures, and some syndromes can be associated with low bone density. There is a potential risk of iatrogenic injury. These conditions represent increased demands for exact positioning. Correct but considerate prone positioning, respecting joint mobility, and the pressure distribution on the chest and pelvis decrease the rate of complications. Aside from careful positioning on the operating room table, the aesthesia team should elevate the upper part of the body to decrease the intraocular pressure and reduce the risk of visual loss. Other factors in reducing the risk of postoperative visual loss are avoiding anemia, hypotension (see above), and preventing venous return obstruction due to malpositioning. Besides ensuring appropriate positioning before surgery, the anesthetic team should control the

body position during surgery. The patient may be harmed by manipulation by the operating team during surgery [45,46].

Advanced cardiopulmonary resuscitation with chest compressions is possible in a prone position. External cardiac massage may be performed with the palms placed over the patient's scapulae. Internal cardiac massage and direct defibrillation were performed successfully via left posterior thoracotomy in a patient with Duchenne's muscular dystrophy during scoliosis correction in a prone position [48]. However, anesthesiologists should consider turning the patient to a supine position in the case of a stabilized spine without prominent orthopedic tools for manipulation with instrumentation (rod pushers, connect ratchets, downtubes, etc.) [10,47,48].

3.2.5. Blood Loss and Patient Blood Management

Patients with neuromuscular disease are at a high risk of extensive blood loss because of prolonged and extensive procedures or bones with lower density. Strategies to reduce blood loss are still being discussed. Antifibrinolytics' effect in reducing blood loss and transfusion administration has been described in scoliosis surgery, especially in patients with neuromuscular disorders. Tranexamic acid is one of the most widely used antifibrinolytics. The recommended prophylactic dose is about 15 mg/kg IV. The optimal maintenance dose is unclear; current data mention infusions of 1–20 mg/kg/h. The risk of adverse events, thromboembolism included, has not been increased in prophylactic administration during scoliosis surgery [49–51].

Another means to reduce allogeneic blood transfusion is intraoperative cell salvage (Cell Saver). The blood is collected from the wound into a reservoir. Red blood cells can be re-infused to the patient after purification of the collected blood. It is a preferred method, especially in high-risk patients with neuromuscular disorders and a presumed low bone density [52,53].

Desmopressin increases von Willebrand factor and factor VIII levels. However, it does not have an effect in reducing blood loss. Prophylactic administration is not recommended [54].

Protocols for red blood cell transfusion triggers describe the administration of Red Blood Cells (RBC) at levels between 7 and 8 g Hb/dL. Other coagulation factors should be administered according to the laboratory or viscoelastic hemostatic assays ideally [54,55].

Patients with neuromuscular disorders or immobilization after extensive surgery, in combination with a post-surgical inflammatory state, are at a higher risk of deep vein thrombosis and pulmonary embolism. Early mobilization and mechanical prevention are recommended. Data on pharmacological prophylaxis are scarce. Low-molecular-weight heparin administration in the perioperative period until the normalization of the patient's condition should be considered after the validation of risk factors [56].

3.2.6. Body Temperature Management

As mentioned above, severe hypothermia, with a decrease in temperature of more than 2.5 °C from the baseline, interferes with IONM. Patients with neuromuscular disease, a lower body mass index, or a larger Cobb angle (the angle between the extension line of the upper and lower end plate of the most inclined vertebral bodies) are at a higher risk of hypothermia [5]. Other adverse effects include prolonged metabolism of anesthetic agents, coagulopathy with higher blood loss, and wound or respiratory infections. Preoperative and intraoperative active warming, or prewarming before surgery, is recommended to prevent hypothermia in patients with neuromuscular disorders [57,58].

3.3. Postoperative Care

3.3.1. Admission to Intensive Care Unit (ICU)

According to studies, most of the patients require admission to the ICU or pediatric ICU. However, the decision should be made individually, e.g., the recovery after surgeries with a duration under 4 h can be, in some cases, manageable at a postanesthesia care

unit. The possible predicting factors for ICU admission are a low weight, neuromuscular scoliosis, pre-existing respiratory pathology, and other comorbidities. A higher number of operated segments or a higher degree of spine curvature is not associated with ICU admission [59,60].

3.3.2. Airway and Breathing

Patients with neuromuscular scoliosis often suffer from preexisting respiratory diseases such as muscle weakness (e.g., Duchenne's muscular dystrophy) or restrictive disorders, most often caused by chest deformities, which leads to a risk of postoperative respiratory failure [61,62]. Facial dysmorphism in some syndromes is associated with difficult airways. Proper equipment for difficult airway management should be available at the ICU in case of the need for emergent reintubation. Reintubation or prolonged weaning is associated with a risk of ventilator-associated pneumonia or tracheal stenosis, so early successful weaning should be one of the main goals [63]. Bulbar weakness can also be part of some syndromes and lead to dysphagia, gastric regurgitation, dysphonia, or difficult expectoration [62]. Protocols for weaning and monitoring diaphragm function can help to achieve early extubation, leading to better patient outcomes [64,65]. Implementing non-invasive ventilation into weaning processes in high-risk patients can prevent prolonged intubation and tracheostomy [62,66–68].

3.3.3. Circulation

Early after the operation, at least ECG, non-invasive blood pressure, and peripheral oxygen saturation should be monitored. For patients without signs of hemodynamic instability (hypotension, arrhythmias, altered mental status, low diuresis, etc.), standard monitoring is sufficient. In cases of hemodynamically unstable patients, invasive blood pressure should be monitored. Hypotension should be treated with volumotherapy and vasopressors according to its severity. For the prediction of volume responsiveness in hemodynamically unstable children, unresponsive to initial fluid therapy, cardiac output monitoring with echocardiography is recommended if available. Cardiac output could be monitored also with non-invasive or invasive pulse waveform analysis, although the data on the use of these methods in children are limited. Central venous pressure monitoring and central venous oxygen saturation monitoring could provide a more complex view of the patient's status and its trend, but these types of monitoring should not be used as the sole method [69]. In children with pre-existing cardiac disease, transesophageal or transthoracic echocardiography could be helpful to determine the cardiac contractility, preload, signs of pulmonary hypertension, or a possible worsening of valvular diseases. The sources for this topic are rare, and the authors highlight the potential for further research in this area [9,36].

3.3.4. Disability (Neurology, Analgosedation)

Dexmedetomidine sedation, in patients who require sedation after surgery, decreases the use of opioids and the risk of postoperative delirium when compared to midazolam [70].

Scoliosis correction is a type of surgery with an anticipated high postoperative pain level [70–72]. Patients with neuromuscular diseases are at a greater risk of undertreated pain [71,72]. Undertreated pain could lead to prolonged hospitalization, patient psychological trauma, and persistent postoperative pain [71]. The location of the most intense pain is the surgical wound. For most patients, it becomes tolerable after four days [71–73]. For this time period, the patient should be actively screened for their pain level and sufficiently treated. Multimodal analgesia should be chosen and started already during surgery to decrease opioid use. The most frequent opioid during surgery is remifentanil. Remifentanil's conversion to longer-acting opioids, such as sufentanil or piritramide, is necessary before the end of the surgery. Postoperative continuous opioid administration by a patient-controlled analgesia (PCA) pump is the gold standard for patients after idiopathic scoliosis correction. Neuromuscular scoliosis is sometimes associated with syndromes characteristic

of mental or severe physical impairments. Depending on the pain severity, the safe and effective use of PCA delivery may require the assistance of the pediatric patient's parents and/or a nurse. Epidural analgesia and regional analgesia (bilateral erector spinae plane block) initiated at the operating theater reduce postoperative opioid use [71–76]. Epidural analgesia could achieve better analgesia than PCA. The patient's neurologic status should be assessed before the administration bolus of local anesthetics because a sensory or motor blockade could occur. The risks associated with epidural analgesia do not differ from those of other surgery types [71,72]. For patients with idiopathic scoliosis, the intrathecal opioid (most often morphine or sufentanil) administration at the operation theater before the skin incision is associated with reduced intravenous opioid use during anesthesia and sufficient postoperative analgesia for the first 24 h. If morphine is lower than 20 μg/kg, the risk of respiratory depression is not higher than in the intravenous PCA method. Data on intrathecal morphine administration are limited in patients with neuromuscular scoliosis [71]. The bilateral erector spinae block in both the single-shot and catheter techniques has been successfully performed. The maximum dose of local anesthetic per 24 h needs to be respected to avoid systemic toxicity. Continuous wound infiltration seems to be an option for postoperative analgesia, but more research on this topic is required. Regional analgesia is often combined with non-steroidal anti-inflammatory drugs (NSAIDs) if needed [70–72,77]. Perioperative and postoperative low-dose ketamine infusion can also be an efficient part of multimodal pain management [77,78]. The intravenous use of local anesthetics (e.g., lidocaine) or gabapentinoids is controversial [70,77]. The indication, timing, and dosing scheme should undergo further research. The use of glucocorticoids should be explored more, but a single dose of dexamethasone after surgery seems to reduce the pain level without a higher risk of infection [70,77].

3.3.5. Electrolytes

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur after spinal fusion in neuromuscular and idiopathic scoliosis. The therapy is not different compared to that for patients without neuromuscular disorders [79].

3.3.6. Fluids (Kidneys)

Acute kidney injury (AKI) was detected in children after spine surgery. Different stages of AKI were diagnosed in 17% (35 of 208) of patients. The risk factors include nephrotoxic medications (e.g., aminoglycosides, NSAIDs) and a low amount of fluids intraoperatively. The management of NSAIDs is often needed in the postoperative period. However, their administration should be reconsidered daily because NSAIDs reduce prostaglandin synthesis. This can lead to kidney hypoperfusion or nephritis. Moreover, other nephrotoxic medication administration risks versus benefits should be reevaluated every day [80].

3.3.7. Gastrointestinal Tract (GIT) and Nutrition

Preexisting dysphagia or gastroesophageal reflux can be worsened in patients with neuromuscular diseases. Tests and monitoring of dysphagia before postoperative realimentation can be helpful. Early postoperative nutrition should be started in malnourished patients prior to surgery. A good nutritional status can reduce the risk of postoperative infection [81]. Neuromuscular disease is also the leading risk factor for postoperative ileus, which is more likely in patients with extended bed rest. Monitoring symptoms of ileus (e.g., nausea, vomiting, abdomen distension) and early interventions can shorten the length of the hospital stay [81,82]. The risk of pancreatitis rises in cases of prolonged postoperative fasting. No cases of pancreatitis with organ failure, shock, or death have been reported. The impaired mental status or diminished pain due to high doses of analgesics and atypical clinical symptoms can make diagnostics difficult. Liver enzymes, amylase, and lipase measurement can help in obtaining a diagnosis. If pancreatitis develops, the standard treatment should be started immediately [82].

3.3.8. Hematology

The more significant depletion of coagulation factors is present in patients suffering from neuromuscular disorders. Routine control of the thrombin time, prothrombin time, partial thromboplastin time, and fibrinogen in combination with viscoelastic hemostatic assays should be done in postoperative care. In prolonged postoperative bleeding, extended tests should be considered (e.g., factor XIII level), and the standard treatment for coagulopathy should be started [83].

3.3.9. Infections

Infection is a leading complication in postoperative care after scoliosis surgery, with higher incidence in patients with neuromuscular disease. Urinary infection and pneumonia are the most frequent infections. The most common causes of urinary infections in hospitals are urinary catheters. Indications for the insertion and maintenance of urinary catheters should be reconsidered every day. Proper insertion techniques and maintenance care are a solution to reduce the risk of urinary infection [84]. The prevention of pneumonia is mostly the same as in other patients in the ICU. The specifics for patients with neuromuscular diseases are described above. Patients should also be routinely monitored for signs of wound infection [85,86]. The prevention of postoperative wound infection does not differ from standard care for wounds after spinal surgery.

3.3.10. Rehabilitation

Patients with neuromuscular diseases are supposed to have complex physiotherapy. A very important part of rehabilitation is breathing and coughing exercises because of the high incidence of preoperative respiratory complications and weak cough. The prerehabilitation should start prior to the surgery to train high-risk patients to breathe with NIV or use a cough assistant. Chest physiotherapy should be maximized one week prior to surgery [24].

4. Conclusions

Anesthesia and the perioperative management of pediatric patients for neuromuscular scoliosis surgery represent a significant challenge for all healthcare providers. This heterogeneous team involves surgeons, anesthesiologists, neurophysiologists, pediatricians, nurses, nutritionists, and physiotherapists. Every part of the management should be adequately planned because of the higher risk of perioperative complications compared to idiopathic scoliosis. Healthcare providers have to consider all risks arising from the surgery, anesthesia, and the nature of the disease as a multidisciplinary and individual approach to each patient can improve the postoperative outcome. Firstly, mentioned data focus on the maximal optimization of altered functions before surgery and patients´ complex multidisciplinary prehabilitation. Secondly, adequate preparation of the anesthetic management regarding the specifics of neuromuscular syndromes, surgery, or anesthesia is essential for safety in the perioperative period. Thirdly, postoperative care in the ICU with adequate prevention, early identification, and treatment of possible complications can improve the postoperative outcome. All the described steps can lead to improved quality of life in patients with neuromuscular scoliosis.

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References

1. El-Hawary, R.; Chukwunyerenwa, C. Update on Evaluation and Treatment of Scoliosis. *Pediatr. Clin. N. Am.* **2014**, *61*, 1223–1241. [CrossRef]
2. Konieczny, M.R.; Senyurt, H.; Krauspe, R. Epidemiology of adolescent idiopathic scoliosis. *J. Child. Orthop.* **2013**, *7*, 3–9. [CrossRef]
3. Sheehan, D.D.; Grayhack, J. Pulmonary Implications of Pediatric Spinal Deformities. *Pediatr. Clin. N. Am.* **2020**, *68*, 239–259. [CrossRef] [PubMed]
4. Safari, A.; Parsaei, H.; Zamani, A.; Pourabbas, B. A Semi-Automatic Algorithm for Estimating Cobb Angle. *J. Biomed. Phys. Eng.* **2019**, *9*, 317–326. [CrossRef]
5. Jin, C.; Wang, S.; Yang, G.; Li, E.; Liang, Z. A Review of the Methods on Cobb Angle Measurements for Spinal Curvature. *Sensors* **2022**, *22*, 3258. [CrossRef] [PubMed]
6. Rüwald, J.M.; Eymael, R.L.; Upenieks, J.; Zhang, L.; Jacobs, C.; Pflugmacher, R.; Schildberg, F.A. An Overview of the Current State of Pediatric Scoliosis Management. *Z. Orthopädie Unf.* **2019**, *158*, 508–516. [CrossRef]
7. Wishart, B.D.; Kivlehan, E. Neuromuscular Scoliosis: When, Who, Why and Outcomes. *Phys. Med. Rehabil. Clin. N. Am.* **2021**, *32*, 547–556. [CrossRef]
8. Ridderbusch, K.; Spiro, A.S.; Kunkel, P.; Grolle, B.; Stücker, R.; Rupprecht, M. Strategies for Treating Scoliosis in Early Childhood. *Dtsch. Ärzteblatt Int.* **2018**, *115*, 371–376. [CrossRef] [PubMed]
9. Halawi, M.J.; Lark, R.K.; Fitch, R.D. Neuromuscular Scoliosis: Current Concepts. *Orthopedics* **2015**, *38*, e452–e456. [CrossRef]
10. Gibson, P.R.J. Anaesthesia for Correction of Scoliosis in Children. *Anaesth. Intensiv. Care* **2004**, *32*, 548–559. [CrossRef]
11. Weissmann, K.A.; Lafage, V.; Pitaque, C.B.; Lafage, R.; Huaiquilaf, C.M.; Ang, B.; Schulz, R.G. Neuromuscular Scoliosis: Comorbidities and Complications. *Asian Spine J.* **2020**, *15*, 778. [CrossRef] [PubMed]
12. Google Scholar. Google Scholar [Online]. Available online: https://scholar.google.com/ (accessed on 31 August 2022).
13. PubMed. PubMed [online]. Available online: https://pubmed.ncbi.nlm.nih.gov/ (accessed on 31 August 2022).
14. Embase—A Biomedical Research Database. Elsevier | An Information Analytics Business [online]. Available online: https://www.elsevier.com/solutions/embase-biomedical-research (accessed on 31 August 2022).
15. Web of Science. [Online]. Available online: https://www.webofscience.com/wos/author/search (accessed on 31 August 2022).
16. Briggs, E.D.; Kirsch, J.R. Anesthetic implications of neuromuscular disease. *J. Anesth.* **2003**, *17*, 177–185. [CrossRef] [PubMed]
17. Lerman, J. Perioperative management of the paediatric patient with coexisting neuromuscular disease. *Br. J. Anaesth.* **2011**, *107*, i79–i89. [CrossRef]
18. Turakhia, P.; Barrick, B.; Berman, J. Patients with Neuromuscular Disorder. *Med. Clin. N. Am.* **2013**, *97*, 1015–1032. [CrossRef] [PubMed]
19. Thim, T.; Krarup, N.H.V.; Grove, E.L.; Rohde, C.V.; Løfgren, B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. *Int. J. Gen. Med.* **2012**, *5*, 117–121. [CrossRef] [PubMed]
20. Hudec, J.; Kosinova, M. Anesthesia of the Patient with Zhu-Tokita-Takenouchi-Kim (ZTTK) Syndrome: A Case Report. *Children* **2022**, *9*, 869. [CrossRef]
21. Sohn, L.; Peyton, J.; von Ungern-Sternberg, B.S.; Jagannathan, N. Error traps in pediatric difficult airway management. *Pediatr. Anesth.* **2021**, *31*, 1271–1275. [CrossRef]
22. Hsu, G.; von Ungern-Sternberg, B.S.; Engelhardt, T. Pediatric airway management. *Curr. Opin. Anaesthesiol.* **2021**, *34*, 276–283. [CrossRef]
23. Birnkrant, D.J.; Panitch, H.B.; Benditt, J.O.; Boitano, L.J.; Carter, E.R.; Cwik, V.A.; Finder, J.D.; Iannaccone, S.T.; Jacobson, L.E.; Kohn, G.L.; et al. American College of Chest Physicians Consensus Statement on the Respiratory and Related Management of Patients With Duchenne Muscular Dystrophy Undergoing Anesthesia or Sedation. *Chest* **2007**, *132*, 1977–1986. [CrossRef]
24. St-Laurent, A.; Zysman-Colman, Z.; Zielinski, D. Respiratory prehabilitation in pediatric anesthesia in children with muscular and neurologic disease. *Pediatr. Anesth.* **2021**, *32*, 228–236. [CrossRef]
25. Racca, F.; Del Sorbo, L.; Capello, E.C.; Ranieri, V.M. Neuromuscular patients as candidates for non invasive ventilation during the weaning process. *Minerva Anestesiol.* **2012**, *78*, 391.
26. Katz, J.A.; Murphy, G.S. Anesthetic consideration for neuromuscular diseases. *Curr. Opin. Anaesthesiol.* **2017**, *30*, 435–440. [CrossRef]
27. Racca, F.; Mongini, T.; Wolfler, A.; Vianello, A.; Cutrera, R.; Del Sorbo, L.; Capello, E.C.; Gregoretti, C.; Massa, R.; De Luca, D.; et al. Recommendations for anesthesia and perioperative management of patients with neuromuscular disorders. *Minerva Anestesiol.* **2013**, *79*, 419–433.
28. Pane, M.; Messina, S.; Bruno, C.; D'amico, A.; Villanova, M.; Brancalion, B.; Sivo, S.; Bianco, F.; Striano, P.; Battaglia, D.; et al. Duchenne muscular dystrophy and epilepsy. *Neuromuscul. Disord.* **2013**, *23*, 313–315. [CrossRef] [PubMed]

29. Chou, E.; Lindeback, R.; Sampaio, H.; Farrar, M.A. Nutritional practices in pediatric patients with neuromuscular disorders. *Nutr. Rev.* **2020**, *78*, 857–865. [CrossRef]
30. Wollinsky, K.H.; Weiss, C.; Gelowicz-Maurer, M.; Geiger, P.; Mehrkens, H.H.; Naumann, T. Preoperative risk assessment of children with Duchenne muscular dystrophy and relevance for anesthesia and intra- and postoperative course. *Med. Klin.—Intensiv. Und Notf.* **1996**, *91*, 34–37.
31. Vialle, R.; Thévenin-Lemoine, C.; Mary, P. Neuromuscular scoliosis. *Orthop. Traumatol. Surg. Res.* **2013**, *99*, S124–S139. [CrossRef]
32. Prottengeier, J.; Amann, B.; Münster, T. Anästhesie bei neuromuskulären Erkrankungen. *Anaesthesist* **2020**, *69*, 373–387. [CrossRef] [PubMed]
33. Roche, D.; Mahon, P. Depth of Anesthesia Monitoring. *Anesthesiol. Clin.* **2021**, *39*, 477–492. [CrossRef]
34. Munshey, F.; Parra, D.; McDonnell, C.; Matava, C. Ultrasound-guided techniques for peripheral intravenous placement in children with difficult venous access. *Pediatr. Anesth.* **2019**, *30*, 108–115. [CrossRef]
35. Keating, G.M. Sugammadex: A Review of Neuromuscular Blockade Reversal. *Drugs* **2016**, *76*, 1041–1052. [CrossRef] [PubMed]
36. Van de Voorde, P.; Turner, N.M.; Djakow, J.; de Lucas, N.; Martinez-Mejias, A.; Biarent, D.; Bingham, R.; Brissaud, O.; Hoffmann, F.; Johannesdottir, G.B.; et al. European Resuscitation Council Guidelines 2021: Paediatric Life Support. *Resuscitation* **2021**, *161*, 327–387. [CrossRef]
37. Tobias, J.D. Controlled Hypotension in Children. *Pediatr. Drugs* **2002**, *4*, 439–453. [CrossRef] [PubMed]
38. Schmitt, H.J.; Muenster, T. Anesthesia in patients with neuromuscular disorders. *Minerva Anestesiol.* **2008**, *75*, 632–637.
39. Glahn, K.P.E.; Ellis, F.R.; Halsall, P.J.; Müller, C.R.; Snoeck, M.M.J.; Urwyler, A.; Wappler, F. Recognizing and managing a malignant hyperthermia crisis: Guidelines from the European Malignant Hyperthermia Group. *Br. J. Anaesth.* **2010**, *105*, 417–420. [CrossRef]
40. Gurnaney, H.; Brown, A.; Litman, R.S. Malignant Hyperthermia and Muscular Dystrophies. *Obstet. Anesth. Dig.* **2009**, *109*, 1043–1048. [CrossRef]
41. Obata, R.; Yasumi, Y.; Suzuki, A.; Nakajima, Y.; Sato, S. Rhabdomyolysis in association with Duchenne's muscular dystrophy. *Can. J. Anaesth.* **1999**, *46*, 564–566. [CrossRef] [PubMed]
42. Gray, R.M. Anesthesia-induced rhabdomyolysis or malignant hyperthermia: Is defining the crisis important? *Pediatr. Anesth.* **2017**, *27*, 490–493. [CrossRef]
43. Sahinovic, M.M.; Gadella, M.C.; Shils, J.; Dulfer, S.E.; Drost, G. Anesthesia and intraoperative neurophysiological spinal cord monitoring. *Curr. Opin. Anaesthesiol.* **2021**, *34*, 590–596. [CrossRef]
44. Yang, J.; Skaggs, D.L.; Chan, P.; Shah, S.A.; Vitale, M.G.; Neiss, G.; Feinberg, N.; Andras, L.M. Raising Mean Arterial Pressure Alone Restores 20% of Intraoperative Neuromonitoring Losses. *Spine* **2018**, *43*, 890–894. [CrossRef] [PubMed]
45. Kwee, M.M.; Ho, Y.-H.; Rozen, W.M. The Prone Position During Surgery and its Complications: A Systematic Review and Evidence-Based Guidelines. *Int. Surg.* **2015**, *100*, 292–303. [CrossRef]
46. Grover, M.; Bachrach, L.K. Osteoporosis in Children with Chronic Illnesses: Diagnosis, Monitoring, and Treatment. *Curr. Osteoporos. Rep.* **2017**, *15*, 271–282. [CrossRef]
47. Mirski, M.A.; Lele, A.V.; Fitzsimmons, L.; Toung, T.J.K.; Warltier, D.C. Diagnosis and Treatment of Vascular Air Embolism. *Anesthesiology* **2007**, *106*, 164–177. [CrossRef]
48. Reid, J.M.; Appleton, P.J. A case of ventricular fibrillation in the prone position during back stabilisation surgery in a boy with Duchenne's muscular dystrophy. *Anaesthesia* **1999**, *54*, 364–367. [CrossRef] [PubMed]
49. Edler, A.; Murray, D.; Forbes, R.B. Blood loss during posterior spinal fusion surgery in patients with neuromuscular disease: Is there an increased risk? *Pediatr. Anesth.* **2003**, *13*, 818–822. [CrossRef]
50. Wang, M.; Zheng, X.-F.; Jiang, L.-S. Efficacy and Safety of Antifibrinolytic Agents in Reducing Perioperative Blood Loss and Transfusion Requirements in Scoliosis Surgery: A Systematic Review and Meta-Analysis. *PLoS ONE* **2015**, *10*, e0137886. [CrossRef]
51. Shapiro, F.; Zurakowski, D.; Sethna, N.F. Tranexamic Acid Diminishes Intraoperative Blood Loss and Transfusion in Spinal Fusions for Duchenne Muscular Dystrophy Scoliosis. *Spine* **2007**, *32*, 2278–2283. [CrossRef] [PubMed]
52. Esper, S.A. Intra-operative cell salvage: A fresh look at the indications and contraindications. *Blood Transfus.* **2011**, *9*, 139–147. [CrossRef]
53. Klein, A.A.; Bailey, C.R.; Charlton, A.J.; Evans, E.; Guckian-Fisher, M.; McCrossan, R.; Nimmo, A.F.; Payne, S.; Shreeve, K.; Smith, J.; et al. Association of Anaesthetists guidelines: Cell salvage for peri-operative blood conservation 2018. *Anaesthesia* **2018**, *73*, 1141–1150. [CrossRef] [PubMed]
54. Sedra, F.; Shafafy, R.; Sadek, A.-R.; Aftab, S.; Montgomery, A.; Nadarajah, R. Perioperative Optimization of Patients With Neuromuscular Disorders Undergoing Scoliosis Corrective Surgery: A Multidisciplinary Team Approach. *Glob. Spine J.* **2020**, *11*, 240–248. [CrossRef]
55. Koraki, E.; Stachtari, C.; Stergiouda, Z.; Stamatopoulou, M.; Gkiouliava, A.; Sifaki, F.; Chatzopoulos, S.; Trikoupi, A. Blood and fluid management during scoliosis surgery: A single-center retrospective analysis. *Eur. J. Orthop. Surg. Traumatol.* **2020**, *30*, 809–814. [CrossRef] [PubMed]
56. Witmer, C.M.; Takemoto, C.M. Pediatric Hospital Acquired Venous Thromboembolism. *Front. Pediatr.* **2017**, *5*, 198. [CrossRef] [PubMed]

57. Okamura, M.; Saito, W.; Miyagi, M.; Shirasawa, E.; Imura, T.; Nakazawa, T.; Mimura, Y.; Yokozeki, Y.; Kuroda, A.; Kawakubo, A.; et al. Incidence of Unintentional Intraoperative Hypothermia in Pediatric Scoliosis Surgery and Associated Preoperative Risk Factors. *Spine Surg. Relat. Res.* **2021**, *5*, 154–159. [CrossRef]
58. Nemeth, M.; Miller, C.; Bräuer, A. Perioperative Hypothermia in Children. *Int. J. Environ. Res. Public Health* **2021**, *18*, 7541. [CrossRef] [PubMed]
59. Brooks, J.T.; Yaszay, B.; Bartley, C.E.; Bastrom, T.P.; Sponseller, P.D.; Shah, S.A.; Samdani, A.; Cahill, P.J.; Miyanji, F.; Newton, P.O.; et al. Do All Patients With Cerebral Palsy Require Postoperative Intensive Care Admission After Spinal Fusion? *Spine Deform.* **2018**, *7*, 112–117. [CrossRef]
60. Akesen, S. Predictive factors for postoperative ıntensive care unit admission in pediatric patients undergoing scoliosis correction surgery. *Am. J. Transl. Res.* **2021**, *13*, 5386–5394.
61. Mills, B.; Bach, J.R.; Zhao, C.; Saporito, L.; Sabharwal, S. Posterior Spinal Fusion in Children With Flaccid Neuromuscular Scoliosis. *J. Pediatr. Orthop.* **2013**, *33*, 488–493. [CrossRef] [PubMed]
62. Alexander, W.M.; Smith, M.; Freeman, B.J.C.; Sutherland, L.M.; Kennedy, J.D.; Cundy, P.J. The effect of posterior spinal fusion on respiratory function in Duchenne muscular dystrophy. *Eur. Spine J.* **2012**, *22*, 411–416. [CrossRef]
63. Bach, J.R.; Sabharwal, S. High Pulmonary Risk Scoliosis Surgery. *J. Spinal Disord. Tech.* **2005**, *18*, 527–530. [CrossRef]
64. Neto, S.C.G.B.; Torres-Castro, R.; Lima, Í.; Resqueti, V.R.; Fregonezi, G.A.F. Weaning from mechanical ventilation in people with neuromuscular disease: A systematic review. *BMJ Open* **2021**, *11*, e047449. [CrossRef]
65. Hatef, J.; Hatef, S.; Drain, J.P.; Tobias, J.D.; Martin, D.; Shell, R.; Chase, M.; Beebe, A.; Samora, W.; Klamar, J. Protocol-driven early tracheal extubation in patients with flaccid neuromuscular scoliosis and pre-existing lung disease. *Spine Deform.* **2022**, *10*, 689–696. [CrossRef] [PubMed]
66. Krishnakumar, M.; Muthuchellappan, R.; Chakrabarti, D. Diaphragm Function Assessment During Spontaneous Breathing Trial in Patients with Neuromuscular Diseases. *Neurocritical Care* **2020**, *34*, 382–389. [CrossRef]
67. Khirani, S.; Bersanini, C.; Aubertin, G.; Bachy, M.; Vialle, R.; Fauroux, B. Non-invasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. *Eur. Spine J.* **2014**, *23*, 406–411. [CrossRef] [PubMed]
68. Levine, S.B.B.; Fields, M.W.; Boby, A.Z.M.; Matsumoto, H.M.; Skaggs, K.F.B.; Roye, B.D.M.; Vitale, M.G.M. Degree of Postoperative Curve Correction Decreases Risks of Postoperative Pneumonia in Patients Undergoing Both Fusion and Growth-friendly Surgical Treatment of Neuromuscular Scoliosis. *J. Pediatr. Orthop.* **2022**, *42*, 372–375. [CrossRef]
69. Singh, Y.; Villaescusa, J.U.; da Cruz, E.M.; Tibby, S.M.; Bottari, G.; Saxena, R.; Guillén, M.; Herce, J.L.; Di Nardo, M.; Cecchetti, C.; et al. Recommendations for hemodynamic monitoring for critically ill children—Expert consensus statement issued by the cardiovascular dynamics section of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit. Care* **2020**, *24*, 620. [CrossRef] [PubMed]
70. Aydogan, M.S.; Korkmaz, M.; Ozgül, U.; Erdogan, M.A.; Yucel, A.; Karaman, A.; Togal, T.; Durmus, M.; Colak, C. Pain, fentanyl consumption, and delirium in adolescents after scoliosis surgery: Dexmedetomidine vs. midazolam. *Pediatr. Anesth.* **2013**, *23*, 446–452. [CrossRef] [PubMed]
71. Seki, H.; Ideno, S.; Ishihara, T.; Watanabe, K.; Matsumoto, M.; Morisaki, H. Postoperative pain management in patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis: A narrative review. *Scoliosis* **2018**, *13*, 17. [CrossRef]
72. Dinter, K.; Bretschneider, H.; Zwingenberger, S.; Disch, A.; Osmers, A.; Vicent, O.; Thielemann, F.; Seifert, J.; Bernstein, P. Accelerate postoperative management after scoliosis surgery in healthy and impaired children: Intravenous opioid therapy versus epidural therapy. *Arch. Orthop. Trauma Surg.* **2021**, *143*, 301–309. [CrossRef] [PubMed]
73. Chiu, C.K.; I Chong, K.; Chan, T.S.; Mohamad, S.M.; Hasan, M.S.; Chan, C.Y.W.; Kwan, M.K. The anatomical locations of postoperative pain and their recovery trajectories following Posterior Spinal Fusion (PSF) surgery in Adolescent Idiopathic Scoliosis (AIS) patients. *Med. J. Malaysia* **2020**, *75*, 12–17.
74. Chin, K.J.; Lewis, S. Opioid-free Analgesia for Posterior Spinal Fusion Surgery Using Erector Spinae Plane (ESP) Blocks in a Multimodal Anesthetic Regimen. *Spine* **2019**, *44*, E379–E383. [CrossRef]
75. Shrader, M.W.; Nabar, S.J.; Jones, J.S.; Falk, M.; Cotugno, R.; White, G.R.; Segal, L.S. Adjunctive Pain Control Methods Lower Narcotic Use and Pain Scores for Patients With Adolescent Idiopathic Scoliosis Undergoing Posterior Spinal Fusion. *Spine Deform.* **2015**, *3*, 82–87. [CrossRef]
76. Diwan, S.; Altinpulluk, E.Y.; Khurjekar, K.; Nair, A.; Dongre, H.; Turan, A. Bloqueo bilateral en el plano del músculo erector de la columna para cirugía de escoliosis: Serie de casos. *Rev. Española Anestesiol. Reanim.* **2020**, *67*, 153–158. [CrossRef] [PubMed]
77. Lee, C.S.; Merchant, S.; Chidambaran, V. Postoperative Pain Management in Pediatric Spinal Fusion Surgery for Idiopathic Scoliosis. *Pediatr. Drugs* **2020**, *22*, 575–601. [CrossRef] [PubMed]
78. Zhou, L.; Yang, H.; Hai, Y.; Cheng, Y. Perioperative Low-Dose Ketamine for Postoperative Pain Management in Spine Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain Res. Manag.* **2022**, *2022*, 1507097. [CrossRef]
79. Lieh-Lai, M.W.; Stanitski, D.F.; Sarnaik, A.P.; Uy, H.G.; Rossi, N.F.; Simpson, P.M.; Stanitski, C.L. Syndrome of inappropriate antidiuretic hormone secretion in children following spinal fusion. *Crit. Care Med.* **1999**, *27*, 622–627. [CrossRef]
80. Jöbsis, J.J.; Alabbas, A.; Milner, R.; Reilly, C.; Mulpuri, K.; Mammen, C. Acute kidney injury following spinal instrumentation surgery in children. *World J. Nephrol.* **2017**, *6*, 79–85. [CrossRef] [PubMed]

81. Verhofste, B.P.; Harms Study Group; Berry, J.G.; Miller, P.E.; Crofton, C.N.; Garrity, B.M.; Fletcher, N.D.; Marks, M.C.; Shah, S.A.; Newton, P.O.; et al. Risk factors for gastrointestinal complications after spinal fusion in children with cerebral palsy. *Spine Deform.* **2020**, *9*, 567–578. [CrossRef]
82. Bureta, C.; Tominaga, H.; Yamamoto, T.; Kawamura, I.; Abematsu, M.; Yone, K.; Komiya, S. Risk Factors for Postoperative Ileus after Scoliosis Surgery. *Spine Surg. Relat. Res.* **2018**, *2*, 226–229. [CrossRef]
83. Kannan, S.; Meert, K.L.; Mooney, J.F.; Hillman-Wiseman, C.; Warrier, I. Bleeding and coagulation changes during spinal fusion surgery: A comparison of neuromuscular and idiopathic scoliosis patients. *Pediatr. Crit. Care Med.* **2002**, *3*, 364–369. [CrossRef] [PubMed]
84. Gould, C.V.; Umscheid, C.A.; Agarwal, R.K.; Kuntz, G.; Pegues, D.A. Healthcare Infection Control Practices Advisory Committee (HICPAC) Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009. *Infect. Control. Hosp. Epidemiol.* **2010**, *31*, 319–326. [CrossRef]
85. Yousef, M.A.A.; Rosenfeld, S. Evaluation of postoperative fever after surgical correction of neuromuscular scoliosis: Implication on management. *Eur. Spine J.* **2018**, *27*, 1690–1697. [CrossRef] [PubMed]
86. Shillingford, J.N.; Laratta, J.L.; Reddy, H.; Ha, A.; Lehman, R.A.; Lenke, L.G.; Fischer, C.R. Postoperative Surgical Site Infection After Spine Surgery: An Update From the Scoliosis Research Society (SRS) Morbidity and Mortality Database*. *Spine Deform.* **2018**, *6*, 634–643. [CrossRef] [PubMed]

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General versus Neuraxial Anesthesia on Clinical Outcomes in Patients Receiving Hip Fracture Surgery: An Analysis of the ACS NSQIP Database

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Abstract: Whether the use of neuraxial anesthesia or general anesthesia leads to more favorable postoperative outcomes in patients receiving hip fracture surgery remains unclear. We used data from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Data Files between 2016 and 2020 to investigate the association of neuraxial anesthesia and general anesthesia with morbidity and mortality after hip fracture surgery. Inverse probability of treatment weighting (IPTW) was used to balance the baseline characteristics, and multivariable Cox regression models were used to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for postoperative morbidity and mortality among the different anesthesia groups. A total of 45,874 patients were included in this study. Postoperative adverse events occurred in 1087 of 9864 patients (11.0%) who received neuraxial anesthesia and in 4635 of 36,010 patients (12.9%) who received general anesthesia. After adjustment for IPTW, the multivariable Cox regressions revealed that general anesthesia was associated with increased risks of postoperative morbidity (adjusted HR, 1.19; 95% CI, 1.14–1.24) and mortality (adjusted HR, 1.09; 95% CI, 1.03–1.16). The results of the present study suggest that, compared with general anesthesia, neuraxial anesthesia is associated with lower risks of postoperative adverse events in patients undergoing hip fracture surgery.

Keywords: hip fracture; anesthesia; postoperative outcomes; propensity score; morbidity; mortality

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1. Introduction

Hip fractures are one of the most common healthcare problems in older adults. The worldwide annual incidence of hip fracture was reported as 1.6 million in 2000, and this incidence is expected to increase to 6.3 million by 2050 [1]. As nonsurgical management is associated with higher mortality and poor functional recovery, surgical repair has become the mainstay treatment for hip fractures [2]. The majority of hip fractures occur in the older adult population; thus, patients with hip fractures are at substantial risk of mortality and cardiovascular, pulmonary, thrombotic, infectious, and bleeding complications, which contribute to tremendous medical costs [3]. The annual cost of treatment for hip fractures was reported to be more than $10 billion in the United States alone [4].

Despite efforts to improve the perioperative care of patients with hip fractures, the postoperative 30-day mortality rate was reported to be 10%, and approximately 20% of patients developed severe postoperative complications [5]. Anesthesia is an essential aspect of multidisciplinary perioperative care, which improves clinical outcomes in patients with hip fractures [6]. The most frequently used anesthesia techniques for hip fracture surgery are general anesthesia and neuraxial anesthesia [7]. Neuraxial anesthesia was reported

in a meta-analysis to be associated with a reduced risk of in-hospital mortality, acute respiratory failure, and readmission in older adults undergoing hip fracture surgery [8]. However, the results of a different meta-analysis revealed no significant difference in 30-day mortality and the prevalence of pneumonia, acute myocardial infarction, and renal failure between patients who received neuraxial and those who received general anesthesia during hip fracture surgery [9]. Differences in the definition of outcome, follow-up time, and methodology in previous studies may be reasons for the inconsistent results of these meta-analyses. Therefore, whether the use of neuraxial anesthesia or general anesthesia leads to more favorable postoperative outcomes in patients undergoing surgical repair of hip fractures remains controversial.

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) is a nationally validated program for measuring and improving the quality of surgical care; the program has compiled high-quality data from more than 600 participating hospitals in the United States and around the world [10]. The ACS NSQIP database contains data based on patients' medical charts that were collected by trained and certified reviewers, which are more trustworthy than those derived from insurance claims and were used in previous studies. Therefore, this study aimed to use the clinical data from the ACS NSQIP to investigate the associations of neuraxial anesthesia and general anesthesia with postoperative outcomes in patients who received hip fracture surgery and provide optimal anesthesia technique recommendations.

2. Materials and Methods

2.1. Data Source

The data used in this matched prospective cohort study were collected from the ACS NSQIP database [10]. The ACS NSQIP database contains more than 150 surgical variables for up to 30 days following surgery; the data were collected from patients' medical charts by trained and certified Surgical Clinical Reviewers. The data from the ACS NSQIP database have been demonstrated to be highly trustworthy, with an inter-reviewer disagreement rate of below 2% [11]. In addition to the essential Participant Use Data File (PUF), Procedure-Targeted PUF datasets, which address specific predictors and outcomes for many types of operations, were also released from the ACS NSQIP database. The ACS NSQIP Hip Fracture Procedure-Targeted PUFs consisting of additional variables specific to hip fracture patients treated with open reduction and internal fixation (Current Procedural Terminology (CPT) codes: 27236, 27244, and 27245) from 2016 to 2020 were also available. Therefore, we used the ACS NSQIP Hip Fracture Procedure-Targeted PUFs to investigate the association between different anesthesia techniques and clinical outcomes in patients receiving hip fracture surgery.

2.2. Study Population Selection and Clinical Characteristics

The present study comprised patients in the ACS NSQIP Hip Fracture Procedure-Targeted PUFs between 2016 and 2020; patients who were aged $\geq$18 years and who received hip fracture surgery with CPT codes 27236, 27244, and 27245 were included. The baseline demographics and comorbidities of the study population were obtained from the essential ACS NSQIP PUFs and Hip Fracture Procedure-Targeted PUF datasets; these included age, sex, race or ethnicity, body mass index, functional health status, smoking, diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), dialysis, dementia, cancer, bleeding disorder, type of fracture, American Society of Anesthesiologists (ASA) physical status classification, deep venous thrombosis (DVT) prophylaxis, and type of anesthesia. The patients' major comorbidities were identified according to the surgeons' preoperative notes. The definitions of variables in the ACS NSQIP database are available in the NSQIP User Guide [10]. To compare the effects of general anesthesia and neuraxial anesthesia on postoperative clinical outcomes, patients who were administered anesthesia other than general or neuraxial were excluded. Patients who had outcome diagnoses at the time of surgery or who had missing data on baseline

characteristics were excluded to prevent confounding factors. In addition, patients with missing data regarding the time of outcome occurrence were excluded.

2.3. Study Outcomes

The primary outcome was any postoperative 30-day adverse event, which was a composite outcome including postoperative 30-day morbidity and mortality. The secondary outcomes included postoperative 30-day morbidity and mortality. Postoperative 30-day morbidity consisted of major postoperative adverse events, including myocardial infarction, cardiac arrest, stroke, pneumonia, pulmonary embolism, ventilator support for more than 48 h, acute renal failure or progressive renal insufficiency, surgical site infection, sepsis or septic shock, and DVT [8,9,12]. Detailed definitions of each adverse event can be found in the NSQIP User Guide [10].

2.4. Statistical Analysis

The baseline characteristics of the study population were summarized using counts and percentages for both neuraxial and general anesthesia. To balance the baseline characteristics between the different anesthesia groups, inverse probability of treatment weighting (IPTW) based on the propensity score was used [13,14]. The propensity score was defined as the probability that a patient was assigned general anesthesia based on the observed covariates. We estimated the propensity score using a multivariable logistic regression model with all the baseline characteristics listed in Table 1. Using the IPTW approach, each patient was weighted by the inverse of the probability of receiving general anesthesia. This approach created a weighted pseudosample of patients in which the selection of general anesthesia was independent of the baseline characteristics. The standardized mean difference (SMD) was used to compare the baseline characteristics between the neuraxial and general anesthesia groups. An SMD of less than 0.1 was considered a negligible difference between the two groups.

Table 1. Characteristics of patients receiving hip fracture surgery before and after adjustment for the inverse probability of treatment weighting (IPTW).

	Unweighted Study Population			**After IPTW**		
	Neuraxial Anesthesia	**General Anesthesia**		**Neuraxial Anesthesia**	**General Anesthesia**	
	(*n* = 9864)	**(*n* = 36,010)**				
Characteristics	**Number (Percent of Patients)**		**SMD ***	**Percent of Patients**		**SMD ***
Demographics						
Age, years						
<65	741 (7.5)	4422 (12.3)	0.160	12.3	11.3	0.033
65–74	1410 (14.3)	6407 (17.8)	0.095	16.8	17.0	0.007
75–84	3079 (31.2)	10,725 (29.8)	0.031	29.4	30.0	0.014
≥85	4634 (47.0)	14,456 (40.1)	0.138	41.6	41.7	0.002
Sex						
Female	6974 (70.7)	24,277 (67.4)	0.071	68.1	68.1	0.002
Male	2890 (29.3)	11,733 (32.6)	0.071	32.0	31.9	0.002
Race/ethnicity						
White	4807 (48.7)	28,447 (79.0)	0.664	72.7	72.5	0.003
Other	5057 (51.3)	7563 (21.0)	0.664	27.4	27.5	0.003
Body mass index						
Normal	4938 (50.1)	16,375 (45.5)	0.092	46.7	46.5	0.005
Underweight	926 (9.4)	2803 (7.8)	0.057	8.1	8.1	0.001
Overweight	2667 (27.0)	10,472 (29.1)	0.045	28.4	28.6	0.004
Obese	1333 (13.5)	6360 (17.7)	0.115	16.8	16.8	0.001

Table 1. *Cont.*

Characteristics	Unweighted Study Population			After IPTW		
	Neuraxial Anesthesia	General Anesthesia		Neuraxial Anesthesia	General Anesthesia	
	(*n* = 9864)	(*n* = 36,010)				
	Number (Percent of Patients)		SMD *	Percent of Patients		SMD *
Functional health status						
Independent	7827 (79.4)	28,302 (78.6)	0.019	78.3	78.8	0.011
Partially dependent	1770 (17.9)	6764 (18.8)	0.022	19.1	18.6	0.012
Totally dependent	267 (2.7)	944 (2.6)	0.005	2.6	2.6	0.002
Comorbidities						
Smoking	1074 (10.9)	4585 (12.7)	0.057	12.7	12.3	0.011
Diabetes mellitus	1652 (16.8)	6986 (19.4)	0.069	19.3	18.9	0.012
Hypertension	6166 (62.5)	24,144 (67.1)	0.095	66.6	66.2	0.009
Congestive heart failure	297 (3.0)	1334 (3.7)	0.039	3.4	3.6	0.007
COPD	1120 (11.4)	3745 (10.4)	0.031	10.8	10.6	0.007
Dialysis	130 (1.3)	786 (2.2)	0.066	2.4	2.0	0.028
Dementia	2741 (27.8)	9501 (26.4)	0.032	26.9	26.7	0.004
Disseminated cancer	279 (2.8)	1306 (3.6)	0.045	3.6	3.5	0.008
Bleeding disorder	684 (6.9)	6884 (19.1)	0.368	16.1	16.5	0.013
Operative information						
Type of fracture						
Femoral neck fracture	4075 (41.3)	13,572 (37.7)	0.074	38.0	38.4	0.008
Intertrochanteric	5009 (50.8)	19,393 (53.9)	0.062	53.5	53.3	0.005
Subtrochanteric/other	780 (7.9)	3045 (8.5)	0.020	8.5	8.3	0.005
ASA classification						
I or II	1888 (19.1)	6001 (16.7)	0.065	18.0	17.3	0.017
III	5819 (59.0)	22,964 (63.8)	0.098	63.0	62.8	0.005
IV or V †	2157 (21.9)	7045 (19.6)	0.057	19.1	19.9	0.022

* An SMD of less than 0.1 was considered a negligible difference between the two groups. † Includes 9119 (2130 received neuraxial anesthesia and 6989 received general anesthesia) ASA IV and 83 (27 received neuraxial anesthesia and 56 received general anesthesia) ASA V patients. Abbreviations: IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists.

Cox regression models were used to estimate the hazard ratio (HR) with a 95% confidence interval (CI) for clinical outcomes between the different anesthesia groups. Adjusted HRs were calculated after adjustment for age, sex, race or ethnicity, body mass index, functional health status, smoking, diabetes mellitus, hypertension, congestive heart failure, COPD, dialysis, dementia, cancer, bleeding disorder, type of fracture, ASA physical status classification, and DVT prophylaxis.

To evaluate the robustness of our findings, we conducted propensity score matching as a sensitivity analysis. Patients who received general anesthesia and those who received neuraxial anesthesia were matched 1:1 using greedy matching with a caliper width of 0.2 times the standard deviation of the logits of the propensity score [14].

All analyses were performed using the SAS System for Windows 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was determined as a p value less than 0.05.

3. Results

3.1. Study Sample Selection

A total of 59,931 cases were reported in the ACS NSQIP Hip Fracture Procedure-Targeted PUFs between 2016 and 2020. After excluding 5697 patients who received anesthesia other than general or neuraxial anesthesia, 7915 patients with missing data on baseline characteristics, and 445 patients who had outcome diagnoses at the time of surgery or had missing data on the date of outcome occurrence, we included a total of 45,874 patients (Figure 1).

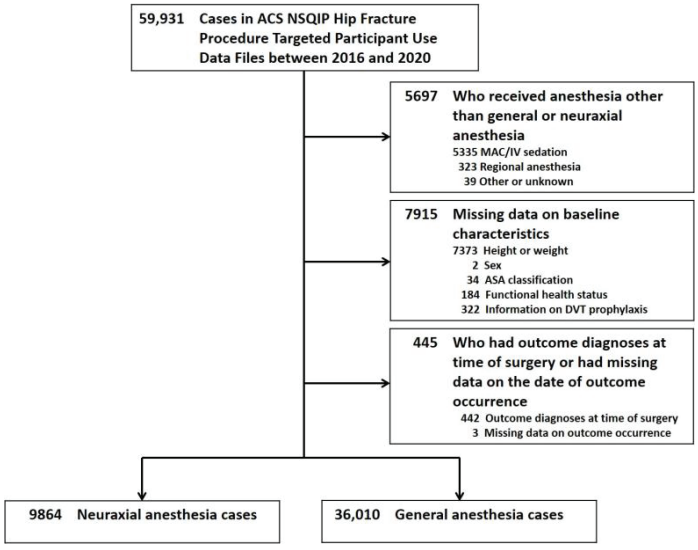

Figure 1. Flowchart of Study Sample Selection. Abbreviations: MAC, monitored anesthesia care; IV, intravenous; ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; ASA, American Society of Anesthesiologists; DVT, deep venous thrombosis.

3.2. Baseline Characteristics

Among the 45,874 patients who received hip fracture surgery, 9864 and 36,010 received neuraxial and general anesthesia, respectively. The baseline characteristics before and after adjustment for IPTW are listed in Table 1. Before adjustment for IPTW, patients who received general anesthesia were generally younger, more likely to be white and obese, and more likely to have bleeding disorders. After adjustment for IPTW, all baseline characteristics of the two groups were well-balanced.

3.3. Associations between General Anesthesia and Postoperative Adverse Events

3.3.1. Unweighted Multivariable Analysis

Postoperative adverse events occurred in 1087 of 9864 patients (11.0%) who received neuraxial anesthesia and in 4635 of 36,010 patients (12.9%) who received general anesthesia (Table 2). In the unweighted multivariable regressions, general anesthesia was associated with a 15% increased risk of postoperative adverse events (adjusted HR, 1.15; 95% CI 1.07–1.23) in patients receiving hip fracture surgery (Table 2). We further analyzed the relationship between the types of anesthesia and postoperative morbidity and mortality in patients receiving hip fracture surgery. Similarly, we found general anesthesia to be associated with higher risks of postoperative morbidity (adjusted HR, 1.17; 95% CI, 1.08–1.27) and mortality (adjusted HR, 1.13; 95% CI, 1.01–1.26) (Table 2).

Table 2. Association between general anesthesia and risk of postoperative 30-Day adverse events in patients receiving hip fracture surgery.

Postoperative 30-Day Outcomes	Total Number of Patients	Number of Events (%)	Unweighted Adjusted HR (95% CI) *	After IPTW Adjusted HR (95% CI) *
Any adverse events				
Neuraxial anesthesia	9864	1087 (11.0)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	4635 (12.9)	1.15 (1.07–1.23)	1.14 (1.10–1.19)
Morbidity				
Neuraxial anesthesia	9864	809 (8.2)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	3463 (9.6)	1.17 (1.08–1.27)	1.19 (1.14–1.24)
Mortality				
Neuraxial anesthesia	9864	437 (4.4)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	1951 (5.4)	1.13 (1.01–1.26)	1.09 (1.03–1.16)

* Adjusted HRs were computed after adjustment for age, sex, race or ethnicity, body mass index, functional health status, smoking, diabetes mellitus, hypertension, congestive heart failure, COPD, dialysis, dementia, cancer, bleeding disorder, type of fracture, ASA physical status classification, and DVT prophylaxis. Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; DVT, deep venous thrombosis.

3.3.2. Multivariable Analysis after IPTW

After IPTW adjustment, general anesthesia remained associated with increased risks of postoperative adverse events (Table 2). In the IPTW multivariable Cox regression model, general anesthesia was associated with higher risks of postoperative adverse events (adjusted HR, 1.14; 95% CI 1.10–1.19), morbidity (adjusted HR, 1.19; 95% CI, 1.14–1.24), and mortality (adjusted HR, 1.09; 95% CI, 1.03–1.16).

Furthermore, we analyzed the relationship between general anesthesia and specific postoperative morbidities, including myocardial infarction, cardiac arrest, stroke, pneumonia, pulmonary embolism, ventilator support, acute renal failure or progressive renal insufficiency, surgical site infection, sepsis or septic shock, and DVT. The results revealed general anesthesia to be associated with an increased risk of cardiac arrest (adjusted HR, 1.23; 95% CI, 1.04–1.45), pneumonia (adjusted HR, 1.18; 95% CI, 1.09–1.27), ventilator support (adjusted HR, 1.42; 95% CI, 1.17–1.74), acute renal failure or progressive renal insufficiency (adjusted HR, 1.29; 95% CI, 1.10–1.51), surgical site infection (adjusted HR, 1.37; 95% CI, 1.20–1.56), sepsis or septic shock (adjusted HR, 1.32; 95% CI, 1.17–1.47), and DVT (adjusted HR, 1.38; 95% CI, 1.21–1.57) (Table 3).

Table 3. Association between general anesthesia and risk of individual postoperative 30-Day morbidity in patients receiving hip fracture surgery.

Postoperative 30-Day Outcomes	Total Number of Patients	Number of Events (%)	Unweighted Adjusted HR (95% CI) *	After IPTW Adjusted HR (95% CI) *
Myocardial infarction				
Neuraxial anesthesia	9864	207 (2.1)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	722 (2.0)	0.98 (0.83–1.16)	1.03 (0.94–1.13)
Cardiac arrest				
Neuraxial anesthesia	9864	44 (0.5)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	264 (0.7)	1.39 (1.00–1.95)	1.23 (1.04–1.45)
Stroke				
Neuraxial anesthesia	9864	71 (0.7)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	288 (0.8)	1.06 (0.81–1.40)	0.95 (0.83–1.10)

Table 3. *Cont.*

Postoperative 30-Day Outcomes	Total Number of Patients	Number of Events (%)	Unweighted Adjusted HR (95% CI) *	After IPTW Adjusted HR (95% CI) *
Pneumonia				
Neuraxial anesthesia	9864	270 (2.7)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	1075 (3.0)	1.12 (0.97–1.29)	1.18 (1.09–1.27)
Pulmonary embolism				
Neuraxial anesthesia	9864	73 (0.7)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	285 (0.8)	1.11 (0.84–1.45)	1.00 (0.86–1.16)
Ventilator support †				
Neuraxial anesthesia	9864	22 (0.2)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	202 (0.6)	1.84 (1.17–2.91)	1.42 (1.17–1.74)
Renal failure ‡				
Neuraxial anesthesia	9864	43 (0.4)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	284 (0.8)	1.49 (1.06–2.09)	1.29 (1.10–1.51)
Surgical site infection				
Neuraxial anesthesia	9864	89 (0.9)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	410 (1.1)	1.34 (1.05–1.71)	1.37 (1.20–1.56)
Sepsis or septic shock				
Neuraxial anesthesia	9864	104 (1.1)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	556 (1.5)	1.28 (1.03–1.60)	1.32 (1.17–1.47)
DVT				
Neuraxial anesthesia	9864	76 (0.8)	1.00 (reference)	1.00 (reference)
General anesthesia	36,010	411 (1.1)	1.38 (1.07–1.78)	1.38 (1.21–1.57)

* Adjusted HRs were computed after adjustment for age, sex, race or ethnicity, body mass index, functional health status, smoking, diabetes mellitus, hypertension, congestive heart failure, COPD, dialysis, dementia, cancer, bleeding disorder, type of fracture, ASA physical status classification, and DVT prophylaxis. † Ventilator support. ‡ Includes both acute renal failure and progressive renal insufficiency. Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; DVT, deep venous thrombosis; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists.

3.3.3. Propensity Score-Matched Analysis

Similar results regarding the relationship between general anesthesia and postoperative adverse events were found in the propensity score-matched cohort. In the propensity score-matched cohort, 9864 and 9864 patients received neuraxial and general anesthesia, respectively. After propensity score matching, all baseline characteristics of the two groups were well-balanced (Table 4). The relationship between general anesthesia and postoperative adverse events in the propensity score-matched cohort is presented in Table 5. The results of the multivariable Cox regression analysis revealed general anesthesia to be associated with a 25% increased risk of postoperative adverse events (adjusted HR, 1.25; 95% CI, 1.13–1.39). Further analysis demonstrated general anesthesia to be associated with a 30% higher risk of postoperative morbidity (adjusted HR, 1.30; 95% CI, 1.15–1.46). In addition, general anesthesia seemed to be related to a 19% increased risk of postoperative mortality (adjusted HR, 1.19; 95% CI, 1.00–1.42).

Table 4. Characteristics of patients receiving hip fracture surgery after propensity score matching.

Characteristics	Neuraxial Anesthesia (*n* = 9864) Number (Percent of Patients)	General Anesthesia (*n* = 9864) Number (Percent of Patients)	SMD *
Demographics			
Age, years			
<65	741 (7.5)	722 (7.3)	0.006
65–74	1410 (14.3)	1439 (14.6)	0.008
75–84	3079 (31.2)	3034 (30.8)	0.010
≥85	4634 (47.0)	4669 (47.3)	0.007
Sex			
Female	6974 (70.7)	6992 (70.9)	0.004
Male	2890 (29.3)	2872 (29.1)	0.004
Race/ethnicity			
White	4807 (48.7)	4830 (49.0)	0.005
Other	5057 (51.3)	5034 (51.0)	0.005
Body mass index			
Normal	4938 (50.1)	4948 (50.2)	0.002
Underweight	926 (9.4)	864 (8.8)	0.022
Overweight	2667 (27.0)	2706 (27.4)	0.009
Obese	1333 (13.5)	1346 (13.7)	0.004
Functional health status			
Independent	7827 (79.4)	7840 (79.5)	0.003
Partially dependent	1770 (17.9)	1772 (18.0)	0.001
Totally dependent	267 (2.7)	252 (2.6)	0.009
Comorbidities			
Smoking	1074 (10.9)	977 (9.9)	0.030
Diabetes mellitus	1652 (16.8)	1680 (17.0)	0.007
Hypertension	6166 (62.5)	6314 (64.0)	0.031
Congestive heart failure	297 (3.0)	275 (2.8)	0.012
COPD	1120 (11.4)	996 (10.1)	0.040
Dialysis	130 (1.3)	122 (1.2)	0.006
Dementia	2741 (27.8)	2848 (28.9)	0.024
Disseminated cancer	279 (2.8)	247 (2.5)	0.018
Bleeding disorder	684 (6.9)	665 (6.7)	0.006
Operative information			
Type of fracture			
Femoral neck fracture	4075 (41.3)	3993 (40.5)	0.017
Intertrochanteric	5009 (50.8)	5108 (51.8)	0.020
Subtrochanteric/other	780 (7.9)	763 (7.7)	0.006
ASA classification			
I or II	1888 (19.1)	1943 (19.7)	0.015
III	5819 (59.0)	5930 (60.1)	0.023
IV or V	2157 (21.9)	1991 (20.2)	0.042

* An SMD of less than 0.1 was considered a negligible difference between the two groups. Abbreviations: SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists.

Table 5. Association between general anesthesia and risk of postoperative 30-Day adverse events between propensity score-matched groups.

Postoperative 30-Day Outcomes	Total Number	Number of Events (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI) *
Any adverse events				
Neuraxial anesthesia	9864	1087 (11.0)	1.00	1.00
General anesthesia	9864	1254 (12.7)	1.16 (1.07–1.26)	1.25 (1.13–1.39)
Morbidity				
Neuraxial anesthesia	9864	809 (8.2)	1.00	1.00
General anesthesia	9864	939 (9.5)	1.17 (1.06–1.28)	1.30 (1.15–1.46)
Mortality				
Neuraxial anesthesia	9864	437 (4.4)	1.00	1.00
General anesthesia	9864	504 (5.1)	1.16 (1.02–1.32)	1.19 (1.00–1.42)

* Adjusted HRs were computed after adjustment for age, sex, race or ethnicity, body mass index, functional health status, smoking, diabetes mellitus, hypertension, congestive heart failure, COPD, dialysis, dementia, cancer, bleeding disorder, type of fracture, ASA physical status classification, and DVT prophylaxis. Abbreviations: HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; DVT, deep venous thrombosis.

4. Discussion

The effects of different anesthesia techniques on postoperative outcomes in patients receiving hip fracture surgery remain unclear. Due to the small sample sizes in randomized clinical trials and the lack of clarity in definitions of postoperative outcomes in observational studies, previous meta-analyses have revealed no significant difference in postoperative outcomes between neuraxial anesthesia and general anesthesia in patients undergoing hip fracture surgery [9,15]. In addition, although DVT is a common postoperative complication of hip fracture surgery and antithrombotic prophylaxis is reportedly related to postoperative morbidity and mortality [16], no observational study has considered DVT prophylaxis in comparing the effects of different anesthesia techniques on postoperative complications. The present study collected data from the nationally verified ACS NSQIP database, which included clearly defined postoperative outcomes and data on DVT prophylaxis, to investigate and compare the associations of neuraxial and general anesthesia with postoperative adverse events after hip fracture surgery. To the best of our knowledge, this is the first large-scale, nationwide observational study investigating the association between different anesthesia techniques and postoperative outcomes in consideration of DVT prophylaxis. The results of the current study demonstrated that neuraxial anesthesia is associated with lower risks of postoperative complications, including postoperative morbidity and mortality. In addition, a similar relationship was found between neuraxial anesthesia and reduced postoperative complications, after adjustment for IPTW, and in the propensity score-matched cohort. Furthermore, our findings suggest that neuraxial anesthesia is associated with a reduced risk of cardiac arrest, pneumonia, ventilator support, renal failure, surgical site infection, sepsis or septic shock, and DVT.

The results of the present study reveal that general anesthesia is associated with an increased risk of 30-day mortality, which is in line with the findings of a previous observational study [17]. However, the results of previous randomized clinical trials showed that there was no significant difference in 30-day mortality between the two anesthesia groups [18,19]. The low postoperative mortality rate and the small number of included patients may be the reasons why these randomized clinical trials could not demonstrate differences in 30-day mortality between the two anesthesia techniques. Nevertheless, the results of a randomized trial involving 1600 older adults undergoing hip fracture surgery also showed that the incidence of postoperative mortality did not differ between patients who received neuraxial anesthesia and those who received general anesthesia [7]. In addition, our findings regarding mortality are inconsistent with those of previous observational studies that used propensity score matching, weighting, or stratification to control for

confounders [20–24]. The inconsistency between the 30-day mortality results of the current study and the previous observational studies may be due to the different study populations and the different sources of research data; the present study collected data from the ACS NSQIP database based on patients' medical charts, which would be different from those collected from insurance claims.

Compared with general anesthesia, the advantages of neuraxial anesthesia include the avoidance of intubation and mechanical ventilation, decreased systemic medications, prolonged postoperative analgesia, and decreased blood loss [15,25]. Conversely, general anesthesia may provide hemodynamic stability and avoid complications of neuraxial anesthesia, such as infection, hematoma, and nerve injury. Previous studies comparing the effects of general and neuraxial anesthesia on postoperative morbidity in patients receiving hip fracture surgery have reported conflicting results. The results of the two observational studies have demonstrated no difference in all-cause postoperative morbidity between patients who received general or neuraxial anesthesia for hip fracture surgery [22,23]. However, our findings reveal that general anesthesia is associated with higher all-cause postoperative morbidity. In addition to the composite outcome of postoperative morbidity, we further investigated the relationship between different anesthesia techniques and individual postoperative adverse events. The results of the present study reveal no significant differences between general and neuraxial anesthesia in the risks of postoperative 30-day myocardial infarction, stroke, or pulmonary embolism, which is consistent with the findings of most studies [12,22,23,26]. However, Ahn et al. [16] reported that general anesthesia was related to a higher incidence of pulmonary embolism than neuraxial anesthesia. Our findings additionally suggest that general anesthesia is associated with higher risks of postoperative 30-day surgical site infection and respiratory failure, which is consistent with the findings of previous studies [17,23]. Neuraxial anesthesia has been reported to reduce surgical site infections. This may be due to its effects on the sympathetic blockade and greater vasodilation, which lead to improved tissue oxygenation, increased polymorphonuclear cells at surgical sites, and maintained regional normothermia [27].

DVT is a common postoperative complication following hip fracture surgery and is associated with increased postoperative morbidity and mortality [16,28]. Unlike general anesthesia, neuraxial anesthesia can potentially produce a sympathetic block and vasodilatation, thereby reducing the risk of DVT [29]. With respect to DVT prophylaxis, our findings suggest that neuraxial anesthesia is associated with a lower risk of postoperative DVT, which is consistent with the findings of several studies [12,26,28,30]. However, the results of other observational studies and a meta-analysis of randomized clinical trials revealed no significant difference in the risk of DVT between general anesthesia and neuraxial anesthesia [15,22,23]. In addition, Morgan et al. [24] reported that patients who received spinal anesthesia were more likely to develop postoperative DVT. This inconsistency in the study results regarding postoperative DVT is likely due to the different study designs and definitions of outcomes.

The major strength of this study is that the data were collected from the ACS NSQIP, which is a nationally verified program for measuring and improving the quality of surgical care. The ACS NSQIP database contains data based on patients' medical charts that were collected by trained and certified reviewers, which indicates that these data are highly trustworthy and different from those collected from insurance claims. In addition, all variables and outcomes in the ACS NSQIP database are clearly defined, which enhanced the accuracy of the results. Furthermore, the ACS NSQIP database has compiled data from more than 600 hospitals in the United States and around the world, thereby increasing its external validity. Finally, in addition to using IPTW to balance the measurable confounders between the two anesthesia groups, we used propensity score matching as a sensitivity test to evaluate the robustness of our findings.

Several limitations of the current study should be considered. First, although the data used in the current study were prospectively collected, patients were not randomized to the different anesthesia groups, which may have created a bias in our analysis.

Even though we employed IPTW and propensity score matching to reduce bias, this bias cannot be eliminated. Second, extreme weights can increase the variance and confidence intervals of the effect estimate when using IPTW. However, there were no patients with a very high or very low probability of receiving general anesthesia. Third, the reasons why patients received general or neuraxial anesthesia and detailed clinical information regarding hospital-related factors, such as the size of the administering hospitals and the anesthesia and surgery techniques used for patients undergoing hip fracture surgery, were unavailable in the database, which may have also caused bias. Fourth, the ACS NSQIP collects postoperative outcomes for only up to 30 days; therefore, we were unable to evaluate the postoperative morbidity and mortality beyond that period. In addition, postoperative opioid consumption and adverse events immediately after surgery or in the postanesthesia care unit were not included in the ACS NSQIP database; thus, we were unable to analyze these outcomes.

5. Conclusions

In conclusion, the results of the present study suggest that, compared with general anesthesia, neuraxial anesthesia is associated with lower risks of postoperative adverse events in patients undergoing hip fracture surgery. Although the choice of the preferred anesthesia technique for hip fracture surgery remains controversial, the results of the present study support the administration of neuraxial anesthesia in hip fracture surgery.

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Institutional Review Board Statement: This study was approved by the Joint Institutional Review Board of Taipei Medical University (TMU-JIRB No. N202006076).

Informed Consent Statement: Because this study used only de-identified data, the requirement of patient informed consent was waived.

Data Availability Statement: The data used in this study are from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). Interested researchers can apply for the data by submitting a formal application to the ACS NSQIP.

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References

1. Cooper, C.; Cole, Z.A.; Holroyd, C.R.; Earl, S.C.; Harvey, N.C.; Dennison, E.M.; Melton, L.J.; Cummings, S.R.; Kanis, J.A.; IOF CSA Working Group on Fracture Epidemiology. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporos. Int.* **2011**, *22*, 1277–1288. [CrossRef] [PubMed]
2. Berry, S.D.; Rothbaum, R.R.; Kiel, D.P.; Lee, Y.; Mitchell, S.L. Association of clinical outcomes with surgical repair of hip fracture vs nonsurgical management in nursing home residents with advanced dementia. *JAMA Intern. Med.* **2018**, *178*, 774–780. [CrossRef] [PubMed]
3. Bhandari, M.; Swiontkowski, M. Management of acute hip fracture. *N. Engl. J. Med.* **2017**, *377*, 2053–2062. [CrossRef] [PubMed]
4. Schattner, A. The burden of hip fractures-why aren't we better at prevention? *QJM* **2018**, *111*, 765–767. [CrossRef] [PubMed]
5. HIP ATTACK Investigators. Accelerated surgery versus standard care in hip fracture (HIP ATTACK): An international, randomised, controlled trial. *Lancet* **2020**, *395*, 698–708. [CrossRef] [PubMed]

6. Reguant, F.; Arnau, A.; Lorente, J.V.; Maestro, L.; Bosch, J. Efficacy of a multidisciplinary approach on postoperative morbidity and mortality of elderly patients with hip fracture. *J. Clin. Anesth.* **2019**, *53*, 11–19. [CrossRef] [PubMed]
7. Neuman, M.D.; Feng, R.; Carson, J.L.; Gaskins, L.J.; Dillane, D.; Sessler, D.I.; Sieber, F.; Magaziner, J.; Marcantonio, E.R.; Mehta, S.; et al. Spinal anesthesia or general anesthesia for hip surgery in older adults. *N. Engl. J. Med.* **2021**, *385*, 2025–2035. [CrossRef]
8. Chen, D.X.; Yang, L.; Ding, L.; Li, S.Y.; Qi, Y.N.; Li, Q. Perioperative outcomes in geriatric patients undergoing hip fracture surgery with different anesthesia techniques: A systematic review and meta-analysis. *Medicine* **2019**, *98*, e18220. [CrossRef]
9. O'Donnell, C.M.; McLoughlin, L.; Patterson, C.C.; Clarke, M.; McCourt, K.C.; McBrien, M.E.; McAuley, D.F.; Shields, M.O. Perioperative outcomes in the context of mode of anaesthesia for patients undergoing hip fracture surgery: Systematic review and meta-analysis. *Br. J. Anaesth.* **2018**, *120*, 37–50. [CrossRef] [PubMed]
10. American College of Surgeons. ACS National Surgical Quality Improvement Program. Available online: https://www.facs.org/quality-programs/acs-nsqip (accessed on 18 March 2023).
11. Shiloach, M.; Frencher, S.K., Jr.; Steeger, J.E.; Rowell, K.S.; Bartzokis, K.; Tomeh, M.G.; Richards, K.E.; Ko, C.Y.; Hall, B.L. Toward robust information: Data quality and inter-rater reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J. Am. Coll. Surg.* **2010**, *210*, 6–16. [CrossRef] [PubMed]
12. Basques, B.A.; Bohl, D.D.; Golinvaux, N.S.; Samuel, A.M.; Grauer, J.G. General versus spinal anaesthesia for patients aged 70 years and older with a fracture of the hip. *Bone Jt. J.* **2015**, *97*, 689–695. [CrossRef] [PubMed]
13. Austin, P.C. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat. Med.* **2010**, *29*, 2137–2148. [CrossRef] [PubMed]
14. Austin, P.C. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar. Behav. Res.* **2011**, *46*, 399–424. [CrossRef] [PubMed]
15. Zheng, X.; Tan, Y.; Gao, Y.; Liu, Z. Comparative efficacy of neuraxial and general anesthesia for hip fracture surgery: A meta-analysis of randomized clinical trials. *BMC Anesthesiol.* **2020**, *20*, 162. [CrossRef]
16. Durand, W.M.; Goodman, A.D.; Johnson, J.P.; Daniels, A.H. Assessment of 30-day mortality and complication rates associated with extended deep vein thrombosis prophylaxis following hip fracture surgery. *Injury* **2018**, *49*, 1141–1148. [CrossRef] [PubMed]
17. Ahn, E.J.; Kim, H.J.; Kim, K.W.; Choi, H.R.; Kang, H.; Bang, S.R. Comparison of general anaesthesia and regional anaesthesia in terms of mortality and complications in elderly patients with hip fracture: A nationwide population-based study. *BMJ Open* **2019**, *9*, e029245. [CrossRef]
18. Biboulet, P.; Jourdan, A.; Van Haevre, V.; Morau, D.; Bernard, N.; Bringuier, S.; Capdevila, X. Hemodynamic profile of target-controlled spinal anesthesia compared with 2 target-controlled general anesthesia techniques in elderly patients with cardiac comorbidities. *Reg. Anesth. Pain Med.* **2012**, *37*, 433–440. [CrossRef]
19. Parker, M.J.; Griffiths, R. General versus regional anaesthesia for hip fractures. A pilot randomised controlled trial of 322 patients. *Injury* **2015**, *46*, 1562–1566. [CrossRef]
20. O'Hara, D.A.; Duff, A.; Berlin, J.A.; Poses, R.M.; Lawrence, V.A.; Huber, E.C.; Noveck, H.; Strom, B.L.; Carson, J.L. The effect of anesthetic technique on postoperative outcomes in hip fracture repair. *Anesthesiology* **2000**, *92*, 947–957. [CrossRef]
21. Neuman, M.D.; Rosenbaum, P.R.; Ludwig, J.M.; Zubizarreta, J.R.; Silber, J.H. Anesthesia technique, mortality, and length of stay after hip fracture surgery. *JAMA* **2014**, *311*, 2508–2517. [CrossRef]
22. Seitz, D.P.; Gill, S.S.; Bell, C.M.; Austin, P.C.; Gruneir, A.; Anderson, G.M.; Rochon, P.A. Postoperative medical complications associated with anesthesia in older adults with dementia. *J. Am. Geriatr. Soc.* **2014**, *62*, 2102–2109. [CrossRef] [PubMed]
23. Tung, Y.C.; Hsu, Y.H.; Chang, G.M. The effect of anesthetic type on outcomes of hip fracture surgery: A nationwide population-based study. *Medicine* **2016**, *95*, e3296. [CrossRef] [PubMed]
24. Morgan, L.; McKeever, T.M.; Nightingale, J.; Deakin, D.E.; Moppett, I.K. Spinal or general anaesthesia for surgical repair of hip fracture and subsequent risk of mortality and morbidity: A database analysis using propensity score-matching. *Anaesthesia* **2020**, *75*, 1173–1179. [CrossRef] [PubMed]
25. Neuman, M.D.; Silber, J.H.; Elkassabany, N.M.; Ludwig, J.M.; Fleisher, L.A. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. *Anesthesiology* **2012**, *117*, 72–92. [CrossRef]
26. Fields, A.C.; Dieterich, J.D.; Buterbaugh, K.; Moucha, C.S. Short-term complications in hip fracture surgery using spinal versus general anaesthesia. *Injury* **2015**, *46*, 719–723. [CrossRef]
27. Chang, C.C.; Lin, H.C.; Lin, H.W.; Lin, H.C. Anesthetic management and surgical site infections in total hip or knee replacement: A population-based study. *Anesthesiology* **2010**, *113*, 279–284. [CrossRef] [PubMed]
28. Zhao, K.; Zhang, J.; Li, J.; Meng, H.; Hou, Z.; Zhang, Y. Incidence of and risk factors for new-onset deep venous thrombosis after intertrochanteric fracture surgery. *Sci. Rep.* **2021**, *11*, 17319. [CrossRef] [PubMed]
29. Davis, F.M.; Quince, M.; Laurenson, V.G. Deep vein thrombosis and anaesthetic technique in emergency hip surgery. *Br. Med. J.* **1980**, *281*, 1528–1529. [CrossRef]
30. Guay, J.; Parker, M.J.; Gajendragadkar, P.R.; Kopp, S. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst. Rev.* **2016**, *2*, CD000521. [CrossRef]

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Anterior Quadratus Lumborum Block and Quadriceps Strength: A Prospective Cohort Study

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Abstract: The decrease in quadriceps strength after anterior quadratus lumborum block (AQLB) has not been quantified. This prospective cohort study investigated the incidence of quadriceps weakness after AQLB. We enrolled patients undergoing robot-assisted partial nephrectomy, and AQLB was performed at the L2 level with 30 mL of 0.375% ropivacaine. We evaluated each quadriceps' maximal voluntary isometric contraction using a handheld dynamometer preoperatively and postoperatively at 1 and 4 days. The incidence of muscle weakness was defined as a 25% reduction in muscle strength compared with the preoperative baseline, and "muscle weakness possibly caused by nerve block" was defined as a 25% reduction compared with the non-block side. We also assessed the numerical rating scale and quality of recovery-15 scores. Thirty participants were analyzed. The incidence of muscle weakness compared with preoperative baseline and the non-block side was 13.3% and 30.0%, respectively. Patients with a numerical rating scale ≥ 4 or quality of recovery-15 score < 122, which was classified as moderate or poor, had decreased muscle strength with relative risks of 1.75 and 2.33, respectively. All patients ambulated within 24 h after surgery. The incidence of quadriceps weakness possibly caused by nerve block was 13.3%; however, all patients could ambulate after 1 day.

Keywords: muscle weakness; muscle strength dynamometer; complications; nerve block; quadratus lumborum block; robot-assisted surgery

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1. Introduction

Minimally invasive surgery causes less postoperative pain and provides rapid recovery; however, acute pain scores are reported to be comparable with those after open nephrectomy, possibly leading to the development of chronic pain [1]. Therefore, the optimization of multimodal analgesia is an urgent issue.

Although typical procedure-specific analgesia protocols, such as enhanced recovery after surgery (ERAS®), and procedure-specific postoperative pain management do not exist for robot-assisted laparoscopic partial nephrectomy (RAPN), epidural analgesia, wound infiltration, and peripheral nerve block may have roles in relieving postoperative pain for RAPN. Epidural analgesia is the gold standard for abdominal procedures including nephrectomy. However, it may involve adverse events such as neurological damage, hypotension, epidural hemorrhage, muscle weakness of the lower extremities, and urinary retention, which may be confused with surgical complications. Thus, epidural analgesia is often avoided in patients undergoing RAPN. There is no evidence regarding the efficacy of wound infiltration in laparoscopic nephrectomy or RAPN.

Various studies have investigated the efficacy of peripheral nerve blocks for laparoscopic nephrectomy. Among these, the anterior quadratus lumborum block (AQLB) is a technique intended to provide an analgesic effect for somatic pain from abdominal and

hip surgeries [2–4]. AQLB was originally conducted at the L4 level, and the effect extended to Th11–12. However, a recent study showed that the approach at the L2 level could be expected to anesthetize from Th6–7 to L1–2 and is more effective for laparoscopic nephrectomy [5,6].

Although the frequency of AQLB is increasing, some reports have indicated that QLB causes a decrease in quadriceps strength, and other studies have reported postoperative muscle weakness in the lower limbs [2,7–9] possibly resulting in delayed early ambulation. However, to the best of our knowledge, no study has quantified weakness of the quadriceps muscle after QLB using a handheld dynamometer, which is considered a reliable and valid instrument.

Therefore, we designed a prospective observational study to quantify the quadriceps strength after AQLB by using a handheld dynamometer and assessed its clinical influence under postoperative conditions.

2. Materials and Methods

2.1. Study Design and Setting

The protocol of this prospective observational study was approved by the research ethics committee of our institution. Informed consent was obtained from all participants. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology initiative [10], and it adheres to the tenets of the Helsinki Declaration.

The study participants were enrolled between November 2020 and June 2022 at Nara Medical University, with the final follow-up in July 2022.

2.2. Participants

Adults between 20 and 75 years old scheduled for RAPN who provided written informed consent were enrolled. The exclusion criteria were as follows: inability to cooperate, dementia, allergy to local anesthetics, chronic use of opioids, coagulation disorder (prothrombin time-international normalized ratio > 1.25, activated partial thromboplastin time > 35 s, platelet count < 10.0×10^9/L), coagulopathy, preoperative muscle weakness or lower limb pain, and body weight < 40 kg or body mass index > 35 kg/m^2.

2.3. Intraoperative Management

All participants received volatile general anesthesia per institutional routine. Fentanyl and remifentanil were administered intraoperatively at the discretion of the anesthesiologist in charge. Wound infiltration with local anesthetics was not permitted, and acetaminophen was administered at the end of surgery. The patients were extubated after conforming the sufficient reversal of the neuromuscular blockade with sugammadex under the train-of-four repetition monitoring. Postoperatively, all participants received intravenous patient-controlled fentanyl analgesia with 0.5 μg/kg/min fentanyl concentration, 1 mL per hour continuous infusion, 1 mL bolus on demand, and a 10 min lock-out interval.

2.4. Block Procedure

All blocks were performed using a 20-gauge, 100 mm needle (UNIEVER disposable nerve blockade needle Huber (echogenic), Unisis Corp., Tokyo, Japan). The block operators were YK, NT, and TS, which were familiar with AQLB. The procedure was performed after placement in "nephrectomy position", which is a lateral decubitus position over a slight table break at the waist.

After skin disinfection, we placed the probe transversely, transitioning laterally from the costal margin on the midaxillary line to the L2 vertebral body and identified the L2 transverse process and the quadratus lumborum muscle. A 20-gauge needle was advanced in-plane through the quadratus lumborum muscle in a lateral-to-medial direction, and saline (1–3 mL) was injected between the quadratus lumborum muscle and the anterior layer of the thoracolumbar fascia to confirm the correct needle tip position. We tried to avoid piercing the fascia of the psoas major muscle and spreading local anesthetic within

the psoas major muscle because the local anesthetic would spread to the lumbar plexus through the psoas major muscle [11]. Subsequently, 30 mL of 0.375% ropivacaine was injected to effectuate the AQLB. We recognized the rapid shrinking of the expanded space as successful AQLB.

2.5. Measuring Muscle Strength

We evaluated quadriceps strength as maximal voluntary isometric contractions (MVIC) using a handheld dynamometer (MT-100, Sakai Medical Co., Ltd., Fukuoka, Japan) on the day before surgery and on postoperative days (PODs) 1 and 4. The participants were seated with their hips flexed at approximately 85°, knees flexed at 90°, and hands holding the side of the seat (Figure 1). A strap was placed above the ankle joint and adjusted to the correct length. We investigated the incidence of muscle weakness, defined as a 25% reduction in MVIC on POD 1 compared with the preoperative baseline. We also defined "muscle weakness possibly caused by nerve block" as a 25% MVIC reduction compared with the non-block side. Furthermore, we assessed the postoperative course with the numerical rating scale (NRS range, 0–10, with 0 indicating no pain and 10 quadriceps strength the worst pain imaginable) 2 h after surgery and on PODs 1 and 4, and the Japanese version of the quality of recovery-15 (QoR-15 range, 0–150, with a higher score indicating a better quality of recovery) the day before the surgery and on PODs 1 and 4 [12–14].

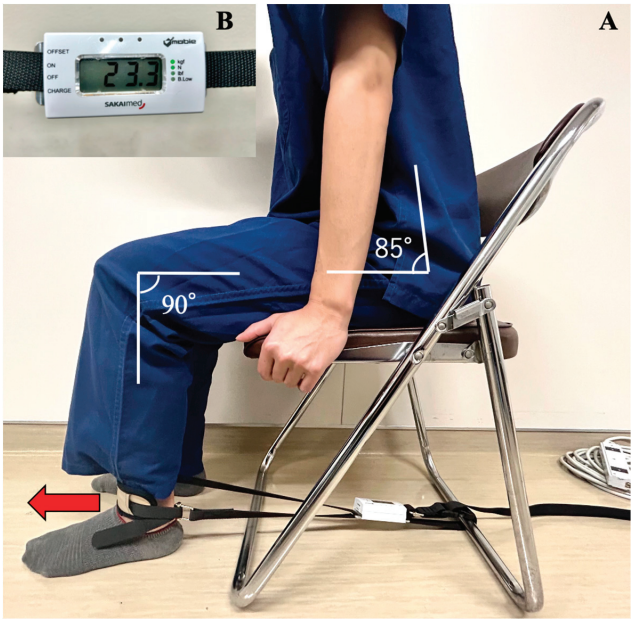

Figure 1. Testing position for strength assessment and the handheld dynamometer. (**A**) One end of the non-elastic belt was fixed on the front of the ankle, and the other was immobilized on the bar of the chair. The red arrow indicates the direction of the force exerted by the participants. The same position and chair were used for all assessments. (**B**) An image of the pull-type handheld dynamometer with non-elastic belts attached to both ends of the device.

2.6. Sample Size Calculation

Because no previous study investigated the incidence of muscle weakness caused by AQLB, we referred to an earlier study that examined the muscle weakness caused by psoas compartment block [15] because the local anesthetics were administered in the similar compartment. This study described that the incidence rate of "no movement" and "active movement only with gravity eliminated" at 6 h after nerve block was 26% and 25%,

respectively. We hypothesized that the "no movement" group (26%) or the "no movement" and "active movement only with gravity eliminated" groups (51%) would affect muscle strength after 24 h.

The incidence of these groups ranged from 26 to 51%, and we set the probability of AQLB causing muscle weakness at 35%. We estimated that the incidence of muscle weakness among the 27 patients could be detected with 90% power and a margin of error of ±20% using the Clopper–Pearson confidence interval. The target sample size was set at 30 cases considering a dropout rate of 10%.

2.7. Statistical Methods

The primary goal of this study was to estimate the incidence of postoperative muscle weakness on POD 1. We simultaneously assessed muscle weakness compared with preoperative baseline and the strength of the non-block side. The incidence was evaluated as the percentage of participants with muscle weakness, and two-sided 95% confidence intervals (CIs) were determined.

The secondary goals were to investigate the association between muscle weakness and the NRS or QoR-15. We determined the cut-off values of the NRS score and QoR-15 to be ≥4 and ≥122, respectively. We evaluated the relative risk and two-sided 95% CIs.

3. Results

We intended to collect 38 participants' complete data; however, 7 were excluded because they refused to undergo the postoperative muscle evaluation because of pain, postoperative nausea, or hyperpnea. One was excluded because of early discharge on POD 4. Therefore, we included 38 participants between November 2020 and June 2022, and 30 patients were included in the analysis, as shown in Figure 2. The patient characteristics, surgical data, and outcome parameters are presented in Tables 1 and 2. No significant differences were observed in the patient characteristics or surgical data. The muscle strength of the block side on POD 1 was significantly lower and the NRS scores 2 h after surgery in the muscle weakness group were significantly higher than those in the no-muscle weakness group.

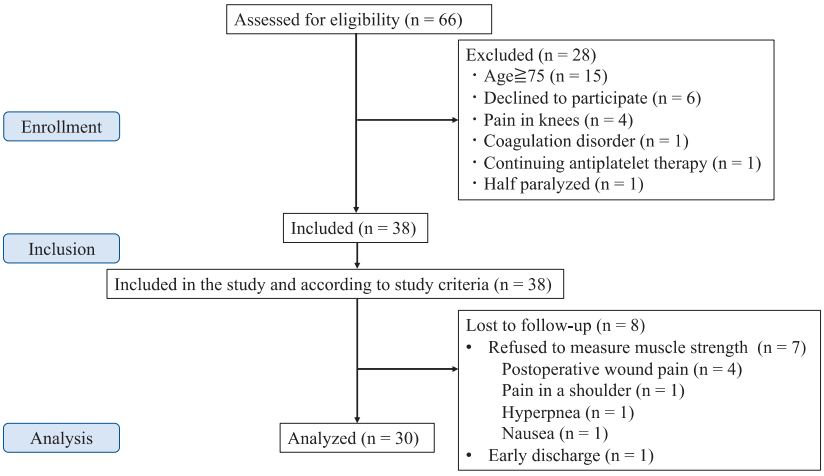

Figure 2. Patient flow diagram.

Table 1. Patient characteristics.

	No-Muscle Weakness Group (n = 21)	Muscle Weakness Group (n = 9)	*p*-Value
Sex			0.10
Male	14 (66.7%)	3 (33%)	
Female	7 (33.3%)	6 (67%)	
Age (years)	64.0 [38, 75]	67.0 [53, 74]	0.70
BMI (kg/m^2)	24.2 [18.4, 31.8]	22.1 [21.6, 29.1]	0.39
ASA-PS			0.08
1	0 (0%)	2 (22%)	
2	21 (100%)	7 (78%)	
3	0 (0%)	0 (0%)	
4	0 (0%)	0 (0%)	

Values are expressed as medians [min, max] or numbers (proportion). BMI: body mass index, ASA-PS: American Society of Anesthesiologists—physical status.

Table 2. Surgical data and outcome parameters.

	No-Muscle Weakness Group (n = 21)	Muscle Weakness Group (n = 9)	*p*-Value
Surgical approach			1.00
Posterior	11 (52.3%)	5 (56%)	
Anterior	10 (47.6%)	4 (44%)	
Ureteral catheter			0.68
With catheter	14 (66.7%)	7 (78%)	
No catheter	7 (33.3%)	2 (22%)	
Duration of surgery (min)	196 [94, 301]	229 [131, 269]	0.39
Muscle strength (kgf)			
Block side			
POD 0	17.8 [6.2, 36.8]	16.7 [10.9–31.4]	0.71
POD 1	18.9 [8.4, 35.2]	12.4 [3.0–21.2]	0.03
POD 4	19.1 [10.0, 42.5]	14.5 [9.1–32.0]	0.20
Non-block side			
POD 0	20.8 [6.0, 35.5]	16.4 [10.6–33.2]	0.59
POD 1	20.3 [6.6, 38.6]	15.6 [5.5–27.1]	0.20
POD 4	15 [9.1, 36.0]	13.1 [10.2–27.0]	0.39
NRS scores at rest			
2 h after surgery	1 [0, 4]	3 [0, 8]	0.02

Table 2. *Cont.*

	No-Muscle Weakness Group (n = 21)	Muscle Weakness Group (n = 9)	*p*-Value
POD 1	1 [0, 5]	2 [0, 4]	0.80
POD 4	0 [0, 4]	0 [0, 4]	0.42
NRS scores at movement			
POD1	4.5 [0, 10]	5 [3, 6]	0.73
POD4	2 [0, 5]	4 [0, 7]	0.13
QoR-15			
Preoperative	148 [117, 150]	147 [138, 150]	0.20
POD 1	120 [43, 150]	109 [59, 137]	0.22
POD 4	138 [108, 149]	138 [88, 143]	0.44

Values are expressed as medians [min, max] or numbers (proportion). NRS: numerical rating scale, POD: postoperative day, QoR-15: quality of recovery-15.

3.1. Muscle Strength

A scatter plot of muscle strength of the block side compared with the preoperative baseline and non-block side on POD 1 is shown in Figure 3. The incidence of muscle weakness on POD 1 was 9 out of 30 (30.0%, 95% CI, 14.7–49.4). The incidence of muscle weakness possibly caused by nerve block was 4 out of 30 (13.3%, 95% CI, 3.76–30.7).

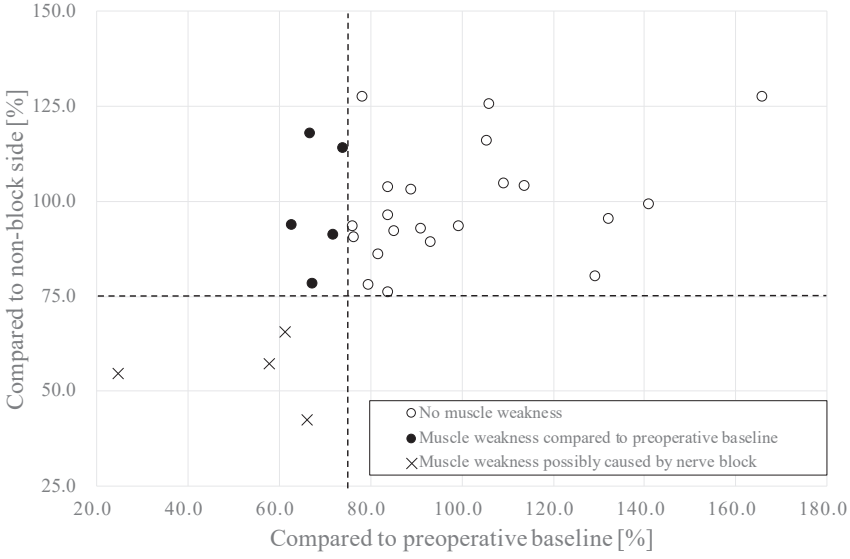

Figure 3. Scatter plot of muscle strength of the block side on postoperative day 1. Dotted lines represent the cut-off values of muscle weakness, which is 25% reduction of muscle strength from the baseline.

3.2. Postoperative Pain and Recovery

The NRS scores at each time point are shown in Figure 4. The median values (mean values) of the NRS scores at rest were 2 (1.9) 2 h after surgery; 1 (1.5) on POD 1; and 0 (0.6) on POD 4. The median values (mean values) of the NRS scores for movement were 4 (4.3) on POD 1 and 2 (2.6) on POD 4. Among 30 patients, 11 showed a score of 0 2 h after surgery.

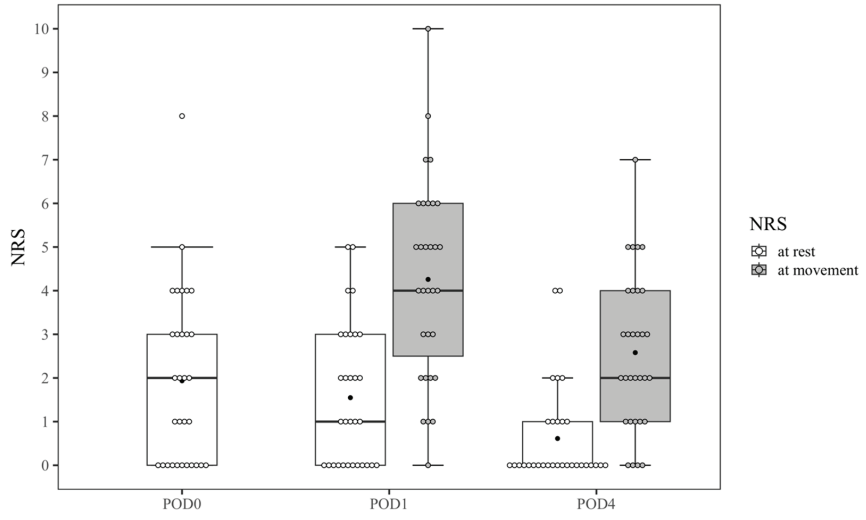

Figure 4. Box plots and dot plots for numerical rating scale scores at each time point. Boxes represent median values (horizontal rule) with the 25th and 75th percentiles (lower and upper limits of boxes, respectively). Error bars indicate the range of non-outlying values. Dots represent the NRS scores of each patient. Black circles represent the mean values of the NRS scores.

The associations between muscle weakness and NRS or QoR-15 scores are shown in Table 3. Patients with an NRS of ≤4 tended to have muscle weakness on POD 1 and POD 4 with a relative risk of 1.75 (95% CI, 0.44–6.93) and 2.33 (95% CI, 0.58–9.43), respectively. Cases with a QoR-15 score of <122, which was classified as moderate or poor [13] tended to have muscle weakness on POD 1 and 4 with a relative risk of 2.33 (95% CI, 0.58–9.38) and 3.25 (95% CI, 0.86–12.31), respectively.

Table 3. Association between NRS or QoR-15 scores and muscle weakness.

		No-Muscle Weakness Group	Muscle Weakness Group	All (n = 30)
POD 1	NRS ≥ 4	13 (65.0%)	7 (35.0%)	20
	NRS < 4	8 (80.0%)	2 (20.0%)	10
	RR		1.75 (0.44–6.93)	
POD 4	NRS ≥ 4	6 (66.7%)	3 (33.3%)	9
	NRS < 4	18 (85.7%)	3 (14.2%)	21
	RR		2.33 (0.58–9.43)	
POD 1	QoR-15 < 122	11 (61.1%)	7 (38.8%)	18
	QoR-15 ≥ 122	10 (83.3%)	2 (16.7%)	12
	RR		2.33 (0.58–9.38)	
POD 4	QoR-15 < 122	2 (50%)	2 (50%)	4
	QoR-15 ≥ 122	22 (84.6%)	4 (66.7%)	26
	RR		3.25 (0.86–12.31)	

RR (risk ratio) is expressed with 95% confidence intervals.

4. Discussion

The incidence of postoperative muscle weakness was 30% and the incidence of muscle weakness possibly caused by nerve block was 13.3% compared with the non-block side. Meanwhile, we defined muscle weakness as a 25% reduction in MVIC compared with the baseline. However, the muscle strength of some patients was distributed around the cut-off values on POD 1. The incidence rates in this study were not definitive. We believe that the significance of this study is that these results provide accurate data on perioperative muscle strength in patients receiving nerve blocks, which may cause muscle weakness.

Although we expected the incidence of quadriceps weakness to be 35 ± 20%, as mentioned above, the incidence in this study was 13.3%. We assume that this low incidence is related to how we performed AQLB. Previous studies have suggested that two pathways of local anesthetics after AQLB cause quadriceps weakness: (1) a pathway posterior to the arcuate ligaments and into the paravertebral space [11,16]; and (2) a pathway into the lumbar plexus through the psoas major muscle. Several cadaveric studies have reported that local anesthetics after AQLB spread into the paravertebral area with a probability of 63–100% [11,17]. This spread into the paravertebral space causes muscle weakness, considering that the paravertebral block is suggested to cause quadriceps motor weakness [18]. Another pathway is through the psoas muscle to the lumbar plexus. A cadaveric study described that local anesthetic in all 10 AQLB procedures had spread consistently to the lumbar plexus and within the psoas major muscle [19]. Another cadaveric study indicated that the lumbar plexus was unaffected if the psoas major muscle was not pierced [11]. Therefore, our approach for avoiding piercing the psoas major muscle in this study may have resulted in the low incidence of quadriceps weakness.

Various factors affect postoperative muscle weakness: pain [20], muscle atrophy [21], inflammation [22–25], surgical complications or nerve block [26], opioid therapy, and residual neuromuscular block [27]. In this study, patients with NRS scores of ≥4 and moderate or poor QoR-15 scores tended to have muscle weakness. Considering these results, postoperative muscle strength in this study was possibly affected by pain and the quality of recovery. We also compared the muscle strength of the block side with that of the non-block side, excluding factors other than nerve block, such as pain, quality of recovery, or inflammation. Although we compared the postoperative NRS and QoR-15 scores between both groups and there were no significant differences, patients in the muscle weakness group showed a tendency to have more postoperative pain and a lower quality of recovery.

We defined muscle weakness as a 25% reduction in MVIC compared with the preoperative baseline. A previous study showed that handgrip strength was reduced by 16.4% on POD 1 owing to postoperative muscle atrophy [21], and it was considered that quadriceps strength on POD 1 was similarly reduced. Therefore, we set the cut-off value considering other factors, such as postoperative pain and inflammation. We defined a 25% reduction compared with the non-block side as muscle weakness possibly caused by the nerve block because a difference of 10% between sides is physiologically normal in healthy volunteers [28].

The incidence of muscle weakness in this study (13.3%) was slightly lower than that reported in a recent study (16.7%) [8] which was published during the study registration period of the present work. We evaluated muscle strength objectively using a handheld dynamometer; however, the recent previous study documented quadriceps weakness as muscle strength grade 2 out of 5 or less in hip flexion and knee extension 2 h after surgery [8]. This difference in measurements and time points may have affected the results. Although the ERAS®Society recommends early ambulation, and some hospitals encourage patients to walk on the same day as surgery [29], our institutional protocol for RAPN demands that the first ambulation occurs on POD 1 to ensure patient safety. Therefore, we measured muscle strength on POD 1 when the patients ambulated for the first time after surgery.

There are four approaches for QLB based on the injection site: lateral, posterior, anterior, and intramuscular QLB. These approaches were reported to be effective for various surgeries [2–4,30]. There has been little evidence of these QLB approaches for laparoscopic nephrectomy; however, AQLB at the L2 level has been reported to be effective for laparoscopic nephrectomy. The original AQLB is performed at the L4 level [31]; however, a previous study showed that its cutaneous sensory blockade is only from T11 to L1 [5]. Therefore, we performed AQLB at the L2 level. In a previous study, the mean NRS scores after RAPN were 5.9, 3.5, and 1.5 on POD 0, 1, and 4, respectively. In this study, the mean NRS scores at rest were 1.9 on POD 0 (11 out of 30 patients showed 0), 1.5 on POD 1, and 0.6 on POD 4, and the NRS scores upon movement were 4.3 on POD 1 and 2.6 on POD 4. These results reflect the effectiveness of AQLB at the L2 level.

We administered 30 mL of 0.375% ropivacaine to all participants, which may have led to a higher incidence of muscle weakness in female participants. To our knowledge, there are no studies that have investigated the minimum effective volume and concentration for AQLB. In previous studies described in a meta-analysis [32], 20–30 mL of 0.2–0.375% ropivacaine was used for QLB, while in a previous study for ATLB at the L2 approach, 20 mL of 0.375% ropivacaine was administered [5]. However, the recent study showed that a larger volume for AQLB contributed to a larger analgesic area [33], supporting our decision to use 30 mL of 0.375% ropivacaine for better analgesia in our surgical settings.

Seven participants were excluded because they refused to provide muscle strength measurements. Among the seven excluded participants, two claimed that nausea and hyperpnea were too severe to participate in the measurements. Four participants refused follow-up owing to wound pain; however, they described low NRS scores (0, 0, 3, and 6 at rest, and 3, 3, 3, and 6 upon movement on POD 1, respectively). It is rational to consider that the participants were hesitant to measure muscle strength because the procedure required maximum strength, which might have caused additional pain. This is a limitation of this study.

There are also other limitations. This was a prospective observational study; hence, a prospective randomized study is required to assess muscle weakness after AQLB compared with placebo in patients undergoing RAPN. However, we investigated the weakness of the block-side quadriceps muscle compared with the non-block side, which can be regarded to show the effect of the nerve block. Furthermore, the influence of postoperative muscle atrophy on muscle strength cannot be excluded. However, our definition of a 25% reduction in MVIC minimized the influence of muscle atrophy in the results.

In conclusion, the incidence of the quadriceps weakness after AQLB on POD 1 was 30.0%, and 13.3% of the total may be affected by AQLB; however, all patients could ambulate on POD 1. A further randomized controlled trial is needed for a clear characterization of AQLB.

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References

1. Alper, I.; Yüksel, E. Comparison of acute and chronic pain after open nephrectomy versus laparoscopic nephrectomy: A prospective clinical trial. *Medicine* **2016**, *95*, e3433. [CrossRef]
2. Yuan, L.; Xu, C.; Zhang, Y.; Wang, G. Comparative efficacy analysis of ultrasound-guided quadratus lumborum block and lumbar plexus block in hip arthroscopy: A pilot prospective randomized controlled trial. *J. Hip Preserv. Surg.* **2022**, *9*, 119–125. [CrossRef] [PubMed]
3. Kim, Y.-J.; Kim, H.-T.; Kim, H.-J.; Yoon, P.-W.; Park, J.-I.; Lee, S.-H.; Ro, Y.-J.; Koh, W.-U. Ultrasound-guided anterior quadratus lumborum block reduces postoperative opioid consumption and related side effects in patients undergoing total hip replacement arthroplasty: A propensity score-matched cohort study. *J. Clin. Med.* **2021**, *10*, 4632. [CrossRef]
4. Ahmed, A.; Fawzy, M.; Nasr, M.A.R.; Hussam, A.M.; Fouad, E.; Aboeldahb, H.; Saad, D.; Osman, S.; Fahmy, R.S.; Farid, M.; et al. Ultrasound-guided quadratus lumborum block for postoperative pain control in patients undergoing unilateral inguinal hernia repair, a comparative study between two approaches. *BMC Anesthesiol.* **2019**, *19*, 184. [CrossRef] [PubMed]
5. Lu, Y.; Zhang, J.; Xu, X.; Chen, W.; Zhang, S.; Zheng, H.; Xia, Y.; Papadimos, T.J.; Xu, X.; Chen, H. Sensory assessment and block duration of transmuscular quadratus lumborum block at L2 versus L4 in volunteers: A randomized controlled trial. *Minerva Anestesiol.* **2019**, *85*, 1273–1280. [CrossRef] [PubMed]
6. He, Y.; Huang, M.; Zhong, Q.; Ni, H.; Yu, Z.; Zhang, X. Analgesic effect of ultrasound-guided anterior quadratus lumborum block at the L2 level in patients undergoing laparoscopic partial nephrectomy: A single-center, randomized controlled trial. *Pain Res. Manag.* **2022**, *2022*, 8958859. [CrossRef]
7. Wikner, M. Unexpected motor weakness following quadratus lumborum block for gynaecological laparoscopy. *Anaesthesia* **2017**, *72*, 230–232. [CrossRef]
8. Shi, R.; Li, H.; Wang, Y. Dermatomal coverage of single-injection ultrasound-guided parasagittal approach to anterior quadratus lumborum block at the lateral supra-arcuate ligament. *J. Anesth.* **2021**, *35*, 307–310. [CrossRef]
9. Nassar, H.; Hasanin, A.; Sewilam, M.; Ahmed, H.; Abo-Elsoud, M.; Taalab, O.; Rady, A.; Zoheir, H.A. Transmuscular quadratus lumborum block versus suprainguinal fascia iliaca block for hip arthroplasty: A randomized, controlled pilot study. *Local Reg. Anesth.* **2021**, *14*, 67–74. [CrossRef]
10. Cuschieri, S. The STROBE guidelines. *Saudi J. Anaesth.* **2019**, *13* (Suppl. 1), S31–S34. [CrossRef]
11. Dam, M.; Moriggl, B.; Hansen, C.K.; Hoermann, R.; Bendtsen, T.F.; Børglum, J. The pathway of injectate spread with the transmuscular quadratus lumborum block: A cadaver study. *Anesth. Analg.* **2017**, *125*, 303–312. [CrossRef]
12. Gerbershagen, H.J.; Rothaug, J.; Kalkman, C.J.; Meissner, W. Determination of moderate-to-severe postoperative pain on the numeric rating scale: A cut-off point analysis applying four different methods. *Br. J. Anaesth.* **2011**, *107*, 619–626. [CrossRef]
13. Campfort, M.; Cayla, C.; Lasocki, S.; Rineau, E.; Léger, M. Early quality of recovery according to QoR-15 score is associated with one-month postoperative complications after elective surgery. *J. Clin. Anesth.* **2022**, *78*, 110638. [CrossRef]
14. Nakatani, S.; Ida, M.; Tanaka, Y.; Okamoto, N.; Wang, X.; Nakatani, H.; Sato, M.; Naito, Y.; Kawaguchi, M. Translation and validation of the Japanese version of the Quality of Recovery-15 questionnaire. *J. Anesth.* **2021**, *35*, 426–433. [CrossRef]
15. Henshaw, D.S.; Jaffe, J.D.; Reynolds, J.W.; Dobson, S.; Russell, G.B.; Weller, R.S. An evaluation of ultrasound-guided adductor canal blockade for postoperative analgesia after medial unicondylar knee arthroplasty. *Anesth. Analg.* **2016**, *122*, 1192–1201. [CrossRef]
16. Blanco, R.; Ansari, T.; Girgis, E. Quadratus lumborum block for postoperative pain after caesarean section: A randomised controlled trial. *Eur. J. Anaesthesiol.* **2015**, *32*, 812–818. [CrossRef]
17. Adhikary, S.D.; El-Boghdadly, K.; Nasralah, Z.; Sarwani, N.; Nixon, A.M.; Chin, K.J. A radiologic and anatomic assessment of injectate spread following transmuscular quadratus lumborum block in cadavers. *Anaesthesia* **2017**, *72*, 73–79. [CrossRef]
18. Wardhan, R.; Auroux, A.-S.M.; Ben-David, B.; Chelly, J.E. Is L2 paravertebral block comparable to lumbar plexus block for postoperative analgesia after total hip arthroplasty? *Clin. Orthop. Relat. Res.* **2014**, *472*, 1475–1481. [CrossRef] [PubMed]
19. Carline, L.; McLeod, G.A.; Lamb, C. A cadaver study comparing spread of dye and nerve involvement after three different quadratus lumborum blocks. *Br. J. Anaesth.* **2016**, *117*, 387–394. [CrossRef] [PubMed]
20. de Menezes, T.C.; Bassi, D.; Cavalcanti, R.C.; Barros, J.E.S.L.; Granja, K.S.B.; Calles, A.C.D.N.; Exel, A.L. Comparisons and correlations of pain intensity and respiratory and peripheral muscle strength in the pre- and postoperative periods of cardiac surgery. *Rev. Bras. Ter. Intensiv.* **2018**, *30*, 479–486. [CrossRef] [PubMed]
21. Lachmann, G.; Mörgeli, R.; Kuenz, S.; Piper, S.K.; Spies, C.; Kurpanik, M.; Weber-Carstens, S.; Wollersheim, T. Perioperatively acquired weakness. *Anesth. Analg.* **2020**, *130*, 341–351. [CrossRef] [PubMed]
22. Edwards, H. Postoperative deterioration in muscular function. *Arch. Surg.* **1982**, *117*, 899–901. [CrossRef]
23. Zeiderman, M.R.; Welchew, E.A.; Clark, R.G. Changes in cardiorespiratory and muscle function associated with the development of postoperative fatigue. *Br. J. Surg.* **2005**, *77*, 576–580. [CrossRef] [PubMed]
24. Maxwell, A. Muscle power after surgery. *Lancet* **1980**, *315*, 420–421. [CrossRef] [PubMed]
25. Gupta, R.; Thurairaja, R.; Johnson, C.D.; Primrose, J.N. Body composition, muscle function and psychological changes in patients undergoing operation for hepatic or pancreatic disease. *Pancreatology* **2001**, *1*, 90–95. [CrossRef]
26. Jæger, P.; Zaric, D.; Fomsgaard, J.S.; Hilsted, K.L.; Bjerregaard, J.; Gyrn, J.; Mathiesen, O.; Larsen, T.K.; Dahl, J.B. Adductor canal block versus femoral nerve block for analgesia after total knee arthroplasty: A randomized, double-blind study. *Reg. Anesth. Pain Med.* **2013**, *38*, 526–532. [CrossRef]

27. Murphy, G.S.; Szokol, J.W.; Marymont, J.H.; Greenberg, S.B.; Avram, M.J.; Vender, J.S. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth. Analg.* **2008**, *107*, 130–137. [CrossRef]
28. Krishnan, C.; Williams, G.N. Evoked tetanic torque and activation level explain strength differences by side. *Eur. J. Appl. Physiol.* **2009**, *106*, 769–774. [CrossRef]
29. Dam, M.; Hansen, C.; Poulsen, T.D.; Azawi, N.H.; Laier, G.H.; Wolmarans, M.; Chan, V.; Bendtsen, T.F.; Børglum, J. Transmuscular quadratus lumborum block reduces opioid consumption and prolongs time to first opioid demand after laparoscopic nephrectomy. *Reg. Anesth. Pain Med.* **2021**, *46*, 18–24. [CrossRef]
30. Guo, M.; Lei, B.; Li, H.; Gao, X.; Zhang, T.; Liang, Z.; Wang, Y.; Wang, L. Anterior quadratus lumborum block at the lateral supra-arcuate ligament versus transmuscular quadratus lumborum block for analgesia after elective cesarean section: A randomized controlled trial. *J. Clin. Med.* **2022**, *11*, 3827. [CrossRef]
31. Blanco, R. Tap block under ultrasound guidance: The description of a "non pops" technique. *Reg. Anesth. Pain Med.* **2007**, *32*, 130. [CrossRef]
32. Kim, S.H.; Kim, H.J.; Kim, N.; Lee, B.; Song, J.; Choi, Y.S. Effectiveness of quadratus lumborum block for postoperative pain: A systematic review and meta-analysis. *Minerva Anestesiol.* **2020**, *86*, 554–564. [CrossRef] [PubMed]
33. Shao, L.; Luo, X.; Ye, Y.; Liu, L.; Cai, Y.; Xia, Y.; Papadimos, T.J.; Wang, Q.; Pan, L. Anterior Quadratus Lumborum block area comparison in the three different volumes of Ropivacaine: A double-blind, randomized controlled trial in healthy volunteers. *BMC Anesthesiol.* **2022**, *29*, 365. [CrossRef] [PubMed]

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The Optimal Fluid Strategy Matters in Liver Surgery: A Retrospective Single Centre Analysis of 666 Consecutive Liver Resections

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Abstract: As optimal intraoperative fluid management in liver surgery has not been established, we retrospectively analyzed our fluid strategy in a high-volume liver surgery center in 666 liver resections. Intraoperative fluid management was divided into very restrictive (<10 m kg^{-1} h^{-1}) and normal (≥10 mL kg^{-1} h^{-1}) groups for study group characterization. The primary endpoint was morbidity as assessed by the Clavien–Dindo (CD) score and the comprehensive complication index (CCI). Logistic regression models identified factors most predictive of postoperative morbidity. No association was found between postoperative morbidity and fluid management in the overall study population (p = 0.89). However, the normal fluid management group had shorter postoperative hospital stays (p = <0.001), shorter ICU stays (p = 0.035), and lower in-hospital mortality (p = 0.02). Elevated lactate levels (p < 0.001), duration (p < 0.001), and extent of surgery (p < 0.001) were the most predictive factors for postoperative morbidity. In the subgroup of major/extreme liver resection, very low total (p = 0.028) and normalized fluid balance (p = 0.025) (NFB) were associated with morbidity. Moreover, fluid management was not associated with morbidity in patients with normal lactate levels (<2.5 mmol/L). In conclusion, fluid management in liver surgery is multifaceted and must be applied judiciously as a therapeutic measure. While a restrictive strategy appears attractive, hypovolemia should be avoided.

Keywords: intravenous infusion; fluid management; surgical procedures; hepatectomy; adverse effects

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1. Introduction

Liver surgery has become a safe treatment for primary and secondary liver tumors due to refinements in parenchymal transection and improved perioperative management. Compared to intestinal surgery, liver surgery is generally associated with higher blood loss, different metabolic stress responses, and organ-specific complications. In addition, liver surgery has higher morbidity and mortality rates compared to other surgical patient populations (e.g., colorectal surgery) [1,2]. Inflow occlusion (Pringle maneuver) is an established measure to prevent bleeding during parenchymal transection. As liver ischemia may cause significant liver injury and impaired liver function, most surgeons prefer intermittent inflow occlusion during prolonged transection phases [3]. Total vascular exclusion (TVE) in addition to inflow occlusion or ante-situm resections completely prevents bleeding and allows reconstruction of hepatic veins [4]. However, these procedures affect the patient's

circulatory status and increase the requirements for optimal anesthetic management during liver surgery. Consequently, these useful procedures should only be used when necessary.

More than 20 years ago, a low central venous pressure (CVP) strategy was identified as a strategy to reduce blood loss during liver surgery [5], since a lower CVP is considered to be associated with lower pressures in the venous system of the liver, resulting in less blood loss, particularly during inflow occlusion periods. Since then, this low-CVP strategy has been adopted by many expert centers, and a recent survey among expert centers for liver surgery revealed that more than 60% of respondents follow this low-CVP strategy. However, fluid management varies widely among these centers, with 22% following goal-directed therapy and 6% aiming for euvolemia to minimize blood loss [6].

The enhanced recovery after surgery (ERAS) society also recommends balanced fluid management with the goal of euvolemia in liver surgery [1]. According to the ERAS recommendations, balanced crystalloids should be preferred over saline as the primary fluid replacement, and a low-CVP strategy is also recommended to reduce blood loss [1].

However, optimal perioperative fluid management in patients undergoing major abdominal and, in particular, liver surgery is still under debate. Parameters to guide intraoperative fluid management have not yet been defined. Excessive fluid administration may compromise oxygenation [7] due to hemodilution, cause pulmonary complications [8], and increase the risk of wound infection and anastomotic leakage due to intestinal edema and impaired collagen regeneration. On the other hand, intraoperative hypovolemia can impair cardiac output and lead to hypoperfusion and organ dysfunction [9]. Current research mainly focuses on comparing liberal, restrictive, and goal-directed fluid management, with conflicting results [10–13].

The aim of this study was to define solid parameters for optimal fluid management during general anesthesia for patients undergoing liver resection. Therefore, we compare the outcomes of patients with regard to intraoperative fluid management at a high-volume liver surgery center where general anesthesia is based on a low-fluid/low-CVP strategy.

2. Materials and Methods

2.1. Procedures

The data from patients who underwent liver resection at the Department of General, Visceral, and Transplantation Surgery of the University Medical Centre Mainz between December 2014 and September 2018 were analyzed. The primary data source was the hospital's digital clinical database. The electronic health records were searched for operating codes 5-501 and 5-502 for liver procedures. Data were collected primarily to evaluate the influence of intraoperative fluid management on postoperative outcome in patients undergoing liver resection. Other risk factors for postoperative adverse events related to anaesthesiological management were also considered.

The ethics committee of the Medical Association of the State of Rhineland–Palatine (Germany) approved this retrospective study (registration number: 2020-14894-retrospective) and waived the requirement for informed consent.

2.2. Eligibility Criteria

Patients aged at least 18 years who underwent liver resection were eligible for analysis. We excluded liver transplantations and emergency procedures, as well as resections as part of other primary surgical procedures, due to special hemodynamic preconditions. We also excluded liver resections with an operative time of less than 70 min, incomplete documentation of intraoperative fluid administration, estimated blood loss, or diuresis (Figure 1). Only the first procedure for each patient in the study was analyzed, and no subsequent procedures during hospitalization were included.

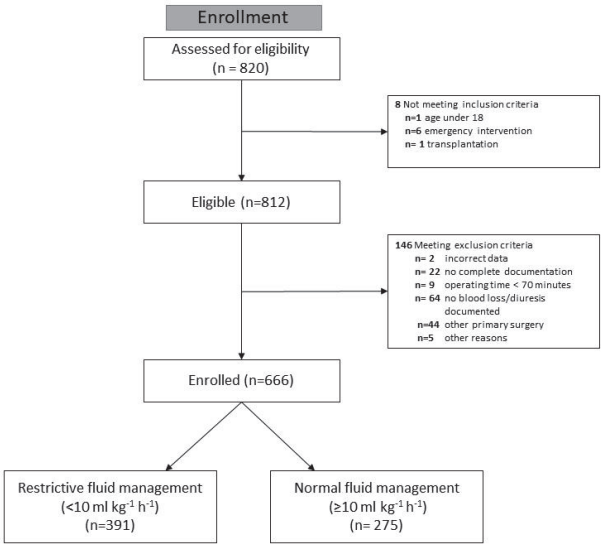


Figure 1. CONSORT Flow chart of patient eligibility.

2.3. Study Design

This is a retrospective analysis. The anesthesia team continuously documented intraoperative anesthesiological parameters (heart rate, blood pressure, fluid and drug administration, and diuresis).

2.4. Perioperative Management

Patients scheduled for liver resection do not receive specific preoperative measures at our center. General anesthesia is routinely induced with propofol- and sufentanil-based injection anesthesia and maintained with balanced sevoflurane inhalation anesthesia. In general, fluid restriction with euvolemia and a low-CVP strategy are anticipated, and a decrease in arterial blood pressure of >20% is avoided. There was no standard operating procedure for fluid management in patients undergoing liver resection. Therefore, the intraoperative management decisions are made by the attending anesthesiologists, with potential patient-to-patient variability in the anesthesiological management based on provider preference. In general, balanced acetate and malate-buffered Sterofundin® ISO (B. Braun, Melsungen, Germany) is used as the standard crystalloid fluid according to ERAS recommendations [1]. For colloid fluid replacement, Hemohes® 6% (B. Braun, Melsungen, Germany), Voluven® 6% (Fresenius Kabi, Germany), or gelatine solutions such as Gelafundin® ISO 40 mg mL^{-1} infusion solution (B. Braun, Melsungen, Germany) are administered. Intraoperative monitoring parameters, such as heart rate registration, invasive and non-invasive blood pressure measurements, SpO2 (% hemoglobin saturation), 5-channel echocardiogram, CVP, diuresis, estimated blood loss, and temperature (°Celsius), are used according to clinical standards. A pringle maneuver is applied on demand using an intermittent clamping strategy. Tissue dissection is usually performed mechanically using scissors or a crush-clamp technique. Hilar structures and hepatic veins are transected using vascular clamps and closed with prolene sutures. Postoperatively, patients are routinely monitored overnight in the recovery room. Depending on comorbidities, the extent of surgery, and the intraoperative course, patients may be transferred to the intermediate care unit (IMC) or intensive care unit (ICU). Patients are transferred to the regular ward the following day if there is no evidence of bleeding and hemodynamic support is not required. Pain management is based on intravenous analgesics such as metamizole and piritramid. Epidural anesthesia is not used for liver surgery.

2.5. Extent of Surgery

Liver resections involving ≤3 segments were considered minor, whereas those involving four or more segments were considered major. Major resections with additional procedures such as portal vein or bile duct resection/reconstruction were categorized as extreme liver surgery.

2.6. Intraoperative Fluid Management

Total intraoperative total fluid balance (TFB) was calculated using the following formula:

$$(\text{Crystalloid-infusion} + \text{colloid-infusion}) - (\text{estimated blood loss} + \text{diuresis}).$$

The total fluid balance was normalized for anesthesia time and patient weight (NFB).

$$\frac{(\text{Crystalloid} - \text{infusion} + \text{colloid} - \text{infusion}) - (\text{estimated blood loss} + \text{diuresis})}{\text{kilogramm bodyweight} \times \text{ansthetic time (hours)}}$$

Based on this intraoperative fluid management, patients were assigned to either a very restrictive fluid management group (<10 mL kg^{-1} h^{-1}) or a normal fluid management group (≥10 mL kg^{-1} h^{-1}) for study group characterization.

The number of intraoperatively administered red blood cell units (220–330 mL $unit^{-1}$; hematocrit: 50–70%, with a tolerated deviation of 5%) was also documented. However, administration of erythrocytes, fresh frozen plasma (FFP), and platelets was not considered, as the volume is not standardized and can vary by 25–30%.

2.7. Hemodynamics

Intraoperative blood pressure was analyzed at 5-min intervals, and hypotension was defined as a decrease in systolic arterial blood pressure below 80% of baseline. Total hypotension time was calculated for each patient based on the number and duration of hypotensive episodes. The intraoperative pharmacological vasoactive support, e.g., norepinephrine, the highest intraoperative lactate level, and the last intraoperative hemoglobin level were also recorded.

In a further step, a more sensitive hypotension limit of mean arterial pressure (MAP) ≤ 65 mmHg was established, and the influence on postoperative morbidity was investigated according to the same protocol.

2.8. Surgical Morbidity

Postoperative morbidity based on the Clavien–Dindo (CD) classification is prospectively graded and documented in the surgical unit [14]. In addition, surgical morbidity was retrospectively re-evaluated from patient records to achieve a complete assessment. Briefly, the CD-classification grades each complication according to the extent of treatment required for the treatment of that complication: grade III complications require intervention, grade IV complications require intensive care treatment, and grade V defines the death of the patient. The CD-classification was applied for postoperative respiratory, hepatic, gastrointestinal, urologic, cardiac, circulatory, and neurologic adverse events, as well as infections and delirium.

For the analysis, the highest complication was considered for each patient, and the comprehensive complication index (CCI) was calculated, as a patient may have had several complications [15].

2.9. Statistical Analysis

The data were collected and independently checked for data entry errors by four authors. Data were analyzed using the statistical software R (R Core Team 2022: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria), version 4.2.2., and presented as mean ± SD or median for continuous variables

and as frequencies and percentages for categorical variables. The primary endpoint was postoperative morbidity during hospitalization as assessed by the CD-classification (0 vs. 1–5) in any organ system. Secondary outcomes included morbidity assessed by the CCI, postoperative hospital and ICU length of stay, and in-hospital mortality. The postoperative hospital length of stay was measured from the date of surgery to hospital discharge. For the purpose of simple group comparison, patients with intraoperative NFB < 10 mL kg^{-1} h^{-1} were categorized as having received very restrictive fluid management, whereas those with ≥10 mL kg^{-1} h^{-1} were categorized as having received normal fluid management. Logistic regression was used to predict a CD sum score of >0 vs. =0 from intraoperative fluid balance as a continuous risk factor, adjusting for sex, age, extent as well as duration of surgery, crystalloid infusion, last hemoglobin-level (<10 vs. ≥10 g/dL), highest intraoperative lactate level (<1.5 vs. ≥1.5 mmol·L^{-1}), norepinephrine, red blood cell transfusion, estimated blood loss, time of relative hypotension (<100 vs. ≥100 min), and ASA physical status (I/II vs. III/IV). Linear regression modelling was used to examine intraoperative fluid management as a continuous risk factor for postoperative complications graded by the CCI, adjusting for the same set of covariates. The association of postoperative length of stay with intraoperative fluid management was analyzed using Cox regression, adjusting for the same set of covariates. For patients admitted to the ICU, the association between ICU length of stay and intraoperative fluid management was examined using Cox regression with the same set of covariates. For these analyses, all IMC and ICU days per patient were summed, whereas overnight observation in the recovery room was not considered an ICU stay. Logistic regression for in-hospital mortality used continuous intraoperative fluid balance as a risk factor, adjusting for age, extent, duration of surgery, and crystalloid infusion rates. Here, the number of possible covariates was limited by the number of observed deaths. Linear regression for the log of norepinephrine normalized to patient weight and duration of anesthesia was used to examine the association of pharmacological vasoactive support with intraoperative fluid management, controlling for age. Hypotheses regarding intraoperative fluid management as a risk factor for postoperative complications were predefined. Additional exploratory analyses were performed to examine other risk factors for postoperative surgical adverse events. Finally, subgroup analyses were performed using logistic regression models for major and extreme liver resections and for the subgroup of normal lactate levels at the end of surgery for the same endpoints.

3. Results

We identified 820 patients scheduled for liver resection during the study period, of whom 666 met the eligibility criteria for this analysis (Figure 1).

Of these, 391 patients were assigned to the very restrictive (<10 mL kg^{-1} h^{-1}) and 275 patients to the normal (≥10 mL kg^{-1} h^{-1}) groups. Patient demographics and characteristics are summarized in Table 1. The standardized mean difference of NFB between ASA groups I/II vs. III/IV is presented as Cohen's d (0.25, 95% confidence interval 0.09–0.40).

Table 1. Patients' characteristics.

Parameter	Overall	<10 mL·kg^{-1}·h^{-1}	≥10 mL·kg^{-1}·h^{-1}	*p*-Value
Study population	666	391 (58.71%)	275 (41.29%)	
Age (years, mean ± SD)	61.7 ± 12.9	61.8 ± 12.9	61.6 ± 13.1	0.71
BMI (kg/cm^2, mean ± SD)	26.8 ± 4.97	28.2 ± 4.93	24.9 ± 4.36	<0.001
ASA I–II	336 (50.5%)	176 (45.01%)	160 (58.18%)	<0.001
ASA III–IV	330 (49.5%)	215 (54.99%)	115 (41.82%)	0.031
Diagnosis				
Hepatocellular carcinoma (HCC)	123 (18.5%)	72 (18.4%)	51 (18.5%)	
Hepatic adenocarcinoma	26 (3.9%)	16 (4.1%)	10 (3.6%)	
Extrahepatic Cholangiocarcinoma (CCC)	62 (9.3%)	48 (12.3%)	14 (5.1%)	

Table 1. *Cont.*

Parameter	Overall	<10 mL·kg^{-1}·h^{-1}	≥10 mL·kg^{-1}·h^{-1}	*p*-Value
Intrahepatic Cholangiocarcinoma (CCC)	67 (10%)	39 (10.0%)	28 (10.2%)	
Colorectal metastases	290 (43.5%)	165 (42.2%)	125 (45.5%)	
Others	98 (14.7%)	51 (13.0%)	47 (17.1%)	
Extent of surgery				
Minor liver resections	430 (64.6%)	238 (60.87%)	192 (69.82%)	0.031
Major liver resections	96 (14.4%)	58 (14.83%)	38 (13.82%)	
Extreme liver resections	140 (21.0%)	95 (24.3%)	45 (16.36%)	
Duration of surgery (h, mean ± SD)	4.29 ± 1.77	4.7 ± 1.81	3.71 ± 1.54	<0.001
Anesthesia time (h, mean ± SD)	5.78 ± 1.85	6.2 ± 1.91	5.2 ± 1.6	<0.001
Estimated blood loss (ml, mean ± SD)	1188 ± 1011	1127 ±910	1200 ± 1031	<0.001
Red blood cell transfusion	175 (26.3%)	27 (24.32%)	148 (26.67%)	0.012
Total Norepinephrine (µg/kg ×min, mean ± SD)	0.0416 ± 0.0408	0.040 ± 0.0381	0.043 ± 0.0444	0.64
Maximum Lactate (mmol/L, mean ± SD)	2.16 ± 1.37	2.33 ± 1.5	1.93 ± 1.13	<0.001
Last Hemoglobin (g/dL, mean ± SD)	10.7 ± 1.79	10.9 ± 1.84	10.5 ± 1.7	0.011
Time of relative hypotension † (min, mean ± SD)	138 ± 120	154 ± 126	116 ± 106	<0.001
Sterofundin (ml·kg^{-1}·h^{-1}, mean ± SD)	15 ± 6.13	11.9 ± 3.56	19.5 ± 6.22	<0.001
Total Sterofundin volume (mL, min.–max.)		4000 (1100–14500)	4500 (1500–24000)	0.015
Clavien-Dindo = 0	318 (47.75%)	170 (43.48%)	148 (53.82%)	
Clavien-Dindo > 0	348 (52.25%)	221 (56.52%)	127 (46.18%)	
CCI-Score (mean ± SD)	23.8 ± 26.0	26.4 ± 26.6	20.1 ± 24.9	
Postoperative hospital LOS (days, mean ± SD)	16.2 ± 15.0	17.5 ± 16.5	14.2 ± 12.3	
ICU LOS (days, mean ± SD)	2.96 ± 5.52	3.16 ± 5.99	2.64 ± 4.68	
In-hospital mortality	30 (4.5%)	20 (5.1%)	10 (3.64%)	

BMI: body mass index; LOS: length of stay; SD: standard deviation; † Relative hypotension: ≤80% baseline systolic arterial blood pressure. Minor liver resection: ≤3 segments; major liver resection: ≥4 segments; extreme liver resection: major resections with additional procedures).

Most resections involved less than four segments (minor), and one third of the resections were major/extreme resections (35.5%).

The duration of surgery, postoperative hospital length of stay (Figure 2a), and ICU length of stay (Figure 2b) gradually increased with the extent of liver surgery.

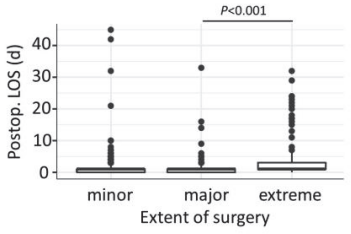
3.1. Intraoperative Circulatory Parameters and Fluid Management

In general, older patients required higher doses of norepinephrine ($p = 0.001$) than younger patients. In addition, higher blood loss was associated with higher norepinephrine doses ($p < 0.001$).

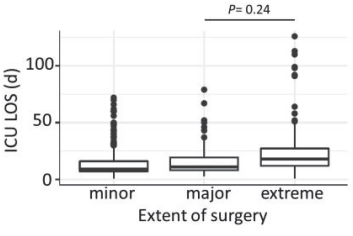
The mean intraoperative NFB was 9.77 ± 5.24 mL kg^{-1} h^{-1} and ranged from −2.71 to 57.4 mL kg^{-1} h^{-1}. NFB gradually decreased with the extent of surgery and was associated with blood loss ($p < 0.001$). Intraoperative NFB showed only an insignificant ($p = 0.86$) association with pharmacological vasoactive support.

A higher NFB was mainly due to a higher crystalloid infusion (19.5 ± 6.22 mL kg^{-1} h^{-1}) compared to patients in the very restrictive group (11.9 ± 3.56 mL kg^{-1} h^{-1}) (Table 1, Figure 3).

Patients in the normal group received 4500 mL (1500–24,000 mL) of crystalloids, in contrast to 4000 mL (1100–14,500 mL) in the very restrictive group. The total crystalloid infusion rate gradually increased with the extent of surgery, with minor liver resections receiving 2723 mL (−600–8700 mL), major resections receiving 3203 mL (100–8100 mL), and extreme resections receiving the highest with 3884 mL (−500–13,000 mL, $p = 0.09$).



(**a**)



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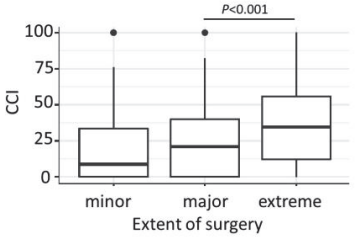

(**c**)

Figure 2. Subgroup analysis on extent of surgery: (**a**) Hospital length of stay (LOS) and extent of surgery; (**b**) ICU length of stay (LOS) and extent of surgery; (**c**) Comprehensive complication index (CCI) and extent of surgery.

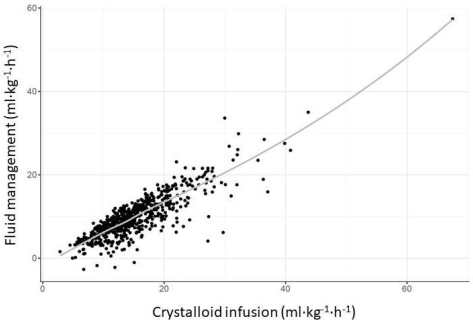

Figure 3. Association between NFB and crystalloid infusion. NFB was mainly based on crystalloid infusion, with a positive correlation between the two values.

3.2. Hospital Stay

The median postoperative hospital length of stay for the entire cohort of patients was 11 days (1–126 days), and 393/666 (59.9%) of patients required an ICU stay during the post-operative period for a median of 1 day (range 1–45 days).

The extent ($p < 0.001$) and duration of liver surgery ($p < 0.001$) were associated with a longer hospital length of stay. While higher total ($p = 0.004$) and NFB ($p < 0.001$, Table 2) were associated with a shorter hospital length of stay, higher volumes of crystalloid infusions ($p = 0.004$) were associated with a longer hospital length of stay (Table 3).

Table 2. Odds Ratios for NFB in logistic regression models and hazard ratios for NFB in Cox regression models.

Endpoints	Odds Ratio	95% CI	*p*-Value
Clavien-Dindo classification >/= 0	1.0	0.97–1.04	0.89
Mortality	0.88	0.78–0.98	0.02
	Hazard Ratio	**95% CI**	***p*-value**
Postoperative hospital LOS	1.05	1.02–1.09	<0.001
ICU LOS	1.04	1.00–1.08	0.035

CI: Confidence Interval; ICU: Intensive Care Unit; LOS: length of stay (Models for Clavien-Dindo classification >/= 0, postoperative LOS and ICU LOS adjusted for sex, age, extent as well as duration of surgery, crystalloid infusion, last hemoglobin-level (<10 vs. ≥10 g/dL), highest intraoperative lactate level (<1.5 vs. ≥1.5 mmol·L^{-1}), norepinephrine, red blood cell transfusion, estimated blood loss, time of relative hypotension (<100 vs. ≥100 min), and ASA physical status (I/II vs. III/IV) Mortality model adjusted for age, extent as well as duration of surgery, and crystalloid infusion).

Table 3. Predictive factors (Hazard Ratios) in Cox regression models for postoperative hospital and ICU stays.

Intraoperative Parameters	Hazard Ratio	95% CI	*p*-Value
Postoperative hospital LOS			
Extent of surgery	0.66	0.52–0.84	<0.001
Duration of surgery	0.79	0.75–0.84	<0.001
Total Fluid balance (TFB)	1.15	1.05–1.26	0.004
Normalized fluid balance (ml kg^{-1} h^{-1}) (NFB)	1.053	1.02–1.09	<0.001
Crystalloid infusion	0.88	0.81–0.96	0.004
ICU LOS			
Intraoperative lactate	0.72	0.56–0.92	0.008
Duration of surgery	0.85	0.8–0.92	<0.002
Normalized fluid balance (ml kg^{-1} h^{-1}) (NFB)	1.04	1.003–1.08	0.035

CI: Confidence Interval; ICU: Intensive Care Unit; LOS: length of stay (All models adjusted for Clavien-Dindo classification >/= 0, postoperative LOS and ICU LOS adjusted for adjusting for sex, age, extent as well as duration of surgery, crystalloid infusion, last hemoglobin-level (<10 vs. ≥10 g/dL), highest intraoperative lactate level (<1.5 vs. ≥1.5 mmol·L^{-1}), norepinephrine, red blood cell transfusion, estimated blood loss, time of relative hypotension (<100 vs. ≥100 min), and ASA physical status (I/II vs. III/IV)).

3.3. ICU Stay

Higher intraoperative lactate levels ($p = 0.008$), a shorter duration of surgery ($p < 0.002$), and a lower NFB ($p = 0.035$, Table 2) were associated with a longer ICU length of stay (Table 3).

3.4. Postoperative Morbidity

Regarding post-operative morbidity, approximately half of the patients (52.25%) had a post-operative complication, the majority of which were grade III (21.5%). The median CCI was 20.9.

The extent ($p < 0.001$) and duration of surgery ($p < 0.001$) were associated with morbidity: the median CCI gradually increased with the extent of surgery, as minor liver resections

had a mean CCI of 18.5 (0–100), whereas major and extreme resections had median CCIs of 23.6 (0–100) and 40.3 (0–100), respectively (Figure 2C).

Increased intraoperative lactate levels ($p < 0.001$, Figure 4), red blood cell transfusion ($p < 0.001$), estimated blood loss ($p < 0.001$), and intraoperative vasoactive support with norepinephrine ($p = 0.02$) were associated with higher morbidity. We found no association of morbidity with the last intraoperative hemoglobin level ($p = 0.022$), the time of relative hypotension ($p = 0.29$), or intraoperative NFB ($p = 0.89$) (Table 4).

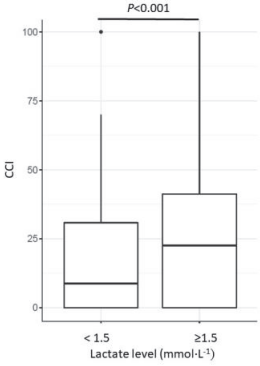

Figure 4. Association of intraoperative lactate levels and surgical morbidity (CCI). Patients with higher lactate levels revealed higher morbidity, according to the CCI ($p < 0.001$).

Table 4. Association of clinical parameters with the comprehensive complication index (CCI) and mortality from linear regression models.

Exploratory Risk Factor	Estimate	t Value	*p*-Value
Morbidity			
Age	0.34	4.77	<0.001
Sex	−1.81	−0.95	0.343
Red blood cell transfusion	2.70	6.02	<0.001
Estimated blood loss	5.41	5.14	<0.001
Relative Hypotension	0.009	1.06	0.29
Lactate	2.59	3.54	<0.001
Norepinephrine (µg kg^{-1} min^{-1})	53.14	2.34	0.02
Duration of surgery	5.19	8.47	<0.001
Hb last	−1.24	−2.30	0.022
	Odds Ratio	**95% CI**	***p*-value**
Mortality			
Age	1.03	0.99–1.06	0.119
Extent of surgery	4.94	2.21–12.12	<0.001
Total fluid balance (TFB)	1.23	1.03–1.24	0.01
Normalized fluid balance (NFB)	0.88	0.78–0.98	0.023

Hb, Hemoglobin; CI, Confidence Interval.

3.5. Mortality

Overall, 30 of the 666 (4.5%) patients died. As expected, major/extreme liver resections were associated with a higher mortality rate ($p < 0.001$). Interestingly, a very low NFB was also associated with a higher mortality rate ($p = 0.023$) compared to the total population in the study ($p = 0.02$, Table 2).

3.6. Hypotension

Additionally, after applying a MAP ≤65 mmHg as the cut-off for hypotension in the regression analysis, we did not find a significant association with postoperative complications as measured by the CD score ($p = 0.10$).

In this analysis, we found a significant association between NFB and CD score ($p = 0.026$). Again, NFB and CCI were not significantly associated ($p = 0.23$).

Moreover, NFB was again significantly associated with perioperative mortality ($p = 0.023$) and length of hospital stay ($p = 0.0057$). However, the length of the ICU stay was no longer significantly associated with NFB.

3.7. Subgroup Analyses

3.7.1. Major/Extreme Liver Resections

As we expected the fluid strategy to be most relevant to the outcome of major/extreme liver resections, we performed subgroup analyses by excluding minor liver resections.

The median CCI of the major/extreme resections (n = 236) was 33.5 (0–100), with a mortality rate of 9.3%.

In major/extreme liver resections, patient age ($p = 0.002$), duration of surgery ($p < 0.002$), as well as very low total ($p = 0.028$), NFB ($p = 0.025$), and crystalloid fluid supplementation ($p = <0.0001$), were associated with a higher CCI. In this subgroup of patients, the highest lactate level ($p = 0.007$), the dose of norepinephrine ($p = 0.004$), the amount of blood loss ($p = 0.003$), and red blood cell transfusions ($p < 0.001$) were also associated with the CCI.

For the other parameters, the duration of surgery ($p = 0.01$) and the use of crystalloids ($p = 0.02$) were associated with a longer hospital length of stay.

In contrast to the overall cohort, only the duration of surgery ($p < 0.0001$) was an independent factor associated with a longer ICU length of stay in this subgroup analysis.

Regarding mortality, only the use of crystalloids was significantly associated with mortality ($p = 0.01$).

3.7.2. Normal Serum Lactate Levels

We found an association between a very low TFB and a longer postoperative hospital length of stay, a longer ICU LOS, and a higher postoperative mortality rate. To analyze whether our general fluid management may have been too restrictive, and hypovolemia is often associated with elevated lactate levels, we excluded patients with elevated lactate levels and focused on patients with normal serum lactate levels (<2.5 mmol L^{-1}).

In this subgroup of 471 patients, the mortality rate was 2.1% (10/471).

Neither morbidity nor ICU length of stay were associated with NFB or crystalloid balance in this subgroup. We only found a longer hospital length of stay following liberal fluid management ($p = 0.01$) in this subgroup. In addition, duration of surgery remained a significant factor for morbidity ($p < 0.001$), length of hospital stay ($p < 0.001$), and ICU ($p < 0.001$) stay.

Due to the very low mortality rate, we could not perform regression analyses for potential risk factors for mortality.

4. Discussion

Intraoperative fluid management has changed dramatically over the past 20 years, with increasing evidence that fluid overload increases surgical morbidity and mortality. This effect has been demonstrated for several surgical procedures, most notably colorectal surgery, and many studies suggest that restrictive fluid management is advantageous over liberal fluid management in various surgical specialties [12,16]. Yet, very restrictive fluid management may also harm patients due to hypovolemia and its consequences [17]. As the evidence for fluid restriction in liver surgery is not yet well studied, we analyzed the outcomes of patients undergoing liver surgery at our center, where low-CVP and restrictive fluid management had been adopted.

Among 666 liver resections, we found no difference between the very restrictive and the normal fluid management groups in terms of postoperative morbidity, as determined by the CD-classification and the CCI. However, very restrictive fluid management was associated with a longer postoperative hospital and ICU length of stay and a higher postoperative mortality rate. In addition, increased lactate levels, higher doses of norepinephrine, the duration and extent of surgery, as well as red blood cell transfusion and estimated blood loss, were associated with the incidence of adverse events. In contrast, the last measured hemoglobin level and cumulative time of relative hypotension were not.

The effect of fluid therapy on postoperative morbidity increased in major/extreme procedures compared to the overall study population. Here, very low total and NFB levels and crystalloid fluid supplementation were associated with higher morbidity.

Subgroup analysis of patients with normal serum lactate levels showed that NFB and crystalloid administration were not associated with morbidity or ICU length of stay in this group.

The substantial sample size allowed for taking into account several potential confounders as covariates in the regression models, such as ASA status, age, sex, and, where appropriate, duration and size of intervention. These confounders are also known risk factors for postoperative complications that are also associated with postoperative intensive care [18]. Other patient- and intervention-specific risk factors were eliminated by applying exclusion criteria.

When statistically comparing baseline characteristics between the two fluid management groups, the large sample size must be taken into account. Here, statistical significance may result from differences that are small from a clinical perspective but can be demonstrated with high statistical power. In contrast to previous studies, intraoperative hypotension was not associated with morbidity in our series [19,20]. Hypotension was defined as a decrease in systolic blood pressure to <80% of baseline. As described by Sessler et al. [21] and Wesselink et al. [20], there is currently no consistent definition of hypotension in the literature. Our relative threshold for hypotension corresponds to the anaesthesiological intraoperative target in non-cardiovascular, non-cardiosurgical patients at our center and is one of the most commonly used thresholds in the literature. Due to the aforementioned variability in the definition of hypotension, we performed a further, more sensitive analysis using a cut-off of MAP $\leq$ 65 mmHg. Again, no significant association with postoperative CCI was found in these models. The CCI is more relevant than the individual complications scored by the CD score alone, as it includes all complications and reflects their severity.

Furthermore, a small, randomized trial of 48 patients undergoing major liver resection showed no difference in morbidity between goal-directed (restrictive) and the normal (liberal) fluid management regimen as assessed by CD-classification [22]. Unfortunately, the thresholds for both fluid management systems are not comparable to ours. In addition, this study may have been underpowered to detect such differences.

Postoperative surgical complications have a major impact on patients' disability-free survival, increase costs, and are a major burden on the healthcare system [23–25]. The prevention of perioperative morbidity is therefore of paramount importance. However, objective assessment of surgical morbidity remains a challenge. The European Perioperative Clinical Outcome (EPCO) definitions [26] recommend the CD-classification [14] as the preferred grading system for individual adverse events due to its clear methodology and definitions: this classification scores the severity of complications according to their therapeutic consequences. Even with this classification, the complete assessment of surgical morbidity in the daily routine remains difficult, despite all efforts at standardization [27]. At least complications requiring intervention (°III-IV) can be reliably assessed, as most of these procedures are usually documented. The CD-classification is also the standard classification system used by the Department of General, Visceral, and Transplantation Surgery at the University Medical Centre of Mainz. In addition, we used the comprehensive complication index (CCI), which summarizes all complications of an individual patient according to the CD-classification and provides a continuous value between 0 and 100 as

the worst (fatal) outcome. Hospital length of stay and mortality are objective parameters that can always be analyzed retrospectively. Due to their clinical importance, we chose morbidity, mortality, and hospital and ICU length of stay as endpoints for this analysis.

As expected, the extent and duration of surgery were independent risk factors for postoperative adverse events. Although we excluded procedures lasting less than 70 min, the effect of "frontloading" cannot be precluded: shorter procedures are associated with higher relative fluid doses as they are given during the induction period. This assumption is supported by higher crystalloid infusion rates in shorter procedures. In addition to intraoperative parameters, comorbidities and postoperative management may influence surgical morbidity. Due to the study design, we cannot completely exclude the effect of such parameters on our results.

With a CCI of 20.9 and a mortality rate of 4.5%, our results are well comparable with other large series on the outcome of liver surgery [28] and superior to the reported outcome in Germany [29], mainly due to the high degree of specialization and volume of the center.

Furthermore, the exclusion of high-risk patients by subgroup analysis suggests that optimization of perioperative management further improves outcomes. In our center, we have generally adopted a restrictive fluid policy, using mainly crystalloids for fluid replacement as recommended by the ERAS society [1]. In addition, patient blood management is being increasingly implemented, resulting in lower transfusion rates and increasing crystalloid infusions.

Moreover, these data should support a less dogmatic fluid management strategy in liver surgery. The aim of intraoperative fluid management is to support the surgical strategy of minimizing blood loss by reducing CVP, as this is a well-established outcome parameter in liver surgery [30]. Accordingly, avoiding fluid overload by restricting fluid infusion is beneficial, which is particularly evident in laparoscopic liver surgery, where a very restrictive fluid strategy is indeed anticipated by most surgeons in order to maintain a dry surgical field [31]. However, sudden events can dramatically destabilize a "dry" patient and place the patient at a particular risk during liver surgery.

The complex relationship between fluid administration and morbidity has been described as a U-shape, with the lowest morbidity in normovolemia and increased morbidity in hypo- and hypervolemia [13,17]. Our results support this U-shape hypothesis: after excluding patients with elevated lactate levels, fluid management was no longer associated with the endpoints of this analysis, and outcome was only related to the extent of surgery.

A wide range and variability in fluid management among patients undergoing liver resection have been shown to be multifaceted and influenced by factors at the patient, surgical, and provider levels [32]. Considering these general measures, only a very few patients met the criteria for a very liberal fluid replacement policy, and the vast majority would fit into the moderate range, while obviously some also met the very restrictive criteria proposed by Shin et al. [13]. Moreover, our fluid management is much lower than that reported by others [32].

Therefore, a more sophisticated strategy is required, and several parameters have been proposed to optimize intraoperative fluid management. However, the ideal parameters for optimal fluid management have not yet been identified. Moreover, calculated fluid balances between centers and publications are difficult to compare since different parameters have been included. In addition, some authors report total fluid administration or a total fluid balance, while others normalize for body weight and/or duration of anesthesia. Consequently, the crude parameters are difficult to compare. We provide a range of parameters that all demonstrate the same associations with our endpoints. Still, intraoperative fluid loss due to perspiration and blood, platelet, or fresh frozen plasma resuscitation has not been included in our fluid management due to the wide variation in volume included and the study design.

Serum lactate is a surrogate parameter for impaired tissue perfusion and a widely used outcome indicator in critically ill patients. Our data are consistent with the findings of Wiggans et al. [33].

The current trend in abdominal surgery is shifting towards goal-directed fluid management [34]. In liver surgery, the data are limited, and our work contributes to the re-evaluation of overly restrictive fluid management and a goal-directed strategy aiming at low euvolemia and restriction by normative lactate. The threshold of 10 mL kg^{-1} h^{-1} to define fluid management groups was based on heuristics and should be regarded as exploratory. Future studies will need to assess whether end-point-specific thresholds or possibly non-linear dose–response models for continuous fluid management better reflect the underlying mechanisms.

Due to the association between elevated lactate levels and outcomes, we are now using this parameter more intensively to control fluid management. Each center should decide on its own individual strategy to avoid peripheral hypoperfusion due to hypovolemia. Blood transfusions should also be used with caution in major liver resections, given the association with morbidity in our series.

Our study has several limitations. First, our study is retrospective, which limits our ability to control for confounding variables such as patient lifestyle factors and treatment compliance. These factors may have influenced the results we observed.

Second, our study was conducted at a single center, which may limit the generalizability of our findings.

Thirdly, we relied on electronic medical records to collect data on patient outcomes and intraoperative anesthetic management, so missing or incomplete information cannot be completely ruled out.

Finally, despite the large sample size of 666 patients, no power calculation was performed prior to the study, which may limit the statistical power of our findings.

5. Conclusions

In this retrospective study, the influence of intraoperative fluid management on postoperative morbidity in 666 patients undergoing liver surgery was assessed using the CD-score and CCI. Low NFB was associated with longer hospital and ICU lengths of stay and higher mortality. In the major extreme procedure subgroup, low NFB was associated with increased postoperative morbidity. In patients with normal lactate levels, there was no association between fluid management and morbidity.

Our results suggest that fluid management in liver surgery requires a more sophisticated approach to optimal fluid administration. Our study provides important insights into the relationship between fluid management and postoperative outcome in liver surgery and adds to the scarce literature in this area. Due to the apparent impact of intraoperative fluid management, further research in this area is required. Large-scale, standardized, preferably prospective, randomized controlled trials in patients undergoing liver surgery are needed to define the ideal parameter for fluid assessment and optimal intraoperative fluid management. Future standards should be based on the size of the procedure.

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Informed Consent Statement: Patient consent was waived due to the retrospective design of the study.

Data Availability Statement: The data, as well as the study protocol, are available from the authors upon request.

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References

1. Melloul, E.; Hübner, M.; Scott, M.; Snowden, C.; Prentis, J.; Dejong, C.H.; Garden, O.J.; Farges, O.; Kokudo, N.; Vauthey, J.N.; et al. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J. Surg.* **2016**, *40*, 2425–2440. [CrossRef] [PubMed]
2. Hughes, M.J.; Ventham, N.T.; Harrison, E.M.; Wigmore, S.J. Central venous pressure and liver resection: A systematic review and meta analysis. *HPB* **2015**, *17*, 863–871. [CrossRef] [PubMed]
3. Belghiti, J.; Noun, R.; Malafosse, R.; Jagot, P.; Sauvanet, A.; Pierangeli, F.; Marty, J.; Farges, O. Continuous versus intermittent portal triad clamping for liver resection: A controlled study. *Ann. Surg.* **1999**, *229*, 369–375. [CrossRef] [PubMed]
4. Heinrich, S.; Baumgart, J.; Mittler, J.; Lang, H. Vascular reconstruction in hepatic surgery. *Chirurg* **2016**, *87*, 100–107. [CrossRef]
5. Jones, R.M.; Moulton, C.E.; Hardy, K.J. Central venous pressure and its effect on blood loss during liver resection. *Br. J. Surg.* **1998**, *85*, 1058–1060. [CrossRef]
6. Mungroop, T.H.; Geerts, B.F.; Veelo, D.P.; Pawlik, T.M.; Bonnet, A.; Lesurtel, M.; Reyntjens, K.M.; Noji, T.; Liu, C.; Jonas, E.; et al. Fluid and pain management in liver surgery (MILESTONE): A worldwide study among surgeons and anesthesiologists. *Surgery* **2019**, *165*, 337–344. [CrossRef]
7. Voldby, A.W.; Brandstrup, B. Fluid therapy in the perioperative setting—A clinical review. *J. Intensive Care* **2016**, *4*, 27. [CrossRef]
8. Siemionow, K.; Cywinski, J.; Kusza, K.; Lieberman, I. Intraoperative fluid therapy and pulmonary complications. *Orthopedics* **2012**, *35*, e184–e191. [CrossRef]
9. Kendrick, J.B.; Kaye, A.D.; Tong, Y.; Belani, K.; Urman, R.D.; Hoffman, C.; Liu, H. Goal-directed fluid therapy in the perioperative setting. *J. Anaesthesiol. Clin. Pharmacol.* **2019**, *35* (Suppl. 1), S29–S34.
10. Futier, E.; Constantin, J.M.; Petit, A.; Chanques, G.; Kwiatkowski, F.; Flamein, R.; Slim, K.; Sapin, V.; Jaber, S.; Bazin, J.E. Conservative vs restrictive individualized goal-directed fluid replacement strategy in major abdominal surgery: A prospective randomized trial. *Arch. Surg.* **2010**, *145*, 1193–1200. [CrossRef]
11. Zhang, J.; Qiao, H.; He, Z.; Wang, Y.; Che, X.; Liang, W. Intraoperative fluid management in open gastrointestinal surgery: Goal-directed versus restrictive. *Clinics* **2012**, *67*, 1149–1155. [CrossRef] [PubMed]
12. Nisanevich, V.; Felsenstein, I.; Almogy, G.; Weissman, C.; Einav, S.; Matot, I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology* **2005**, *103*, 25–32. [CrossRef] [PubMed]
13. Shin, C.H.; Long, D.R.; McLean, D.; Grabitz, S.D.; Ladha, K.; Timm, F.P.; Thevathasan, T.; Pieretti, A.; Ferrone, C.; Hoeft, A.; et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes: A Hospital Registry Study. *Ann. Surg.* **2018**, *267*, 1084–1092. [CrossRef]
14. Dindo, D.; Demartines, N.; Clavien, P.A. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* **2004**, *240*, 205–213. [CrossRef] [PubMed]
15. Clavien, P.A.; Vetter, D.; Staiger, R.D.; Slankamenac, K.; Mehra, T.; Graf, R.; Puhan, M.A. The Comprehensive Complication Index (CCI®): Added Value and Clinical Perspectives 3 Years "Down the Line". *Ann. Surg.* **2017**, *265*, 1045–1050. [CrossRef] [PubMed]
16. Adesanya, A.; Rosero, E.; Timaran, C.; Clagett, P.; Johnston, W.E. Intraoperative fluid restriction predicts improved outcomes in major vascular surgery. *Vasc. Endovascular. Surg.* **2008**, *42*, 531–536. [CrossRef] [PubMed]
17. Bellamy, M.C. Wet, dry or something else? *Br. J. Anaesth.* **2006**, *97*, 755–757. [CrossRef]
18. Onwochei, D.N.; Fabes, J.; Walker, D.; Kumar, G.; Moonesinghe, S.R. Critical care after major surgery: A systematic review of risk factors for unplanned admission. *Anaesthesia* **2020**, *75* (Suppl. 1), e62–e74. [CrossRef]
19. Walsh, M.; Devereaux, P.J.; Garg, A.X.; Kurz, A.; Turan, A.; Rodseth, R.N.; Cywinski, J.; Thabane, L.; Sessler, D.I. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. *Anesthesiology* **2013**, *119*, 507–515. [CrossRef]
20. Wesselink, E.M.; Kappen, T.H.; Torn, H.M.; Slooter, A.J.C.; Van Klei, W.A. Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. *Br. J. Anaesth.* **2018**, *121*, 706–721. [CrossRef]
21. Sessler, D.I.; Bloomstone, J.A.; Aronson, S.; Berry, C.; Gan, T.J.; Kellum, J.A.; Plumb, J.; Mythen, M.G.; Grocott, M.P.; Edwards, M.R.; et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br. J. Anaesth.* **2019**, *122*, 563–574. [CrossRef] [PubMed]
22. Weinberg, L.; Ianno, D.; Churilov, L.; Mcguigan, S.; Mackley, L.; Banting, J.; Shen, S.H.; Riedel, B.; Nikfarjam, M.; Christophi, C. Goal directed fluid therapy for major liver resection: A multicentre randomized controlled trial. *Ann. Med. Surg.* **2019**, *45*, 45–53. [CrossRef] [PubMed]
23. Jencks, S.F.; Williams, M.V.; Coleman, E.A. Rehospitalizations among patients in the Medicare fee-for-service program. *N. Engl. J. Med.* **2009**, *14*, 1418–1428. [CrossRef]

24. Vonlanthen, R.; Slankamenac, K.; Breitenstein, S.; Puhan, M.A.; Muller, M.K.; Hahnloser, D.; Hauri, D.; Graf, R.; Clavien, P.A. The impact of complications on costs of major surgical procedures: A cost analysis of 1200 patients. *Ann. Surg.* **2011**, *254*, 907–913. [CrossRef] [PubMed]
25. Selby, L.V.; Gennarelli, R.L.; Schnorr, G.C.; Solomon, S.B.; Schattner, M.A.; Elkin, E.B.; Bach, P.B.; Strong, V.E. Association of Hospital Costs with Complications Following Total Gastrectomy for Gastric Adenocarcinoma. *JAMA Surg.* **2017**, *152*, 953–958. [CrossRef] [PubMed]
26. Jammer, I.B.; Wickboldt, N.; Sander, M.; Smith, A.; Schultz, M.J.; Pelosi, P.; Leva, B.; Rhodes, A.; Hoeft, A.; Walder, B.; et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur. J. Anaesthesiol.* **2015**, *32*, 88–105.
27. Dindo, D.; Hahnloser, D.; Clavien, P.A. Quality assessment in surgery: Riding a lame horse. *Ann. Surg.* **2010**, *251*, 766–771.
28. Breitenstein, S.; DeOliveira, M.L.; Raptis, D.A.; Slankamenac, K.; Kambakamba, P.; Nerl, J.; Clavien, P.A. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. *Ann. Surg.* **2010**, *252*, 726–734. [CrossRef]
29. Filmann, N.; Walter, D.; Schadde, E.; Bruns, C.; Keck, T.; Lang, H.; Oldhafer, K.; Schlitt, H.J.; Schön, M.R.; Herrmann, E.; et al. Mortality after liver surgery in Germany. *Br. J. Surg.* **2019**, *106*, 1523–1529. [CrossRef]
30. Margonis, G.A.; Kim, Y.; Samaha, M.; Buettner, S.; Sasaki, K.; Gani, F.; Amini, N.; Pawlik, T.M. Blood loss and outcomes after resection of colorectal liver metastases. *J. Surg. Res.* **2016**, *202*, 473–480. [CrossRef]
31. Heinrich, S.; Mittler, J.; Tripke, V.; Lang, H. Technische Aspekte der laparoskopischen Leberchirurgie. *Chirurg* **2018**, *89*, 984–992. [CrossRef] [PubMed]
32. Kim, Y.; Ejaz, A.; Gani, F.; Wasey, J.O.; Xu, L.; Frank, S.M.; Pawlik, T.M. Crystalloid administration among patients undergoing liver surgery: Defining patient- and provider-level variation. *Surgery* **2016**, *159*, 389–398. [CrossRef] [PubMed]
33. Wiggans, M.G.; Starkie, T.; Shahtahmassebi, G.; Woolley, T.; Birt, D.; Erasmus, P.; Anderson, I.; Bowles, M.J.; Aroori, S.; Stell, D.A. Serum arterial lactate concentration predicts mortality and organ dysfunction following liver resection. *Perioper. Med.* **2013**, *2*, 21. [CrossRef] [PubMed]
34. Sun, Y.; Chai, F.; Pan, C.; Romeiser, J.L.; Gan, T.J. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery—A systematic review and meta-analysis of randomized controlled trials. *Crit. Care* **2017**, *21*, 141. [CrossRef] [PubMed]

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Conscious Sedation Methods for Blepharoplasty in Day Surgery

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Abstract: Midazolam and fentanyl, in combination, are the most commonly used medications for conscious sedation in day aesthetic surgeries. Dexmedetomidine is popularly used in the sedation protocol of our hospital due to its reduced respiratory depression. However, its sedation benefits in facial aesthetic surgeries, like blepharoplasty, have not been well-evaluated. We retrospectively compared individuals sedated with midazolam and fentanyl bolus injection (N = 137) and those sedated with dexmedetomidine infusion (N = 113) to determine which is more suitable for blepharoplasty with a mid-cheek lift. The total amount of local anesthetic ($p < 0.001$), postoperative pain ($p = 0.004$), ketoprofen administration ($p = 0.028$), and the number of hypoxia episodes ($p < 0.001$) and intraoperative hypertension ($p = 0.003$) were significantly lower in the dexmedetomidine group. Hypoxia severity ($p < 0.001$) and minor hematoma formation ($p = 0.007$) were also significantly lower in the dexmedetomidine group. Sedation with dexmedetomidine infusion is associated with less hematoma formation than sedation with midazolam and fentanyl bolus pattern due to hemodynamic stability and analgesic effects. Dexmedetomidine infusion may be a good alternate sedative for lower blepharoplasty.

Keywords: blepharoplasty; dexmedetomidine; conscious sedation; hematoma; aesthetic surgery

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1. Introduction

Blepharoplasty is the most popular cosmetic surgery in South Korea, and its demand is increasing yearly worldwide. Anatomically, the eyelids are composed of a very thin dermis and little subcutaneous fat [1]. Opening the eyes and the eyelid shape are profoundly affected by swelling during or after surgery, which could increase the patient's discomfort, decrease operation satisfaction, and delay recovery to daily life [2]. Blepharoplasty success depends on the minimization of swelling during the intraoperative and immediate postoperative periods.

Insufficient pain management increases blood pressure and the risk of postoperative ecchymosis, hematoma, and swelling [3]. Additionally, hematomas increase the likelihood of intraoperative and immediate postoperative swelling. Hematomas can have negative consequences in facial surgery, leading to scarring and increasing the chances of infection, facial edema, skin hyperpigmentation, neuropraxia, and prolonged recovery [4,5]. Specifically, hematomas can cause long-standing "knots", contour irregularities, and puckering under the skin. Plastic surgeons must consider sedation that minimizes swelling and hematoma formation.

Several studies have reported that there may be a relationship between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the incidence of hematomas [6,7]. Considering that NSAIDs could increase the tendency to bleed, a decrease in the use of NSAIDs may reduce the formation of postoperative hematomas. We reviewed a total of 419 patients who underwent lower blepharoplasty with a mid-cheek lift under sedation anesthesia between 2018 and 2022, to determine which sedation method is more suitable for lower blepharoplasty and a mid-cheek lift.

2. Materials and Methods

2.1. Materials

The study protocol was approved by our Institutional Review Board (approval number: 2021AS0004). This study was conducted per the principles of the Declaration of Helsinki. We retrospectively reviewed the medical records of 419 patients who underwent lower blepharoplasty with mid-cheek lift at our institution between March 2018 and May 2022. Lower eyelid and midface rejuvenation was performed in patients who wanted to improve infraorbital hollowness, tear trough deformity, and lower lid fat bulging. We evaluated the operation time, intraoperative airway depression, pain visual analog scale (VAS) score, amount of local anesthetic injected, length of stay in the post-anesthesia care unit (PACU), and surgical details using medical charts. Of the 419 patients, those who met the following inclusion criteria were included: (a) primary lower blepharoplasty or midface lift; (b) American Society of Anesthesiologists (ASA) physical status classification $\leq$ II; (c) no recent drug history of anticoagulants, opioid analgesics, or herbal medicine; and (d) patients who wanted to undergo conscious sedation in day surgery. We obtained informed consent from all patients.

2.2. Sedation Regimens

Anesthesiologists performed all of the sedations. The sedation protocol subgroups were categorized as (a) bolus fashion using midazolam with or without fentanyl (N = 137; conventional group) and (b) continuous fashion using dexmedetomidine hydrochloride (N = 113; dexmedetomidine group). Oxygen was supplied through nasal prongs during surgery in both groups. At a flow rate of 2–5 L/min, oxygen was administered, and following the application of an aseptic drape, the sterilized nasal prongs were opened and taped securely in place with the intention of preventing contact with the operative site of the blepharoplasty.

2.3. Sedation Protocols

2.3.1. Bolus Fashion Using Midazolam and Fentanyl: The Conventional Method

Patients in the midazolam/fentanyl group received midazolam (0.05 mg/kg or 5 mg) and fentanyl (0.5–1.5 μg/kg), injected as a bolus before the incision. Midazolam was titrated in 1 mg/bolus increments until the patient was visibly relaxed but responsive (maximum midazolam dose: 5 mg). Fentanyl was titrated in 25 μg/bolus injections before surgical incision, and 25 μg/bolus increments were utilized when patients could not tolerate pain or had a VAS score $\geq$ 4. The interval between the bolus doses was 5 min (maximum fentanyl dose: 1.5 μg/kg). 100 mg of ketoprofen (maximum dose, 300 mg/day) was administered, or more local anesthetics were infiltrated when the maximum fentanyl dose was administered (1.5 μg/kg).

2.3.2. Continuous Fashion Using Dexmedetomidine

Patients in the dexmedetomidine group (Precedex; Pfizer, New York, NY, USA) received a loading dose of dexmedetomidine (1 μg/kg) over 10 min followed by a continuous infusion (0.2–0.7 μg/kg/h). Fentanyl and ketoprofen were not administered, and only dexmedetomidine was used as a sedative. Local anesthetics were infiltrated at the surgical site.

2.4. Postoperative Analgesic Regimen

A dose of 100 mg of ketoprofen was administered to patients with a VAS score $\geq$ 4 for rescue analgesia. This was repeated after 5 min, if necessary (maximum dose of ketoprofen: 300 mg/day).

Meperidine (0.25 mg/kg) was given for rescue analgesia if postoperative pain was not controlled (VAS score $\geq$ 4), despite the maximum rescue dose of ketoprofen.

2.5. Perioperative Monitoring and Definition

Cardiac function (electrocardiogram), noninvasive arterial pressure, and peripheral oxygen saturation (SpO_2) were monitored. The anesthetic depth was monitored using the cortical activity index (CAI) via the CAI™ Monitoring System (BrainU Inc., Seongnam, Gyeonggi-do, Republic of Korea). The anesthetic depth was maintained at a CAI level between 60–80, which is equivalent to the bispectral index (BIS) sedation range. Notably, 2 L of O_2 was administered during sedation.

2.6. Definition of Variables

The degree of pain was assessed using the VAS, consisting of a 10 cm line, with two end-points representing 0 (no pain) and 10 (worst pain). Hypoxia during surgery was graded as follows: (a) normal, 95–100% SpO_2; (b) mild hypoxia, 91–94% SpO_2; (c) moderate hypoxia, 86–90% SpO_2; and (d) severe hypoxia, $\leq$85% SpO_2. Postoperative hematomas were classified as major and minor hematomas. Major hematomas were emergent and required open evacuation by removing sutures and coagulating the offending bleeders. Minor hematomas involved smaller amounts of blood or serum that could be resorbed with a massage or spontaneously without treatment. Hypotension was defined as systolic blood pressure SBP $<$ 100 mmHg and a decrease of >20% from baseline for more than 5 min. Hypertension was defined as SBP $>$ 160 mmHg and an increase of >20% from baseline for more than 5 min [8]. The length of PACU stay was defined as arrival to the PACU to the shift to the day-care center.

2.7. Surgical Procedures

All surgical procedures were performed under local anesthesia with 1% lidocaine and 1:100,000 epinephrine and conscious sedation. The pretarsal crease, nasojugal groove, and palpebromalar groove were marked preoperatively with the patient in a seated position. An incision was made 2 mm below the ciliary line with a lateral extension. After elevating the skin flap by 5–6 mm, the orbicularis oculi muscle (OOM) was split transversely. The skin-muscle flap was elevated using monopolar electrocautery. Premaxillary space dissection was performed from the arcus marginalis to 2–3 mm below the orbital rim. The periosteum was then resected. A subperiosteal dissection was performed 3–4 mm down to make a periosteum cuff. The palpebral part of the OOM, tear trough ligament, and orbital part of the OOM were sequentially released. When visualizing the levator labii superioris muscle fibers on the floor, the entrance to the premaxillary space was visible. Premaxillary space dissection was performed using periosteal elevators to raise the deep nasolabial and suborbicularis oculi fat areas. Laterally, the orbicularus-retaining ligament was released using monopolar electrocautery. When the dissection was complete, medial and central orbital fat were transposed and placed under the periosteal cuff. The authors used a modified method of the fat preservation technique (fixing the capsulopalpebral fascia to the arcus marginalis) first reported by Mendelson. By fixing the capsulopalpebral fascia to the periosteal cuff, the orbital fat transposes into the periosteal pocket, creating a secure septal tightening effect. Then, the surgeon evaluated the bulging of the lateral fat pad. Excess fat was removed if necessary, followed by plication of the septum to prevent herniation. The elevated deep nasolabial fat was suspended superolaterally and fixed to the arcus marginalis using 4-0 nylon sutures (deep nasolabial fat lifting). The OOM was subsequently suspended and secured to the inner aspect of the lateral orbital rim using a vicryl 5-0 suture (OOM suspension). The lower lid skin was draped over the lower eyelid, and excess skin was marked while the patient looked upward with their mouth open. The excess skin was then excised conservatively, and the incision was repaired using a 7-0 nylon suture.

2.8. Statistical Analysis

We used Pearson's chi-square test or Fisher's exact test to compare the categorical variables and an independent *t*-test to compare the quantitative variables of the subgroups.

We performed all statistical analyses using SPSS version 10 (SPSS Inc., Chicago, IL, USA). The statistical significance was set at $p < 0.05$.

3. Results

A total of 250 patients were included in this study, 161 (64.4%) of whom were women. The subjects' mean age was 57.8 years (range, 23–84 years). On average, the patients were of normal weight with a body mass index of 24.4 kg/m^2 (range, 17.4–35.5 kg/m^2). The proportion of ASA class was 12.8% for class I and 87.2% for class II. There were no significant differences between the demographic characteristics of the two groups (Table 1).

Table 1. Demographic characteristics of the patients.

		Dexmedetomidine Group (n = 113)	Conventional Group (n = 137)	Total (n = 250)	*p*-Value
Age (years)		57.9 ± 7.6	57.6 ± 12.2	57.8 ± 10.4	0.817
Sex	Male (%)	43 (38.1)	46 (33.6)	89 (35.6)	0.462
	Female (%)	70 (61.9)	91 (66.4)	161 (64.4)	
ASA class	I	11 (9.7)	21 (15.3)	32 (12.8)	0.188
	II	102 (90.3)	116 (84.7)	218 (87.2)	
BMI (kg/m^2)		24.1 ± 2.5	24.6 ± 3.3	24.4 ± 3.0	0.159

Values are presented as mean ± standard deviation. Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body Mass Index.

The distribution of sedation methods was assessed according to each year (Table 2). There was no significant difference observed between the two groups ($p = 0.517$). The dexmedetomidine group was slightly more frequently utilized during the initial three years, while the conventional group consistently remained in use, with over 60% utilization in the latter two years.

Table 2. Characteristics of sedation methods according to the year.

	Dexmedetomidine Group (n = 113)	Conventional Group (n = 137)	*p*-Value
2018 (Year)	23 (52.3)	21 (47.7)	0.517
2019 (Year)	26 (44.1)	33 (55.9)	
2020 (Year)	34 (50.0)	34 (50.0)	
2021 (Year)	22 (38.6)	35 (61.4)	
2022 (Year)	8 (36.4)	14 (63.6)	

Table 3 shows the differences in surgery-related profiles between the conventional and dexmedetomidine groups. The total amount of local anesthetic was significantly lower ($p < 0.001$), but the total length of the incision and the operation duration were longer in the dexmedetomidine group, although this difference was not significant. The number of incisions was two in both groups.

Table 3. Characteristics of the surgery-related profiles.

		Dexmedetomidine Group (n = 113)	Conventional Group (n = 137)	*p*-Value
Total local anesthetic (cc)		5.6 ± 2.3	7.4 ± 2.3	<0.001 *
Incision	Total length (cm)	8.3 ± 0.9	8.2 ± 0.9	0.202
	Number: two (%) **	113 (100.0)	137 (100.0)	1.000
Duration of operation (min)		96.0 ± 30.3	94.0 ± 29.0	0.605

Values are presented as mean ± standard deviation. * Statistically significant. ** The number of incisions was two in both groups.

Hypoxia, hematoma, and intraoperative hypertension events were analyzed to compare the complication-related profiles (Table 4). The number of hypoxia episodes was significantly higher ($p < 0.001$) in the conventional group than in the dexmedetomidine group, and there were only three episodes of hypoxia reported in the dexmedetomidine group. Hypoxia severity ($p < 0.001$) and minor hematoma formation ($p = 0.007$) were also significantly different between the conventional and dexmedetomidine groups. In the dexmedetomidine group, the incidence of mild/moderate hypoxia was observed in only three patients (2.7%), and there were no cases of severe hypoxia. There was one (0.7%) patient with major hematomas in the conventional group. One major hematoma required open evacuation and coagulation of the offending bleeders. Minor hematoma occurred in 16 patients: 2 in the dexmedetomidine group and 14 in the conventional group, indicating a significant difference between the groups. Exploration of minor hematomas was not necessary, and they spontaneously disappeared after compression dressing. Hypertension events were significantly higher in the conventional group compared to the dexmedetomidine group ($p = 0.003$).

Table 4. Characteristics of complication-related profiles.

		Dexmedetomidine Group (n = 113)	Conventional Group (n = 137)	*p*-Value
Hypoxia episode (%)		3 (2.7)	28 (20.4)	0.001 *
Hypoxia severity	Normal (%)	110 (97.3)	109 (79.6)	<0.001 *
	Mild/Moderate (%)	3 (2.7)	26 (19.0)	<0.001 *
	Severe (%)	0 (0)	2 (1.4)	0.503
Hematoma (%)	Major	0 (0)	1 (0.7)	1.000
	Minor	2 (1.8)	14 (10.2)	0.007 *
BP change	Hypertension	4 (3.5)	20 (14.6)	0.003 *
	Hypotension	7 (6.2)	4 (2.9)	0.231

Values are presented as mean ± standard deviation. Hypoxia severity was graded as follows: (a) normal: 95–100% SpO_2; (b) mild hypoxia: 91–94% SpO_2; (c) moderate hypoxia: 86–90% SpO_2; and (d) severe hypoxia: ≤85% SpO_2. Major hematomas were defined as those requiring open evacuation and coagulation of the offending bleeders, while minor hematomas were defined as those that resorbed with a massage or spontaneously without treatment. Abbreviations: BP, Blood pressure. * Statistically significant.

To compare the recovery-related profiles, we analyzed the length of PACU stay, pain, nausea, and urinary catheterization (Table 5). The length of PACU stay was significantly longer ($p < 0.001$) in the dexmedetomidine group, while postoperative pain ($p = 0.004$) and analgesic (ketoprofen) administration ($p = 0.028$) were significantly lower. However, postoperative nausea and antiemetic administration rates were not significantly higher in the dexmedetomidine group. Six (4.4%) patients underwent urinary catheterization in the conventional group, while two (1.8%) patients in the dexmedetomidine group did. These differences were not significant.

Table 5. Characteristics of the recovery-related profiles.

		Dexmedetomidine Group (n = 113)	Conventional Group (n = 137)	*p*-Value
Duration of PACU stay (min)		110.5 ± 30.7	84.3 ± 41.4	<0.001 *
Pain	VAS Score	1.0 ± 0.4	1.2 ± 0.8	0.004 *
	Ketoprofen use (%)	3 (2.7)	13 (9.5)	0.028 *
Nausea	Complain (%)	12 (10.6)	10 (7.3)	0.356
	Antiemetic drug use (%)	12 (10.6)	9 (6.6)	0.251
Urinary catheterization (%)		2 (1.8)	6 (4.4)	0.300

Values are presented as mean ± standard deviation. The pain score consists of two end-points representing 0 (no pain) and 10 (maximal pain). Ketoprofen was used to control postoperative pain in the PACU. Abbreviations: PACU, post-anesthesia care unit; VAS, visual analog scale. * Statistically significant.

4. Discussion

The most commonly used combination for conscious sedation in day aesthetic surgeries is midazolam and fentanyl [9]. Midazolam is ideal for conscious sedation because it provides moderate sedation and has an acceptable side-effect profile [10]. Fentanyl is also an ideal analgesic agent for most conscious sedation regimens [10]. Midazolam has been used successfully in both continuous and bolus fashions [11]. The bolus fashion is preferred for blepharoplasty, which has a relatively short operation time and requires patient cooperation (opened eyes) during surgery. However, more cases of respiratory depression and a sudden increase in blood pressure were reported in surgeries involving the bolus fashion compared to continuous infusion [9,12]. These side effects may exacerbate swelling and increase comorbidities in facial aesthetic surgeries.

Dexmedetomidine is a new sedative approved by the United States Food and Drug Administration in 1999 that was recently introduced in outpatient anesthesia in Korea. Dexmedetomidine is a highly selective alpha-2 agonist that has several advantages as a sedative [12]. It secures the airway and respiration even under moderate sedation and carries a low risk of cardiopulmonary instability [13]. Additionally, it inhibits the sympathetic nerve. Dexmedetomidine decreases the amount of analgesic needed during and after surgery, presenting analgesic effects [14]. Notably, there was no difference in the degree of sedation in a comparative study with other sedatives [12,15]; however, dexmedetomidine was the preferred sedative of practitioners because it made facial procedures more comfortable and safe [16]. An elimination half-life of 2.1–3.1 h was reported in healthy volunteers using dexmedetomidine. Pharmacologically, the advantage of a long half-life is that stable and safe sedation is possible. The disadvantage is that early recovery is difficult, and recovery is often late, so it is suitable for surgery of more than 2 h.

Successful surgical treatment depends on the administration of an optimal amount of local anesthesia. Excessive local anesthetics can cause facial swelling, which may interfere with sophisticated facial surgery. Local anesthetics alone are less profound and suffer from the limitation of a short duration of action compared with local anesthetics with adjuvants. The adjuvants are coadministered with local anesthetic agents to improve the onset and/or duration of analgesia, which include both opioids and nonopioids, including epinephrine and an alpha-2 agonist. In the literature [17–19], dexmedetomidine blunted pain signals by inhibiting epinephrine release and exhibiting analgesic properties. Pharmacokinetically, continuous infusion better controls intraoperative pain management compared to a bolus injection [20]. In our study, the total amount of local anesthetic was significantly lower ($p < 0.001$) in the dexmedetomidine group despite the longer incision length and surgery duration. Based on these results, the local anesthetic demand was decreased more in the dexmedetomidine group due to analgesic effects.

In our hospital, NSAIDs are usually used for postoperative pain control. As they tend to increase bleeding, increasing NSAID dosages may increase hematoma formation. Lee et al. reported that postoperative pain and two or more doses of ketorolac postoperatively were significantly associated with the risk of postoperative hematoma formation [6]. The perioperative risk factors of hematoma formation in multivariate analysis and the use of ketorolac postoperatively showed more than twice the tendency of hematoma formation than postoperative pain. Moreover, Cawthorn et al. reported that patients who received ketorolac were at an increased risk of requiring surgical re-exploration for hematoma evacuation (relative risk [RR] = 3.6; 95% confidence interval [CI], 1.4–9.6) [7]. In our study, the ketoprofen dose was significantly lower in the dexmedetomidine group than in the conventional group ($p = 0.028$). The VAS Score, which represents the patient's pain expression in the PACU, was significantly lower in the dexmedetomidine group compared to the conventional group ($p = 0.004$; Table 5). This might be caused by the longer-lasting analgesic effect of dexmedetomidine compared to the conventional sedation method.

Facial hematomas are a possible complication of aesthetic facial surgery [17]. A sudden increase in blood pressure appears to be the single most important cause of hematomas, especially during the postoperative period. Moore et al. found that dexmedetomidine

resulted in a significant reduction and maintenance of blood pressure from anesthesia onset until PACU discharge [3]. Dexmedetomidine's analgesic properties attenuate the hypertensive response and improve hemodynamic stability perioperatively [21]. In the dexmedetomidine group, hypertension events and hematoma formation were decreased simultaneously. This suggests that continuous dexmedetomidine infusion is a more suitable sedation method for perioperative pain control in patients who have undergone blepharoplasty than a midazolam/fentanyl bolus injection. Sedation using dexmedetomidine continuous infusion reduced the incidence of postoperative swelling and hematomas in blepharoplasty patients, resulting in positive effects on surgical outcomes and patient satisfaction.

Dexmedetomidine is known to induce bradycardia as a highly selective alpha-2 agonist. It has been observed that bradycardia (<60 beats/min) had been occasionally experienced during prolonged surgeries when dexmedetomidine was administered. However, since blepharoplasty was a short-duration surgery and the dosage of dexmedetomidine was well controlled during the procedure, severe bradycardia (<50 beats/min) was not observed in this study.

The mechanisms of dexmedetomidine and fentanyl on urinary retention are opposite to each other. Fentanyl has a short duration of action on μ and δ receptors in the spinal cord, reducing sensory input from the urinary tract, decreasing the urge to void and muscle contraction, and increasing bladder capacity. Additionally, this drug reduces the abdominal extract of the spinal nervous system, impairing the regulatory function of internal urethral sphincter relaxation and bladder contraction. On the other hand, dexmedetomidine stimulates α2-adrenergic receptors in the central nervous system to increase urination urge along with muscle relaxation. Ghada et al. reported significant differences in the incidence of urinary retention between the group treated with dexmedetomidine and the group treated with fentanyl [22]. Therefore, the use of dexmedetomidine as a sedative drug may be more effective in preventing postoperative urinary retention. In our study, a lower incidence of urinary catheterization was observed in the dexmedetomidine group compared to the conventional group (Table 5).

Anesthesia-related patient safety has become important to plastic surgeons [23], given recent media attention on medical errors, concerns about day surgery safety, and the increasing number of outpatient aesthetic procedures [24]. Bitar et al. found that the most common sedation-related complications were dyspnea and respiratory depression [23]. The ideal sedative drug in a day surgery does not necessarily induce respiratory depression, but midazolam, fentanyl, and ketamine used in conventional sedation may cause respiratory depression. In our study, severe intraoperative hypoxia was reported in the conventional group, but none of the dexmedetomidine group reported severe hypoxia during sedation. Dexmedetomidine infusion is suitable in facial surgeries such as blepharoplasty.

The occurrence of post-surgical confusion or delirium is an important factor in determining same-day discharge for surgical patients. It is anticipated that the incidence of delirium is very low due to our anesthesia approach involving a combination of light sedation and local anesthesia, as well as the short time of the surgical procedures. In this cohort study, there were no cases where same-day discharge was not feasible due to severe postoperative cognitive impairment. Paul et al. reported that the incidence of postoperative cognitive dysfunction (POCD) was high in major surgeries, with 17% for total hip joint replacement surgery and 43% for coronary artery bypass grafting surgery at postoperative day 7 [25]. However, there has been no specific research on the occurrence rate of cognitive dysfunction, specifically after light sedation, making it difficult to determine the exact incidence rate of POCD. Considering that POCD is influenced by factors such as the surgery itself, the duration of surgery, and the depth of anesthesia, it is anticipated that the occurrence rate of POCD would be very low in this study.

The important thing is that the analgesic effect of dexmedetomidine is higher than that of the conventional sedation method, so in conclusion, the use of ketoprofen in PACU and the total amount of local anesthetic were decreased. However, differences in pain medication use in recovery may be related to the long half-life of dexmedetomidine itself.

Therefore, additional research is necessary to find the exact correlation. Contrary to the existing literature, our study had many complaints of nausea and antiemetics administration in the dexmedetomidine group, but the difference was negligible and not statistically significant (nausea; $p = 0.356$, antiemetic drug use; $p = 0.256$; Table 5). Future studies could explore this and the effect it has on postoperative nausea and vomiting. The other limitations of this study include its retrospective nature, which prevents a direct correlation between changes in perioperative parameters and analysis of direct effects on the response of sedative drugs. Therefore, the following limitations were identified: patients were not randomized, blinding was not implemented, no primary outcome was specified, and the study analyzed data from a four-year period, including data from five years ago. Second, in order to evaluate POCD, a more sophisticated and well-controlled approach is necessary, which may be a limitation of cohort studies. Therefore, we intend to conduct prospective research in the future. Third, we were unable to determine whether dexmedetomidine actually increased postoperative urinary retention. Further investigation is needed to compare the different physiology of urinary retention between the dexmedetomidine group and the benzodiazepine/opioid group.

5. Conclusions

In this study, dexmedetomidine infusion was associated with more hemodynamic stability and postoperative analgesia than midazolam and fentanyl bolus injection during sedation in blepharoplasty patients. NSAIDS consumption and hypertensive events were lower in the dexmedetomidine group. Sedation with dexmedetomidine continuous infusion is associated with less hematoma formation and postoperative bleeding than sedation with midazolam and fentanyl. Dexmedetomidine could secure self-respiration during sedation. Dexmedetomidine infusion may be a good alternate sedative method for blepharoplasty.

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References

1. Choi, Y.; Kang, H.G.; Nam, Y.S. Three Skin Zones in the Asian Upper Eyelid Pertaining to the Asian Blepharoplasty. *J. Craniofac. Surg.* **2017**, *28*, 892–897. [CrossRef] [PubMed]
2. Choi, Y.; Eo, S. Outer Fascia of Orbicularis Oculi Muscle as an Anchoring Target Tissue in Double Eyelid Surgery. *J. Craniofac. Surg.* **2016**, *27*, 322–327. [CrossRef]
3. Moore, A.C.M.; Kachare, S.D.; Barber, D.A.; Barrow, L.; O'Daniel, T.G. Total Intravenous Anesthesia with Dexmedetomidine for Hemodynamic Stability and Enhanced Recovery in Facial Aesthetic Surgery. *Aesthetic Surg. J.* **2022**, *42*, NP602–NP610. [CrossRef]
4. Rees, T.D.; Lee, Y.C.; Coburn, R.J. Expanding hematoma after rhytidectomy. A retrospective study. *Plast. Reconstr. Surg.* **1973**, *51*, 149–153. [CrossRef] [PubMed]
5. Rees, T.D.; Barone, C.M.; Valauri, F.A.; Ginsberg, G.D.; Nolan, W.B., 3rd. Hematomas requiring surgical evacuation following face lift surgery. *Plast. Reconstr. Surg.* **1994**, *93*, 1185–1190. [CrossRef]
6. Lee, M.; Rhee, J.; Kim, Y.; Jung, Y.H.; Ahn, S.H.; Jeong, W.J. Perioperative risk factors for post-thyroidectomy hematoma: Significance of pain and ketorolac usage. *Head Neck* **2019**, *41*, 3656–3660. [CrossRef]
7. Cawthorn, T.R.; Phelan, R.; Davidson, J.S.; Turner, K.E. Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty. *Can. J. Anaesth.* **2012**, *59*, 466–472. [CrossRef] [PubMed]

8. Filiberto, A.C.; Loftus, T.J.; Elder, C.T.; Hensley, S.; Frantz, A.; Efron, P.; Ozrazgat-Baslanti, T.; Bihorac, A.; Upchurch, G.R., Jr.; Cooper, M.A. Intraoperative hypotension and complications after vascular surgery: A scoping review. *Surgery* **2021**, *170*, 311–317. [CrossRef]
9. Taub, P.J.; Bashey, S.; Hausman, L.M. Anesthesia for cosmetic surgery. *Plast. Reconstr. Surg.* **2010**, *125*, 1e–7e. [CrossRef]
10. Mustoe, T.A.; Buck, D.W., 2nd; Lalonde, D.H. The safe management of anesthesia, sedation, and pain in plastic surgery. *Plast. Reconstr. Surg.* **2010**, *126*, 165e–176e. [CrossRef]
11. Bayat, A.; Arscott, G. Continuous intravenous versus bolus parenteral midazolam: A safe technique for conscious sedation in plastic surgery. *Br. J. Plast. Surg.* **2003**, *56*, 272–275. [CrossRef] [PubMed]
12. Barends, C.R.; Absalom, A.; van Minnen, B.; Vissink, A.; Visser, A. Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety. *PLoS ONE* **2017**, *12*, e0169525. [CrossRef] [PubMed]
13. Afonso, J.; Reis, F. Dexmedetomidine: Current role in anesthesia and intensive care. *Rev. Bras. Anestesiol.* **2012**, *62*, 118–133. [CrossRef] [PubMed]
14. Arain, S.R.; Ebert, T.J. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth. Analg.* **2002**, *95*, 461–466. [CrossRef]
15. Singh, V.; Thepra, M.; Kirti, S.; Kumar, P.; Priya, K. Dexmedetomidine as an Additive to Local Anesthesia: A Step to Development in Dentistry. *J. Oral Maxillofac. Surg.* **2018**, *76*, 2091.e2091–2091.e2097. [CrossRef]
16. Kim, N.; Yoo, Y.C.; Lee, S.K.; Kim, H.; Ju, H.M.; Min, K.T. Comparison of the efficacy and safety of sedation between dexmedetomidine-remifentanil and propofol-remifentanil during endoscopic submucosal dissection. *World J. Gastroenterol.* **2015**, *21*, 3671–3678. [CrossRef]
17. Taghinia, A.H.; Shapiro, F.E.; Slavin, S.A. Dexmedetomidine in aesthetic facial surgery: Improving anesthetic safety and efficacy. *Plast. Reconstr. Surg.* **2008**, *121*, 269–276. [CrossRef]
18. Lombana, N.F.; Falola, R.A.; Zolfaghari, K.; Roth, C.; Abraham, J.T.; Saint-Cyr, M.H. Comparison of Liposomal Bupivacaine to a Local Analgesic Cocktail for Transversus Abdominis Plane Blocks in Abdominally Based Microvascular Breast Reconstruction. *Plast. Reconstr. Surg.* **2022**, *150*, 506e–515e. [CrossRef]
19. Calasans-Maia, J.A.; Zapata-Sudo, G.; Sudo, R.T. Dexmedetomidine prolongs spinal anaesthesia induced by levobupivacaine 0.5% in guinea-pigs. *J. Pharm. Pharmacol.* **2005**, *57*, 1415–1420. [CrossRef]
20. Upton, R.N.; Semple, T.J.; Macintyre, P.E. Pharmacokinetic optimisation of opioid treatment in acute pain therapy. *Clin. Pharmacokinet.* **1997**, *33*, 225–244. [CrossRef]
21. Docherty, J.R. Subtypes of functional alpha1- and alpha2-adrenoceptors. *Eur. J. Pharmacol.* **1998**, *361*, 1–15. [CrossRef] [PubMed]
22. El-Saeid, G.M.; Bassiouny, M.A.; Al Sharabasy, T.H.; Abdelrahman, T.N. Dexmedetomidine versus fentanyl effect as adjuvants to bupivacaine on post spinal urinary retention in knee joint arthroscopic surgeries. *Egypt. J. Anaesth.* **2023**, *39*, 226–232. [CrossRef]
23. Bitar, G.; Mullis, W.; Jacobs, W.; Matthews, D.; Beasley, M.; Smith, K.; Watterson, P.; Getz, S.; Capizzi, P.; Eaves, F., 3rd. Safety and efficacy of office-based surgery with monitored anesthesia care/sedation in 4778 consecutive plastic surgery procedures. *Plast. Reconstr. Surg.* **2003**, *111*, 150–156, discussion 157–158. [CrossRef] [PubMed]
24. Byrd, H.S.; Barton, F.E.; Orenstein, H.H.; Rohrich, R.J.; Burns, A.J.; Hobar, P.C.; Haydon, M.S. Safety and efficacy in an accredited outpatient plastic surgery facility: A review of 5316 consecutive cases. *Plast. Reconstr. Surg.* **2003**, *112*, 636–641, discussion 642–636. [CrossRef] [PubMed]
25. Evered, L.; Scott, D.A.; Silbert, B.; Maruff, P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth. Analg.* **2011**, *112*, 1179–1185. [CrossRef]

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Effect of Intravenous Dexamethasone Dose on the Occurrence of Rebound Pain after Axillary Plexus Block in Ambulatory Surgery

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Abstract: Rebound pain (RP) remains a challenge in ambulatory surgery, characterized by severe pain upon resolution of a peripheral nerve block (PNB). Intravenous (IV) administration of Dexamethasone (DEXA) potentiates PNB analgesic effect and reduces RP incidence although preventive effective dose remains undetermined. This retrospective analysis evaluates the preventive effect of IV DEXA on RP in outpatients undergoing upper limb surgery under axillary block. DEXA was divided into high (HD > 0.1 mg/kg) or low (LD < 0.1 mg/kg) doses. RP was defined as severe pain (NRS $\geq$ 7/10) within 24 h of PNB resolution. DEXA HD and LD patients were matched with control patients without DEXA (n = 55) from a previous randomized controlled study. Records of 118 DEXA patients were analyzed (DEXA dose ranged from 0.05 to 0.12 mg/kg). Intraoperative IV DEXA was associated with a significant reduction of the pain felt when PNB wore off as well as to a significant reduction of RP incidence (n = 27/118, 23% vs. 47% in controls, p = 0.002) with no effect related to the dose administered (p = 0.053). Our results support the administration of intraoperative DEXA as a preventive measure to reduce the occurrence of RP.

Keywords: loco-regional anesthesia; rebound pain; dexamethasone; ambulatory surgery

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1. Introduction

Regional anesthesia offers several advantages in ambulatory setting, including high-quality perioperative analgesia and faster discharge from the hospital.

Peripheral nerve blocks (PNBs) using different techniques [1] are extensively used in orthopedic limb surgeries as they ease the surgical procedure and they improve patient satisfaction [2], particularly in terms of long-lasting postoperative analgesia without systemic drug side effects [1]. However, following PNB resolution, a rapid increase in pain intensity commonly referred to as "rebound pain" (RP) may occur. The phenomenon is observed within the first 24 to 48 h of the PNB dissipation. Occurring outside of health care setting, it is actually considered as a clinically relevant problem [3,4]. Further, RP is the most frequent factor of dissatisfaction reported by the patients following PNB. The RP phenomenon is frequent as it may affect nearly 40% to 50% of orthopedic patients operated under PNB [2,5,6].

For the aforementioned reasons, the prevention of RP occurrence has become a priority, particularly in ambulatory surgery setting. Several risk factors have been found to be associated with the phenomenon such as younger age, female gender, high catastrophizing mind set, bone surgery and the absence of perioperative administration of dexamethasone [5,6]. Dexamethasone (DEXA), a synthetic corticosteroid, is widely used in anesthesia practice for its well-known perioperative analgesic and antiemetic properties [7]. Moreover, DEXA

also serves as an adjuvant to PNB to increase the block duration and the analgesic related effect [8]. PNB prolongation has been observed after the administration of DEXA by either the perineural or intravenous (IV) route [9]. The literature suggests that 4 mg of DEXA may be the optimal perineural dose to potentiate PNB, whereas the optimal intravenous dose is likely higher but still remains undetermined [10]. However, the intravenous administration should be preferred because perineural use may cause delayed neurotoxicity and the perineural route is still off-label [9]. Several studies have reported a reduction of RP incidence after PNB dissipation when perioperative DEXA was administered by either the perineural [11,12] or intravenous route [5,13]. To date, the dose-related preventive effect of intravenous DEXA on RP has not been evaluated.

The main objective of this retrospective study was to assess the occurrence of RP when perioperative IV DEXA was administered at analgesic (dose higher than 0.1 mg/kg [14] and/or antiemetic doses [7,15] (i.e., doses ranging between 4 and 10 mg) in ambulatory patients undergoing upper limb orthopedic surgery under axillary plexus block. The secondary objective was to evaluate a potential dose-related preventive effect of IV DEXA on the development of RP.

2. Materials and Methods

This single-center retrospective cohort study was conducted at the Cliniques Universitaires Saint-Luc (Brussels, Belgium). It is a retrospective analysis of data collected prospectively in the context of Quality Reporting in the Out-Patients Unit. The data were collected over a period of 1 year, between January 2021 and February 2022, from patients' files and perioperative questionnaire-based sources.

2.1. Recruitment

Ambulatory adult patients (18 to 80 years old) who underwent elective upper limb surgery (elbow and below) under axillary plexus block between January 2021 and February 2022 were included (Figure 1). Only patients who had complete perioperative data records were considered. Eligible patients had received an intravenous DEXA dose left to the discretion of the anesthesiologist in charge. Intraoperative IV DEXA was administered either as an antiemetic or as an analgesic adjuvant to the PNB, i.e., IV doses ranging from 4 to 10 mg. All the patients underwent axillary PNB under real-time ultrasound guidance by a trained anesthesiologist. The control group was composed of patients included in a previous prospective study on rebound pain, who had not received DEXA [6]. All the patients, in the control group and those included between January 2021 and February 2022, received the same type of PNB, i.e., an axillary plexus block. Each axillary plexus was performed using a 50:50 mixture of ropivacaine (0.5%) and mepivacaine (1%). The reuse of prospective data did not require the consent of the patients concerned for the retrospective analysis by the ethics committee. The authors are not sure that it should be included in the manuscript, but it should only figure in the answers to the reviewers' concerns.

All the patients benefited from the same perioperative analgesic protocol using multimodal analgesia. Patients who had contra-indication to the analgesics used in the perioperative multimodal analgesic protocol (i.e., paracetamol or non-steroidal analgesic use) were not included in the analysis. Patients who received IV DEXA were matched with patients of the control group regarding age, sex and type of surgery (bone or soft tissues surgery) (Table 1).

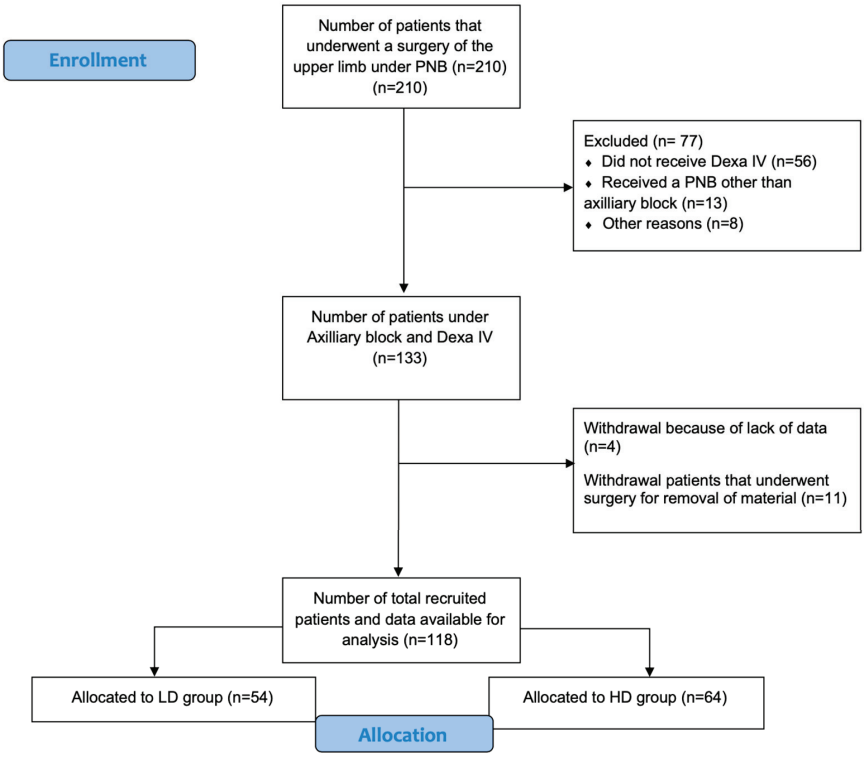

Figure 1. Flow Diagram. Abbreviations: PNB—Peripheral Nerve. Block; Dexa IV—Intravenous Dexamethasone; LD—Low dose; HD—High dose.

Table 1. Comparison between control group and DEXA [1] group.

	Control Group (n = 55)	DEXA Group (n = 118)	p Value
Age (years)	52 ± 18	45 ± 16	0.428
Sex ratio (female/male) (n)	29/26	78/40	0.298
BMI [2] (kg/m^2)	25 (21–29)	26 (22–29)	0.266
Bone surgery (n)	21 (39%)	64 (40%)	0.854
Tourniquet duration (min)	22 (14–38)	21 (12–33)	0.742
Preoperative			
Catastrophizing (0–52)	12 (3–23)	11 (3–22)	0.774
Central sensitization (0–36)	9.0 (6–12)	8.5 (4–15)	0.449
Preoperative pain			
Average pain (NRS 0–10)	2.0 (0–4)	2.0 (0–5)	0.403
Maximal pain (NRS 0–10)	4.5 (1–8)	5.0 (0–7)	0.510
Night pain (NRS 0–10)	0 (0–3)	0 (0–4.5)	0.764
DN4 [3] value (0–10)	3.0 (1–4)	2.0 (1–4)	0.622
PNB [4] duration			
Total duration (min)	630 (506–795)	640 (410–905)	0.892
Pain when PNB wears off (NRS [5] 0–10)	4.5 (2–8)	3.3 (1–6) *	0.030
Incidence of rebound pain (NRS >7/10) (n)	26 (47%)	27 (23%) *	0.002

[1] Dexamethasone; [2] Body Mass Index; [3] Douleur Neuropathique en 4 questions; [4] Peripheral Nerve Block; [5] Numerical Rating Scale; * p Value $\leq$ 0.05.

2.2. Data Collection

To improve the management of postoperative pain by better focusing on patients at risk of developing severe acute postoperative pain when back home, a set of preoperative questionnaires is commonly proposed to the patients to all the ambulatory patients including those undergoing regional anesthesia for ambulatory orthopedic surgery. All the questionnaires are completed on a voluntary basis.

All the patients included in the study had complete perioperative records. Preoperative data collected on day 0 included preoperative pain at rest, pain on movement and pain overnight at the surgical site, using a numerical rating scale (NRS) from 0 to 10 (where 0 = no pain and 10 = worst pain). Preoperative medications, including pain relievers, were also noted. Patients also completed a pre-operative questionnaire that had been developed in 2019 as part of a previous prospective study [6]. The anesthesia team continued to use this questionnaire in their practice to help prevent severe acute postoperative pain at home, mainly related to a rebound pain phenomenon.

Patients were therefore asked to answer a series of preoperative questions such as the French version of the Pain Catastrophizing Scale (PCS) questionnaire, which assess negative thoughts related to pain (i.e., rumination, amplification and helplessness) on a scale from 0 to 52 [14]. Patients were classified as high catastrophizers if they scored higher than the 75th percentile.

The French version of the Central Sensitization Inventory (CSI) was used to measure the main somatic and emotional complaints associated with central sensitization. A validated short-form was used as CSI-9 (i.e., 9 questions derived from the original 40 questions, with a cut-off value of 20 on a 0–36 scale) to distinguish patients presenting with a preoperative positive central sensitization [16]. Finally, the presence of a neuropathic component in the preoperative pain at the surgical site was assessed using the "Douleur Neuropathique 4" (DN4) questionnaire (cutoff value of 4 on a 10-point score) [17].

Before the surgical incision, the effectiveness of the sensory blockade of the axillary plexus was evaluated by a cold test (ether test) in the different territories. Only patients who presented with fully effective axillary PNB were considered for inclusion in the study (Figure 1). For various reasons (surgeon's request, patient comfort, PNB failure ...), 8 patients who received general anesthesia during the procedure in addition to the axillary plexus were excluded. All the patients were operated upon by two orthopedic surgeons (O.B. and X.L). A standardized optimal perioperative multimodal analgesic treatment was applied to all the patients, including intraoperative administration of paracetamol (1 g) and intraoperative ketorolac (0.5 mg/kg). In the recovery room, when the postoperative pain score (NRS) was >3/10, intraveinous tramadol (2 mg/kg) was administered. Patients were discharged with written recommendations for the use of standard postoperative oral analgesics, i.e., ibuprofen 400 mg/6 h, paracetamol 3 g/24 h and, if necessary, tramadol as a rescue analgesic (1–2 mg/kg; Maximum 400 mg/day). The patients were also asked to note in a pain diary the time when the axillary block wears off, as well as the intensity of the pain felt (NRS, 0–10) at that time and the analgesics intake. All the patients were contacted by phone call on day 1 at 24 h after surgery (regular telephone call for quality audit purpose) by a hospital nurse. Postoperative pain intensity was questioned, including average and maximal pain on a NRS scale from 0 to 10.

The definition of RP was the same we used in our previous study [6], i.e., the same used in the control group. RP was defined as severe pain with a NRS score $\geq 7/10$ within the first 24 h after the termination of the axillary plexus block.

2.3. Statistical Analysis

2.3.1. Power Analysis

The sample size was calculated based on the incidence of rebound pain. The presence of RP was defined as pain intensity score > 7 (NRS, 0 to 10) reported by the patient after axillary plexus block resolution [6]. Based on values of RP incidence after peripheral nerve block resolution approaching 45% to 50% [5,6] and assuming that the incidence of RP with

intravenous DEXA administration would be reduced by half and thereby would approach 25% [18], a minimum of 46 patients was needed in each group to have an alpha value of 0.05 and a power of 0.8.

2.3.2. Data Analysis

For analysis of retrospective data, the intravenous DEXA dose was separated into high (HD; >0.1 mg/kg) or low (LD; <0.1 mg/kg) doses. DEXA HD and LD patients were compared to control patients (n = 55) included in a previous randomized controlled trial [6] regarding demographics (age, gender parity and BMI) to ensure adequate matching.

Statistical analysis was performed with SigmaStat 3.5 (Systat Software GmbH, Erkrath, Germany). Results were expressed as proportions, mean ± standard deviation or median value (interquartile range) as specified. According to a Kolmogorov–Smirnov normality test, parametric data between the groups were compared by an unpaired Student t-test and nonparametric data by Mann–Whitney and Kruskal–Wallis Rank Sum tests. Categorical data were compared using the chi-squared test and Fisher exact test using a two-tailed probability. A p-value less than 0.05 was considered to be significant. A backward stepwise regression model ($p < 0.05$ significant) was also be used to test the predictive value of intravenous DEXA prevention on the development of RP.

3. Results

Between January 2021 and January 2022, 210 patients underwent elective upper limb surgery under axillary plexus block, and intraoperative IV DEXA administration was noticed in 133 of these patients. A total of 118 patients were included in the retrospective analysis (Figure 1, Flow diagram).

As reported in Table 1, these patients were comparable regarding age, sex and type of surgery to the control group where patients did not received intraoperative DEXA (patients included in a previous prospective randomized study on RP, n = 55) [6]. Intraoperative administration of IV DEXA was associated with a significant reduction of the pain felt when PNB wore off as well as to a significant reduction of RP incidence (23% versus 47%, p = 0.002) (Table 1). The total duration of PNB however was not influenced by IV DEXA administration at the doses used. The DEXA doses ranged from 0.05 to 0.12 mg/kg.

Thereafter, for statistical analysis, patients who received IV DEXA were divided into a high-dose DEXA group (DEXA HD, dose > 0.1 mg/kg, n = 64) and a low-dose DEXA group (DEXA LD, dose < 0.1 mg/kg, n = 54) as described in Table 2. By comparison with the control group (i.e., no DEXA administration), intraoperative DEXA reduced the occurrence of RP. We observed a dose-related trend which, however, was not significant. Similarly, a DEXA dose-related trend to less pain felt when PNB wore off was noticed by the patients, but it was not either statistically significant.

At the DEXA doses used, no significant impact on the duration of the axillary block was observed. Postoperative pain scores assessed at 24 h after surgery were not affected by the dose of intraoperative DEXA.

The characteristics of patients who had received IV DEXA and presented with and without RP phenomenon are presented in Table 3. The main differences were higher BMI, higher average preoperative pain score at the surgical site, higher catastrophizing score and higher incidence of patients defined as “high catastrophizers” (score > 23/52, i.e., >75th percentile). Bone surgery also was more frequent in RP patients. The dose of IV DEXA did not differ between patients with and without rebound pain.

Table 2. Effect of intraoperative DEXA [1] administration (LD [2] & HD [3]) on PNB [4] outcomes.

	Control Group (n = 55)	DEXA LD (n = 54)	DEXA HD (n = 64)	p Value
DEXA dose (mg/kg)	----	0.06 (0.05–0.07)	0.10 (0.10–0.12)	<0.001
PNB duration				
H1–H2 [5] (min)	400 (309–541)	292 (195–540)	332 (223–577)	0.092
H2–H3 [6] (min)	180 (120–307)	240 (165–300)	205 (79–405)	0.331
Total duration (min)	630 (506–795)	583 (445–825)	661 (402–960)	0.650
Preoperative pain at day 1				
Average pain (NRS [7] 0–10)	25 (1–55)	2.0 (1–4)	2.0 (0–5)	0.408
Maximal pain (NRS 0–10)	4.0 (2–7)	6.0 (2–8)	5.0 (1–8)	0.564
Pain when PNB wears off (NRS 0–10)	4.5 (2–8)	4.0 (1–7)	3.0 (1–6)	0.053
Incidence of rebound pain (NRS > 7/10) (n)	26 (47%)	14 (26%) *	13 (20%) *	0.029

* $p < 0.05$ with control group: [1] Dexamethasone; [2] Low Dose; [3] High Dose; [4] Peripheral Nerve Block; [5] Time interval between the time of the end of the block (H1, day and time) and the beginning of the onset of the paresthesia reported by the subject (H2, day and time after the block); [6] Time interval between the time of beginning of the occurrence of paresthesia reported by the subject (H2, day and time after block) and finally the onset of pain at surgery site (H3, day and time after block); [7] Numerical rating scale.

Table 3. Characteristics of patients with and without rebound pain among patients who received intraoperative DEXA 1 (n = 118).

	Rebound Pain (n = 27)	No Rebound Pain (n = 91)	p Value
Age (years)	45 ± 16	51 ± 18	0.073
Sex female (n)	20 (74%)	48 (53%)	0.075
BMI [2] (kg/m^2)	28 ± 6 *	25 ± 5.5	0.026
Bone surgery (n)	17 (65%) *	31 (34%)	0.013
Tourniquet duration (min)	34 ± 26	24 ± 17	0.121
Preoperative			
Catastrophizing (0–52)	20 (4–37) *	9 (2–21)	0.017
High catastrophizers (n)	11 (42%) *	14 (16%)	0.007
Central sensitization (0–36)	8.5 (2–17)	8.5 (4–15)	0.787
Central sensitization positive (n)	4 (16%)	12 (14%)	0.757
Preoperative pain			
Average pain (NRS [3] 0–10)	4.5 (2–6) *	2.0 (0–4)	0.009
Maximal pain (NRS 0–10)	7.3 (1–9)	4.5 (0–7)	0.065
Night pain (NRS 0–10)	1 (0–6)	0 (0–3.8)	0.222
DN4 [4] value (0–10)	3.0 (2–4.5)	2.0 (1–4)	0.135
PNB [5] duration			
Total duration (min)	630 (506–795)	640 (410–905)	0.892
Pain when PNB wears off (NRS [3] 0–10)	8.0 (7–8.9) *	2.0 (1–4)	<0.001
DEXA dose (mg/kg)	0.08 (0.06–0.10)	0.09 (0.06–0.10)	0.650

* $p < 0.05$ with control group [1] Dexamethasone; [2] Body Mass Index; [3] Numerical rating score; [4] Douleur Neuropathique en 4 questions; [5] Peripheral Nerve Block.

When considering the full population of patients (n = 173, including the control group), a positive correlation was noted between the intensity of RP and the intensity of preoperative pain (0.445, p = 0.000) as well as for the level of preoperative catastrophizing score (0.283, p = 0.000). Important factors associated with the presence of RP (p value < 0.05) were entered in a Backward Stepwise Regression model including the intraoperative administration of DEXA independently of the dose used. In the final model, bone surgery

($p < 0.001$), high catastrophizing ($p < 0.001$) and the absence of intraoperative DEXA ($p = 0.027$) were predictive of RP occurrence when the axillary PNB wore off.

4. Discussion

The present results support the intraoperative use of intravenous DEXA (dose 0.05–0.12 mg/kg) for the prevention of rebound pain after upper limb surgery under axillary plexus block. Regardless the dose of IV DEXA administered, our study showed a significant decrease in RP occurrence (23% vs. 47%; $p = 0.002$). This finding is in agreement with previous reports [5,13]. However, at the doses we used, a dose-dependent effect of DEXA on the occurrence of RP could not be found.

Several studies have assessed the use of perineural DEXA to increase the duration of sensory nerve block, mostly the interscalene plexus block, and to improve postoperative analgesia after upper limb procedures. These studies have shown a dose-dependent effect with a ceiling effect for doses higher than 4 mg [19,20]. Because the rebound pain phenomenon has increased as a subject of interest, some studies have recently evaluated the preventive effect of perineural DEXA. After shoulder surgery, perineural DEXA 5 mg reduced RP occurrence from 83% to 37% [11], and perineural DEXA 8 mg decreased RP from 48.8% to 11% [12]. Despite the effectiveness of perineural DEXA, that route of administration is still considered off-label due to potential neurotoxicity [9].

Intravenous DEXA also potentiates PNB and increases the duration of the sensory block. Equipotent doses between perineural and IV routes have been questioned. From published meta-analyses, perineural DEXA seems more effective to prolong PNB analgesia, but no greater difference is observed between both routes when DEXA doses of 8 mg and higher are used [21]. Regarding lower doses of IV DEXA, Desmet and colleagues found a dose-dependent effect on PNB duration after shoulder surgery but only a significant effect for doses higher than 2.5 mg DEXA (i.e., 0.03 mg/kg) [22]. Studies assessing the preventive effect of IV DEXA on RP incidence are still scarce. First, a large retrospective cohort study [5] which included different types of blocks in both upper and lower limbs procedures reported a beneficial effect for an average DEXA dose of 6 mg (range: 4–20 mg). Second, a prospective randomized study including 51 adult patients scheduled for hand surgery found a reduction of RP within the first postoperative 36 h from 50% in the placebo group to 9% in the 16 mg (i.e., around 0.23 mg/kg) IV DEXA group [13]. To the best of our knowledge, the present study is the first to assess a dose-related preventive effect of low IV DEXA doses on RP after axillary PNB in ambulatory patients.

According to the aforementioned findings, a dose-related preventive effect of IV DEXA on RP might be questioned. However, if we compare the incidence of RP in our DEXA-LD (<0.1 mg/kg) with that of RP in Holmberg's study (0.23 mg/kg), the difference is not statistically significant (14/54 [26%] vs. 2/23 [9%], $p = 0.13$, Fisher exact two-tailed). Similarly, if we compare RP incidence in our DEXA-HD group (20%) with that in Holmberg's study (9%), there is no statistically significant difference ($p = 0.33$) [13]. A ceiling effect in DEXA RP preventive effect should also be taken into account. Based on the fact that perineural and intravenous DEXA doses > 8 mg are equipotent to prolong PNB duration and analgesic effect [21], no significant difference in RP incidence could be found regarding IV DEXA-HD in our patients (0.10–0.12 mg/kg: 13/64 = 20%) versus IV DEXA 16 mg (0.23 mg/kg: 2/23 = 9%) [13] versus perineural DEXA 8 mg (7/63 = 11%) [12]. These results further question the mechanisms underlying the DEXA preventive effect on RP.

Prolonged nerve block, hence a smoother recovery of nociceptive sensations, has been proposed as a mechanism to reduce RP [13]. At the doses used in our patients, we did not observe an increase in the duration of PNB what is in opposition with previous studies. In example, IV DEXA 16 mg significantly prolonged the axillary block analgesia [13], and Desmet reported a time extension to the first analgesic request after PNB at an IV DEXA dose as low as 0.03 mg/kg [22]. In contrast to the aforementioned studies, our study was retrospective and powered to assess the rebound pain incidence and not the PNB duration.

It is worth noting that the sensory block duration may not affect the RP phenomenon as previously underlined [5].

Two studies in healthy volunteers [23,24] using a moderate dose of IV DEXA (4 mg) did not observe a prolongation of nerve block duration but pointed out the fact that benefits observed in patients probably rely on the anti-inflammatory effect of IV DEXA [25]. A previous meta-analysis about intravenous DEXA has suggested that only doses higher than 0.1 mg/kg demonstrate analgesic effects which are not dose-related [15]. Our results show a reduction of both pains felt when PNB wears off and RP incidence at IV DEXA doses is lower than 0.1 mg/kg, independent of the axillary block duration. The individual sensitivity to the anti-inflammatory effect of glucocorticoids is variable as observed for the response to other analgesics with anti-inflammatory properties. Among the risk factors of RP, bone surgery and high catastrophizing score are well known [5,6]. Both risk factors interact with inflammatory processes that may be involved in RP.

Bone surgery leads to the local release of pro-inflammatory cytokines, such as interleukin 6 (IL-6), which activate and sensitize sensory nerves, leading to an amplified pain signal [26]. More, these pro-inflammatory mechanisms may be exacerbated in some patients, enhancing postoperative pain and hyperalgesia [27]. For example, a higher level of catastrophizing is associated with greater reactivity of inflammatory mediators (e.g., IL-6) [28] which suggests that cognitive and emotional responses during the experience of pain may shape the pro-inflammatory responses of the immune system to noxious stimulation. The involvement of inflammatory mechanisms in RP may explain the predisposition to RP in patients with a high catastrophization score. Therefore, by reducing the inflammatory cascade, DEXA may help to reduce hyperalgesia when the PNB wears off.

There are some limitations of this study. First, its retrospective nature involving a single center. Additionally, data regarding DEXA administration and data regarding the control group were collected in different cohorts. Second, the follow-up of DEXA patients was limited to the first 24 h, which could have contributed to the loss of additional data. In the literature, late RP, i.e., at 36 and even 48 h, is reported. Finally, the doses of IV DEXA used were left to the discretion of the anesthesiologists in charge of the patients, which may have led to possible distribution bias due to common practices and habits.

It is worth noting that no adverse effects in relation to the administration of DEXA were found in the patients' files. The relatively low doses of DEXA used in our study may actually have contributed to the absence of glycemic disorders in the patients [29]. Similarly, we did not record any cases of perineal irritation in the patients included in our study which is probably due to a slow administration of DEXA (a common practice within our team of anesthetists) [30].

In conclusion, our results support the administration of intraoperative IV DEXA as a preventive measure to reduce the occurrence of RP.

To our knowledge, this study is the first dedicated to investigating the dose-dependent effect of intraoperative DEXA (low doses used to prevent PONV and to improve postoperative analgesia) in the prevention of RP. We found a preventive effect on RP including at very low doses (<0.1 mg/kg) and independent of the PNB duration. A comparison with the existing literature may be in favor of an IV DEXA ceiling effect on RP prevention which contrasts with the IV DEXA dose-related effect on sensory block duration. Further prospective studies should confirm the present findings and investigate the mechanisms underlying the IV DEXA preventive effect on rebound pain.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12134310/s1, File S1: STROBE Statement—Checklist of items that should be included in reports of cohort studies.

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References

1. Kolny, M.; Stasiowski, M.J.; Zuber, M.; Marciniak, R.; Chabierska, E.; Pluta, A.; Jałowiecki, P.; Byrczek, T. Randomized, comparative study of the effectiveness of three different techniques of interscalene brachial plexus block using 0.5% ropivacaine for shoulder arthroscopy. *Anaesthesiol. Intensive Ther.* **2017**, *49*, 47–52. [CrossRef] [PubMed]
2. Hade, A.D.; Okano, S.; Pelecanos, A.; Chin, A. Factors associated with low levels of patient satisfaction following peripheral nerve block. *Anaesth. Intensive Care* **2021**, *49*, 125–132. [CrossRef] [PubMed]
3. Lavand'homme, P. Rebound pain after regional anesthesia in the ambulatory patient. *Curr. Opin. Anaesthesiol.* **2018**, *31*, 679–684. [CrossRef] [PubMed]
4. Dada, O.; Gonzalez Zacarias, A.; Ongaigui, C.; Echeverria-Villalobos, M.; Kushelev, M.; Bergese, S.D.; Moran, K. Does Rebound Pain after Peripheral Nerve Block for Orthopedic Surgery Impact Postoperative Analgesia and Opioid Consumption? A Narrative Review. *Int. J. Environ. Res. Public Health* **2019**, *16*, 3257. [CrossRef]
5. Barry, G.S.; Bailey, J.G.; Sardinha, J.; Brousseau, P.; Uppal, V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. *Br. J. Anaesth.* **2021**, *126*, 862–871. [CrossRef] [PubMed]
6. Touil, N.; Pavlopoulou, A.; Barbier, O.; Libouton, X.; Lavand'homme, P. Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: A prospective randomised, double-blind, placebo-controlled study. *Br. J. Anaesth.* **2022**, *128*, 734–741. [CrossRef]
7. Myles, P.S.; Corcoran, T. Benefits and Risks of Dexamethasone in Noncardiac Surgery. *Anesthesiology* **2021**, *135*, 895–903. [CrossRef]
8. Albrecht, E.; Kern, C.; Kirkham, K.R. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. *Anaesthesia* **2015**, *70*, 71–83. [CrossRef]
9. Desai, N.; El-Boghdadly, K.; Albrecht, E. Peripheral nerve blockade and novel analgesic modalities for ambulatory anesthesia. *Curr. Opin. Anaesthesiol.* **2020**, *33*, 760–767. [CrossRef]
10. Kirkham, K.R.; Albrecht, E. Perineural or intravenous dexamethasone in interscalene brachial plexus block. *Br. J. Anaesth.* **2020**, *124*, 15–17. [CrossRef]
11. Woo, J.H.; Lee, H.J.; Oh, H.W.; Lee, J.W.; Baik, H.J.; Kim, Y.J. Perineural dexamethasone reduces rebound pain after ropivacaine single injection interscalene block for arthroscopic shoulder surgery: A randomized controlled trial. *Reg. Anesth. Pain Med.* **2021**, *46*, 965–970. [CrossRef] [PubMed]
12. Fang, J.; Shi, Y.; Du, F.; Xue, Z.; Cang, J.; Miao, C.; Zhang, X. The effect of perineural dexamethasone on rebound pain after ropivacaine single-injection nerve block: A randomized controlled trial. *BMC Anesthesiol.* **2021**, *21*, 47. [CrossRef] [PubMed]
13. Holmberg, A.; Hassellund, S.S.; Draegni, T.; Nordby, A.; Ottesen, F.S.; Gulestøl, A.; Raeder, J. Analgesic effect of intravenous dexamethasone after volar plate surgery for distal radius fracture with brachial plexus block anaesthesia: A prospective, double-blind randomised clinical trial. *Anaesthesia* **2020**, *75*, 1448–1460. [CrossRef] [PubMed]
14. Quartana, P.J.; Buenaver, L.F.; Edwards, R.R.; Klick, B.; Haythornthwaite, J.A.; Smith, M.T. Pain catastrophizing and salivary cortisol responses to laboratory pain testing in temporomandibular disorder and healthy participants. *J. Pain* **2010**, *11*, 186–194. [CrossRef] [PubMed]
15. De Oliveira, G.S., Jr.; Almeida, M.D.; Benzon, H.T.; McCarthy, R.J. Perioperative single dose systemic dexamethasone for postoperative pain: A meta-analysis of randomized controlled trials. *Anesthesiology* **2011**, *115*, 575–588. [CrossRef]
16. Tanaka, K.; Nishigami, T.; Mibu, A.; Manfuku, M.; Yono, S.; Yukioka, M.; Miki, K. Cutoff Value for Short Form of Central Sensitization Inventory. *Pain. Pract.* **2020**, *20*, 269–276. [CrossRef]
17. Bouhassira, D.; Attal, N.; Alchaar, H.; Boureau, F.; Brochet, B.; Bruxelle, J.; Cunin, G.; Fermanian, J.; Ginies, P.; Grun-Overdyking, A.; et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* **2005**, *114*, 29–36. [CrossRef]

18. Garnaud, B.; Mares, O.; L'Hermite, J.; Vialles, N.; Gricourt, Y.; Lannelongue, A.; Lefrant, J.Y.; Cuvillon, P. Multimodal oral analgesia strategy after ambulatory arthroscopic shoulder surgery: Case series using adaptive therapeutic approaches by sequential analysis. *J. Shoulder Elbow Surg.* **2021**, *30*, 250–257. [CrossRef]
19. Albrecht, E.; Reynvoet, M.; Fournier, N.; Desmet, M. Dose-response relationship of perineural dexamethasone for interscalene brachial plexus block: A randomised, controlled, triple-blind trial. *Anaesthesia* **2019**, *74*, 1001–1008. [CrossRef]
20. Woo, J.H.; Kim, Y.J.; Kim, D.Y.; Cho, S. Dose-dependency of dexamethasone on the analgesic effect of interscalene block for arthroscopic shoulder surgery using ropivacaine 0.5%: A randomised controlled trial. *Eur. J. Anaesthesiol.* **2015**, *32*, 650–655. [CrossRef]
21. Zorrilla-Vaca, A.; Li, J. Dexamethasone Injected Perineurally is More Effective than Administered Intravenously for Peripheral Nerve Blocks: A Meta-Analysis of Randomized Controlled Trials. *Clin. J. Pain* **2018**, *34*, 276–284. [CrossRef] [PubMed]
22. Desmet, M.; Vanneste, B.; Reynvoet, M.; Van Cauwelaert, J.; Verhelst, L.; Pottel, H.; Missant, C.; Van de Velde, M. A randomised controlled trial of intravenous dexamethasone combined with interscalene brachial plexus blockade for shoulder surgery. *Anaesthesia* **2015**, *70*, 1180–1185. [CrossRef] [PubMed]
23. Marhofer, P.; Columb, M.; Hopkins, P.M.; Greher, M.; Marhofer, D.; Bienzle, M.; Zeitlinger, M. Dexamethasone as an adjuvant for peripheral nerve blockade: A randomised, triple-blinded crossover study in volunteers. *Br. J. Anaesth.* **2019**, *122*, 525–531. [CrossRef]
24. Short, A.; El-Boghdadly, K.; Clarke, H.; Komaba, T.; Jin, R.; Chin, K.J.; Chan, V. Effect of intravenous dexamethasone on the anaesthetic characteristics of peripheral nerve block: A double-blind, randomised controlled, dose-response volunteer study. *Br. J. Anaesth.* **2020**, *124*, 92–100. [CrossRef]
25. Desmet, M.; Braems, H.; Reynvoet, M.; Plasschaert, S.; Van Cauwelaert, J.; Pottel, H.; Carlier, S.; Missant, C.; Van de Velde, M.I.V. and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: A prospective, randomized, placebo-controlled study. *Br. J. Anaesth.* **2013**, *111*, 445–452. [CrossRef] [PubMed]
26. Newman, H.; Shih, Y.V.; Varghese, S. Resolution of inflammation in bone regeneration: From understandings to therapeutic applications. *Biomaterials* **2021**, *277*, 121114. [CrossRef] [PubMed]
27. Kidd, B.L.; Urban, L.A. Mechanisms of inflammatory pain. *Br. J. Anaesth.* **2001**, *87*, 3–11. [CrossRef]
28. Edwards, R.R.; Kronfli, T.; Haythornthwaite, J.A.; Smith, M.T.; McGuire, L.; Page, G.G. Association of catastrophizing with interleukin-6 responses to acute pain. *Pain* **2008**, *140*, 135–144. [CrossRef]
29. Corcoran, T.B.; O'Loughlin, E.; Chan, M.T.V.; Ho, K.M. Perioperative ADministration of Dexamethasone And blood Glucose concentrations in patients undergoing elective non-cardiac surgery—The randomised controlled PADDAG trial. *Eur. J. Anaesthesiol.* **2021**, *38*, 932–942. [CrossRef]
30. Crandell, J.T. Perineal pruritus after the administration of iv dexamethasone. *Can. J. Anaesth.* **2004**, *51*, 398. [CrossRef]

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