prosthesis

MDPI

Article

Perioperative Blood Management Programme in Jehovah's Witnesses Undergoing Total Hip Arthroplasty

Giuseppe Solarino [1,*], Giovanni Vicenti [1], Davide Bizzoca [1], Domenico Zaccari [1], Walter Ginestra [1], Davide Ferorelli [2], Matteo D'aprile [1] and Biagio Moretti [1]

[1] Orthopaedics Unit, Department DiBRaiN, University of Bari "Aldo Moro", AOU Consorziale Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy; dott.gvicenti@gmail.com (G.V.); da.bizzoca@gmail.com (D.B.); biagio.moretti@uniba.it (B.M.)

[2] Section of Legal Medicine, Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", AOU Consorziale Policlinico di Bari, Piazza Giulio Cesare, 11, 70124 Bari, Italy

* Correspondence: giuseppe.solarino@uniba.it

Abstract: Total hip arthroplasties aim to improve quality of life and reduce pain in patients suffering from late-stage hip osteoarthritis. On the other hand, it may represent a risky surgical procedure in people who refuse blood products because of religious beliefs, such as Jehovah's Witnesses (JW). Preoperative optimisation protocols of these patients allow medical professionals to perform arthroplasties in a safer manner, avoiding allogeneic blood transfusion. In our retrospective study, two groups of patients were evaluated. Group 1 included JW patients who underwent a preoperative Hb optimisation program; Group 2 included non-JW patients authorizing transfusion in case of necessity. Differences in Hb levels were as follows: before surgery (JW 14.24 $\pm$ 1.10 vs. non-JW 12.48 $\pm$ 1.00, p-value $\leq$ 0.05), and after surgery (day 1 Hb: JW 12.88 $\pm$ 0.90 vs. non-JW 10.04 $\pm$ 1.30, p-value $\leq$ 0.05; day 3 Hb: JW 14.65 $\pm$ 0.80 vs. non-JW 9.10 $\pm$ 0.90 p-value $\leq$ 0.05). Moreover, cost-effectiveness strategies were evaluated in both groups. Our findings support that patient blood management programs are a safe and good strategy in hip prosthetic surgery, decreasing risks and transfusion overuse.

Keywords: Jehovah's witnesses; patient blood management; total hip arthroplasty; no blood transfusion

Citation: Solarino, G.; Vicenti, G.; Bizzoca, D.; Zaccari, D.; Ginestra, W.; Ferorelli, D.; D'aprile, M.; Moretti, B. Perioperative Blood Management Programme in Jehovah's Witnesses Undergoing Total Hip Arthroplasty. *Prosthesis* **2023**, *5*, 1011–1019. https://doi.org/10.3390/prosthesis5040070

Academic Editor: Marco Cicciu

Received: 13 July 2023
Revised: 23 August 2023
Accepted: 3 October 2023
Published: 6 October 2023

1. Introduction

Major Orthopaedic surgery, including total hip arthroplasty, may result in significant perioperative bleeding, thus requiring allogeneic red blood cell (RBC) transfusions. Since pre-operative haemoglobin (Hb) concentration is a major predictor of peri-operative transfusion, Hb optimisation before surgery is a cornerstone in patient blood management (PBM) [1,2].

Healthcare institutions are showing an increasing interest towards the PBM program to reduce blood transfusion rates, since it is one of the most abused and expensive treatments [2]. In recent years, moreover, National Blood Centre (CNS) data have reported a decreasing trend in blood donor rates in Italy [3].

Furthermore, the population's mean age is increasing, meaning that, in future years, there will be an increased need for blood components for elderly patients and a concomitantly reduced pool of donors among young people [3]. Finally, blood component quality and safety requirements are higher nowadays, thus also having an increased cost [3].

The multimodal PBM approach is more effective than the traditional transfusion approach, from both a clinical and an economic point of view. Nevertheless, the cost-effectiveness of Hb optimisation as a single PBM strategy has not been evaluated in patients undergoing orthopaedic surgery [4–13].

PBM programs that reduce the risk and use of transfusions also have reverberations about ethical, spiritual, and religious issues [4–13].

In many National Health contexts, especially in Western Countries, several Laws have been promulgated according to the Hippocratic ethical tradition, where the patient's conscious and freely expressed concern about his/her health condition becomes the nodal point of the lawfulness of medical/surgical treatment.

Many of these laws, such as Italian Law n. 219, regulate informed consent for patients who must undergo medical treatment and concerning the future diagnostic therapeutic practices known as a living will [14].

Although religiosity and spirituality are sometimes underestimated in daily clinical practice, they play a central role in medicine and surgery. This datum is confirmed when considering Jehovah's Witness patients' "religious restrictions" in the approach to the healthcare system. These restrictions rely on the principles which state that a human being's soul lies in the blood and, as such, it cannot be passed on to another person.

The current legislative direction in Western countries is to promote and enhance the relationship of care and trust between doctor and patient, the professional autonomy and responsibility of the doctor, the decisional autonomy and right to self-determination, to make an informed and voluntary choice about the possible treatment of the patient [15].

This study aims to evaluate the Hb levels and the cost-effectiveness of pre-operative Hb optimisation, to avoid the need for RBC transfusion, in Jehovah's Witness (JW) patients undergoing THA and refusing allogeneic blood.

2. Materials and Methods

A retrospective study recruiting 60 patients undergoing primary total hip arthroplasty (THA) for primary hip osteoarthritis (HOA), between January 2018 and January 2023 was conducted at our university hospital.

The recruited patients were divided into two different groups. Group 1 included 30 JW patients who refused blood transfusions and underwent a pre-operative Hb optimization program to avoid severe postoperative anaemia and subsequent transfusion indication. The preoperative Hb optimisation program started 1 month before surgery. At recruitment, all Group-1 patients underwent a complete blood count test and a Transfusion Medicine Specialist's (TSM) consultation and complementary lab exams, including serum ferritin, serum transferrin, TSAT, folate, vitamin B12. were performed when necessary to investigate the underlying cause of anaemia. Based on the lab test results, the TSM evaluated the need to start one of the following treatments: oral iron therapy, intravenous (IV) ferric gluconate, IV ferric carboxymaltose (Ferinject® 500 mg or 1000 mg), vitamin B12, oral folate, or recombinant erythropoietin.

Additional TSM consultations were required to re-evaluate the patients' anaemia until no surgery contraindication was finally declared. Intraoperative blood saving (IOS) was used during all of the Group-1 patients' surgical procedures.

Group 2 included 30 gender-, age-, and comorbidity-matched non-JW patients, who underwent THA for primary HOA between January 2016 and December 2017 at our institution, approving intraoperative/postoperative homologous blood transfusions if needed. They did not receive a routine TSM consultation nor erythropoietic stimulating therapy unless anaemia was diagnosed during the first pre-hospitalization visit after lab tests. All Group-2 patients received RBC transfusions to correct postoperative anaemia. Homologous blood transfusion was performed in the presence of all the following conditions: Hb between 7–10 g/dL; clinical signs of anaemia; and cardiac or pulmonary comorbidities.

Comparison between the groups showed no significant differences in terms of gender representation, mean age, and comorbidities (ASA score, Charlson Comorbidity Index).

According to clinical and radiographic parameters, the preoperative diagnosis was late-stage hip osteoarthritis for all patients [16–19].

The study aimed to evaluate Hb levels at pre-hospitalization, before and after surgery (day 1, day 3).

Results are reported as the mean ± SD. The Shapiro–Wilk test was performed to assess the normal distribution of the data. An unpaired t-test was used to perform pairwise

comparisons for pre-hospitalization, preoperative, day 1, day 2, and day 3 Hb mean values between the 2 groups. The Wilcoxon rank sum test was performed to compare Group-1 and Group-2 costs. Significance was set for p-values ≤ 0.05.

Drug prices were gathered from the Italian Drug Administration Agency (AIFA) website, while the cost of a single hospital transfusion medicine consultation was gathered from the local regional price list. Two different price values were taken into consideration for RBC transfusion. The price of a single RBC unit is EUR 181.00 (as established by local law [5]), while the estimated cost of the entire transfusion procedure (blood group tests, type and screen, medical consultation, distribution procedures of blood components, traceability, hemovigilance, and adverse reactions management) is EUR 400.00 according to CNS orthopaedic recommendations [3].

Surgical Procedure and Aftercare

Surgical procedures were performed by the same surgical team in both groups with identical operative techniques for primary THA, using a posterolateral approach to the hip. The following pharmacological anti-thromboembolic prophylaxis was administered in both groups: low molecular weight heparin (Enoxaparin 40,000 UI) at a dose of 0.4 mL per day subcutaneously, starting from the evening before the operation and continuing for an average of 30 days. No postoperative intraarticular drainage has been used since there are no significant advantages regarding blood loss, transfusion rate, and pain, meaning it was also cost-saving [19].

3. Results

The main data of the study are summarized in Table 1. Table 2 compares the perioperative Hb levels in both groups.

Table 1. Main data of the study.

	JW (Group 1)	Non-JW (Group 2)
Age		
Mean ± SD	64.7 ± 4.77	64.33 ± 5.35
Range	56–73	57–74
Gender		
Female, *n* (%)	16 (53.3%)	16 (53.3%)
BMI		
Mean ± SD	26.54 ± 3.44	26.21 ± 3.76
HHS		
Mean ± SD	56.35 ± 4.67	55.77 ± 5.35

SD = Standard deviation; HHS = Harris Hip Score.

Table 2. Summary of Hb values.

	JW (Group 1)	Non-JW (Group 2)	*p*-Value *
Hb values (mean ± SD, g/dL)			
Pre hosp.	13.71 ± 1.00	12.69 ± 1.10	0.08
Pre-surgery	14.12 ± 1.10	12.48 ± 1.44	0.023
Post-op day 1	12.88 ± 0.90	10.04 ± 1.30	0.01
Post-op day 3	11.68 ± 1.23	9.10 ± 0.90	0.003
Mean post-op Hb decrease (mean ± SD, g/dL)	−0.90 ± 0.73	−2.43 ± 0.81	0.006

* Comparison between groups.

In the JW group (Group 1), each patient was screened for preoperative anaemia detection and management. The Hb optimisation program was even employed in non-anaemic patients, to obtain better preoperative Hb levels.

The Hb optimisation program in the JW group proved effective since a significant difference between after-treatment mean preoperative Hb (14.24 ± 1.10 g/dL) and pre-hospitalisation mean Hb (13.71 ± 1.00 g/dL) was observed.

In the non-JW group (Group 2), no patient received preoperative Hb level optimisation. They were all transfused after surgery since they all developed post-operative anaemia, while in the JW group, no patient received blood transfusion even when they developed postoperative anaemia.

A statistically significant difference between patients who underwent perioperative Hb optimisation (the JW group), and the non-JW group was evident. Comparison between the groups shows (Table 1) Hb levels (g/dL) before surgery were as follows: JW 14.12 ± 1.10 vs. non-JW 12.48 ± 1.44 (p-value = 0.023); after surgery, day 1 Hb: JW 12.88 ± 0.9 vs. non-JW 10.04 ± 1.30 (p-value = 0.01); day 3 Hb: JW 11.68 ± 1.23 vs. non-JW 9.10 ± 0.90 (p-value = 0.003). Hb concentrations declined following surgery. In the JW group, the mean Hb concentration decrease was 0.9 ± 0.63 g/dL. In the non-JW group, the mean Hb concentration decrease was 2.43 ± 0.80 g/dL.

A statistically significant difference was observed in the magnitude of the mean operative decrease in Hb concentration between the JW group and the non-JW group (p-value ≤ 0.05) (Figure 1). This was caused by the employment of intraoperative blood salvage, more accurate haemostasis and the employment of intravenous tranexamic acid during surgery.

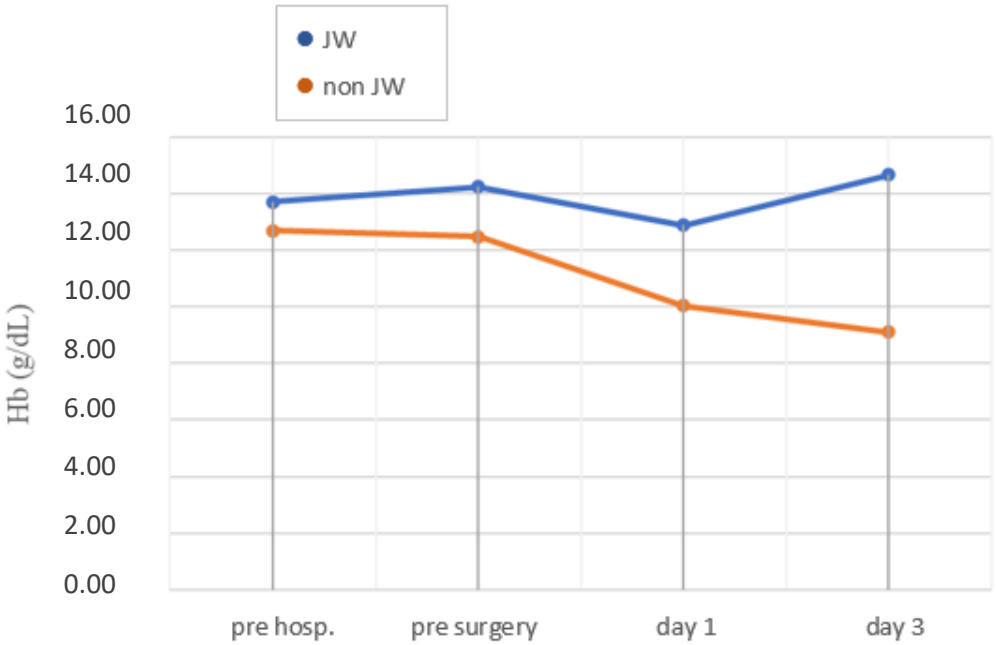

Figure 1. Evolution of mean Hb values in the JW and control groups pre-hospitalisation, pre-surgery, day 1, and day 3.

Cost-wise, the mean expense of treating the JW group (including drugs and transfusion medicine consultations) was EUR 561.16, while the non-JW mean cost was EUR 318.88 per transfused RBC unit.

Furthermore, considering the costs of the transfusion procedure (blood group tests, type and screen, medical consultation, distribution procedures of blood components, traceability, hemovigilance, and adverse reactions management) the mean cost of a non-JW patient rises to EUR 669.29. Nevertheless, in both cases the mean cost of the two groups had no statistically significant difference (p > 0.05), meaning that the two groups of treatment have the same economic burden.

4. Discussion

THA has been elected the operation of the 20th century, as its introduction in daily orthopaedic practice has radically revolutionized the natural history of hip osteoarthritis, with very satisfying long-term results reported [1].

Currently, THA surgery is one of the surgical procedures most frequently performed in orthopaedics and traumatology. The main surgical indications for THA are intracapsular hip fractures and both primary and secondary hip osteoarthritis [2,3].

Osteoarthritis (OA), because of its high prevalence in Western countries, is a leading cause of disability and pain in elderly people. The Osteoarthritis Research Society International (OARSI) defines OA as "a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro-and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity" [14].

OA, affecting 250 million individuals worldwide, especially adults older than 65, is a significant social health problem [15]. Although several genetic and environmental risk factors promote the development of OA, including body mass index (BMI), gender, age, physical activity, ethnicity, and muscle weakness, the exact pathogenesis of OA remains unclear [14]. Recent studies have discussed a potential relationship between gut microbiota alterations and OA-related functional limitations and pain [14–21].

Iron deficiency (ID) is a pathologic condition characterized by insufficient iron availability concerning the organism's needs [22]. It could be present with or without anaemia [22]. ID is the most common nutritional deficiency worldwide, especially in the female sex, and can be found in several chronic diseases including chronic kidney disease, chronic heart failure, and inflammatory bowel disease. I could be asymptomatic or present with specific signs and symptoms, including impairment of cognitive functioning, restless leg syndrome, chronic fatigue, musculoskeletal dysfunction, and anaemia [22]. Consequently, ID is often underdiagnosed [22]. If anaemia is absent, ID should be diagnosed with the following consensus laboratory test cut-off values: serum ferritin < 100 ng/mL or transferrin saturation (TSAT) < 20% [22].

Treatment options for ID fall into two broad categories, oral and intravenous (IV) iron preparations. When choosing adequate therapy, the following factors should be considered: the degree of the iron deficit; the patient's inflammatory status; and the time frame that is available to achieve adequate iron stores [22].

Oral iron treatments (i.e., ferrous sulphate) are the most widely used, mainly because of their lower costs, but several limitations impact their effectiveness in patients with inflammatory conditions. Oral iron absorption from the ingested amount is low (on average 10%). During active inflammation, iron absorption is further reduced because of hepcidin-mediated ferroportin inhibition. Thus, in these cases, oral iron supplementation may fail to supply sufficient iron amounts. In addition, the efficacy of oral iron preparations may be limited by the prolonged treatment course (typically months) required to replenish iron stores and the high rate of treatment-related gastroenteric adverse effects, potentially resulting in poor patient compliance and suboptimal response to medication [23].

The alternative solution, IV iron treatment, can deliver a larger iron supply, effectively replenishing iron stores more rapidly than oral iron and bypassing the risk of GI side effects because of the administration route. The IV treatment options include iron sucrose, ferric gluconate, iron isomaltose, iron poly-maltose, and ferric carboxymaltose. IV ferric carboxymaltose (Ferinject®) is a colloidal solution composed of a polynuclear iron III-oxyhydroxide core stabilized by carboxymaltose. This complex is phagocyted by the macrophages, degraded in the reticuloendothelial system and further delivered to the iron transporter protein transferrin [23]. Consequently, no large amounts of ionic iron are released into the serum [23].

In the Randomised Control Trials (RCTs), ferric carboxymaltose was revealed to be effective in the postoperative treatment of patients suffering from anaemia following TKA [24] or major orthopaedic surgery [25]. In TKA patients with perioperative anaemia,

ferric carboxymaltose was more effective than oral ferrous glycine sulphate in achieving a Hb level > 12 g/dL [24].

In the previous perspective, non-interventional multicentre studies recruiting patients undergoing major orthopaedic surgery, preoperative ferric carboxymaltose was compared with retrospective cohorts of anaemic patients treated with preoperative iron sucrose [26]. Patients receiving ferric carboxymaltose were significantly more likely to achieve iron replenishment than the historical cohort receiving iron sucrose (82 vs. 62% of patients; $p < 0.05$). Moreover, patients treated with ferric carboxymaltose received fewer drug doses (mean 2 vs. 5 doses) and were less likely to require a blood transfusion (9 vs. 24%) [26]. Furthermore, a recent randomised multicentre study has demonstrated the superiority and safety of carboxymaltose iron infusion compared to oral marital therapy in the correction of iron deficiency anaemia, especially in patients who were non-responders to oral therapy [27,28]. The mean Hb increase was significantly greater in FCM receivers than in the oral iron-treated group (1.57 g/dL vs. 0.80 g/dL, $p = 0.001$) [27].

In the EU, ferric carboxymaltose administration is advised when oral iron preparations are ineffective or contraindicated. Common adverse drug reactions observed during clinical studies or reported in post-marketing experiences include nausea (the most frequent reaction), injection site reactions, hypophosphataemia, headache, flushing, dizziness, fever, and hypertension [29–31].

This retrospective study aims to evaluate the effectiveness of a change of practice in the preoperative treatment of anaemia using iron supplementation as recommended by CNS orthopaedic recommendations [3] to reduce the rate of allogenic blood transfusions.

This new approach testing took place firstly in JW patients who refuse blood transfusions for religious reasons, considering their bloodless-surgery approach an opportunity to implement blood-saving strategies whose benefits will affect every patient. Previous studies proved that the preoperative Hb optimisation program reduced the incidence of postoperative anaemia and the use of allogenic blood transfusion in THA [5]. Hou et al. found that an Hb level at admission < 12.4 g/dL is a predictor of blood transfusion [6] thus, a good optimisation program can permit to performance of this type of surgery safely. This is confirmed by another study showing that a good preoperative Hb protocol allows the execution of joint arthroplasties without allogenic transfusion in anaemic patients [7].

In addition, this is in line with the data reported by Mottla et al., who stated that arthroplasties are safer with a preoperative optimisation program [8]. Moreover, RBC transfusion has several adverse effects identified in different studies. These comprise longer hospital stays, increased 90-day mortality, post-operative cardiac complications, acute haemolytic reactions, pneumonia, and bacterial infections [9–11]. We compared this approach (in the JW group) to the transfusion-based approach without preoperative Hb optimisation (in the non-JW group), proving that JW patients have better Hb values pre-and post-operatively.

A significative difference was shown among the pre-and post-operative (day 1, day 3) Hb values of the JW patients who underwent Hb optimisation preoperatively and the control group of non-JW patients ($p \leq 0.05$).

Other studies showed higher Hb values postoperatively in patients who underwent perioperative Hb optimisation [5].

In this study, the costs of these two approaches have been analysed, since the PBM approach is more effective from an economic point of view than the traditional transfusion approach [4], but the cost-effectiveness of Hb optimisation as a single PBM strategy has not been evaluated in patients undergoing orthopaedic surgery so far. We found that, despite the great number of expensive drugs, lab tests, and transfusion medicine consultations, there, is no significative difference ($p > 0.05$) between the mean cost of Hb optimisation in a JW patient and the mean cost for transfusions in non-JW patients. Costs directly borne by our clinic may seem greater for a Hb optimisation program than a blood-transfusion approach but considering the overall esteemed cost of the whole transfusion

procedure for the national health service (EUR 400.00) [3], the PBM approach reveals its economic convenience.

It is important to consider saving blood components, given the decreasing rates of blood donors and the increasing blood component costs, because of stricter safety requirements. This point of view was not considered in our study, since all non-JW patients received a blood transfusion, but it is proven by other studies [5]. Furthermore, several studies on the restrictive haemoglobin transfusion threshold showed the same or better perioperative outcomes compared to a more liberal transfusion threshold [12–19]. This is also confirmed by Gupta et al. who demonstrated how a restrictive haemoglobin policy, combined with good patient blood management, is well tolerated even in elderly patients [1].

Furthermore, it is important to note that recently the use of allogenic blood transfusion has been related to a higher risk of periprosthetic joint infections (PJIs) [20], thus reducing the number of blood transfusions could be also a useful strategy to lower the risk of PJIs.

Several studies on restrictive haemoglobin transfusion threshold showed the same or better perioperative outcomes compared with a more liberal transfusion threshold [20]. This is also confirmed by Gupta et al., who demonstrated how a restrictive haemoglobin policy, combined with good patient blood management, is well tolerated even in elderly patients [1]. Other studies analysed the cost-effectiveness of preoperative Hb optimisation strategies, and they also found seemingly increased costs in the optimisation group [21]. A hypothetical computer-simulated trial study calculated the cost per transfused patient avoided and RBC unit spared for the different probability of transfusion in the optimisation group. As expected, costs increased exponentially as the probability of transfusion decreased. There were no differences in transfusion requirements between the optimisation and control groups for probabilities of transfusion over 20%. Cost savings fall to zero when the proportion of patients who would require transfusion in the optimisation arm decreases.

In other words, Hb optimisation is disadvantageous when applied to patients with low transfusion probabilities, while it is cost-effective when applied to patients with high transfusion risk. optimisation

One limitation of this study is that the Hb optimisation program was applied to all patients in Group 1 since they were JW refusing blood transfusion in any case, including when of vital necessity, so we had to eliminate every risk of recurring blood transfusion.

Furthermore, this is a retrospective study, and the surgeon was unblinded, therefore he could take special care of JW patients during surgery.

5. Conclusions

PBM programs offer different treatment strategies to face Hb optimisation in elective surgery. Our study adds to the growing body of literature regarding the efficacy of PBM that can be applied to patients other than JWs. It is a safe strategy, reducing risk and cost, and improving outcomes. Less importantly, PBM improves perioperative bleeding management and reduces the incorrect use of blood transfusions.

Author Contributions: Conceptualization, G.S., G.V., B.M. and D.B.; methodology, G.V. and D.B.; investigation, D.Z., W.G. and M.D.; data curation, G.V. and G.S.; writing—original draft preparation, D.Z., W.G., D.F. and M.D.; writing—review and editing, G.V. and D.B.; visualization, G.S.; supervision, D.B.; project administration, G.S. and B.M.; funding acquisition, G.S. and B.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted by the Declaration of Helsinki and approved by the Ethics Committee of AOU Policlinico di Bari (protocol code 6479, date of approval 27 July 2020).

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Data Availability Statement: Data is available upon request to the corresponding author.

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

References

1. Gupta, P.B.; DeMario, V.M.; Amin, R.M.; Gehrie, E.A.; Goel, R.; Lee, K.H.K.; Yang, W.W.; Khanuja, H.S.; Sterling, R.S.; Ness, P.M.; et al. Patient Blood Management Program Improves Blood Use and Clinical Outcomes in Orthopedic Surgery. *Anesthesiology* **2018**, *129*, 1082–1091. [CrossRef]
2. Gómez-Ramírez, S.; Maldonado-Ruiz, M.Á.; Campos-Garrigues, A.; Herrera, A.; Muñoz, M. Short-term perioperative iron in major orthopaedic surgery: State of the art. *Vox Sang.* **2019**, *114*, 3–16. [CrossRef]
3. Vaglio, S.; Prisco, D.; Biancofiore, G.; Rafanelli, D.; Lisanti, M.; Andreani, L.; Antonioli, P.; Basso, L.; Velati, C.; Grazzin, G.; et al. *Raccomandazioni per l'implementazione del Programma di Patient Blood Management, Applicazione in Chirurgia Ortopedica Maggiore Elettiva dell' Adulto (a Cura di PBM IT)*; Centro Nazionale Sangue: Rome, Italy; Available online: http://pbm.centronazionalesangue.it/MC-API/Risorse/Raccomandazioni%20Patient%20Blood%20Management.pdf (accessed on 24 January 2023).
4. Hofmann, A.; Ozawa, S.; Farrugia, A.; Farmer, S.L.; Shander, A. Economic considerations on transfusion medicine and patient blood management. *Best Pract. Res. Clin. Anaesthesiol.* **2013**, *27*, 59–68. [CrossRef]
5. Kopanidis, P.; Hardidge, A.; McNicol, L.; Tay, S.; McCall, P.; Weinberg, L. Perioperative blood management programme reduces the use of allogenic blood transfusion in patients undergoing total hip and knee arthroplasty. *J. Orthop. Surg. Res.* **2016**, *11*, 28. [CrossRef]
6. Kadar, A.; Chechik, O.; Steinberg, E.; Reider, E.; Sternheim, A. Predicting the need for blood transfusion in patients with hip fractures. *Int. Orthop.* **2013**, *37*, 693–700. [CrossRef]
7. Suh, Y.S.; Nho, J.H.; Choi, H.S.; Ha, Y.C.; Park, J.S.; Koo, K.H. A protocol avoiding allogeneic transfusion in joint arthroplasties. *Arch. Orthop. Trauma Surg.* **2016**, *136*, 1213–1226. [CrossRef]
8. Mottla, J.L.; Murphy, J.P.; Keeling, L.E.; Verstraete, R.; Zawadsky, M.W. Role of arthroplasty in the Jehovah's Witness population. *Eur. J. Orthop. Surg. Traumatol.* **2021**, *31*, 1097–1104. [CrossRef]
9. Pedersen, A.B.; Mehnert, F.; Overgaard, S.; Johnsen, S.P. Allogeneic blood transfusion and prognosis following total hip replacement: A population-based follow-up study. *BMC Musculoskelet. Disord.* **2009**, *10*, 167. [CrossRef]
10. Arshi, A.; Lai, W.C.; Iglesias, B.C.; McPherson, E.J.; Zeegen, E.N.; Stavrakis, A.I.; Sassoon, A.A. Blood transfusion rates and predictors following geriatric hip fracture surgery. *Hip Int.* **2021**, *31*, 272–279. [CrossRef]
11. Viberg, B.; Gundtoft, P.H.; Schønnemann, J.; Pedersen, L.; Andersen, L.R.; Titlestad, K.; Madsen, C.F.; Lauritsen, J.; Overgaard, S. Introduction of national guidelines for restrictive blood transfusion threshold for hip fracture patients—A consecutive cohort study based on complete follow-up in national databases. *J. Orthop. Surg. Res.* **2018**, *13*, 116. [CrossRef]
12. Amin, R.M.; DeMario, V.M.; Best, M.J.; Shafiq, B.; Hasenboehler, E.A.; Sterling, R.S.; Frank, S.M.; Khanuja, H.S. A Restrictive Hemoglobin Transfusion Threshold of Less Than 7 g/dL Decreases Blood Utilization Without Compromising Outcomes in Patients with Hip Fractures. *J. Am. Acad. Orthop. Surg.* **2019**, *27*, 887–894. [CrossRef] [PubMed]
13. Basora, M.; Pereira, A.; Coca, M.; Tió, M.; Lozano, L. Cost-effectiveness analysis of ferric carboxymaltose in pre-operative haemoglobin optimisation in patients undergoing primary knee arthroplasty. *Blood Transfus.* **2018**, *16*, 438–442. [CrossRef] [PubMed]
14. Di Paolo, M.F.; Gori, L.P.; Turillazzi, E. A review and analysis of new Italian law 219/2017: Provisions for informed consent and advance directives treatment. *BMC Med. Ethics* **2019**, *20*, 17. [CrossRef] [PubMed]
15. Delbon, P. The protection of health in the care and trust relationship between doctor and patient: Competence, professional autonomy and responsibility of the doctor and decision-making autonomy of the patient. *J. Public Health Res.* **2018**, *7*, 1423. [CrossRef]
16. Laforgia, R.; Specchiulli, F.; Solarino, G.; Nitti, L. Radiographic variables in normal and osteoarthritic hips. *Bull. Hosp. Jt. Dis.* **1996**, *54*, 215–221.
17. Solarino, G.; Bizzoca, D.; Moretti, A.M.; D'Apolito, R.; Moretti, B.; Zagra, L. Sex and Gender-Related Differences in the Outcome of Total Hip Arthroplasty: A CurrentConcepts Review. *Medicina* **2022**, *58*, 1702. [CrossRef]
18. Solarino, G.; Moretti, L.; Vicenti, G.; Bizzoca, D.; Piazzolla, A.; Moretti, B. Hip hemiarthroplasty with modular-neck: Is it useful in residents' learning curve? A prospective clinical trial. *Hip Int.* **2020**, *30* (Suppl. S2), 30–36. [CrossRef]
19. Solarino, G.; Zagra, L.; Piazzolla, A.; Morizio, A.; Vicenti, G.; Moretti, B. Results of 200 Consecutive Ceramic-on-Ceramic Cementless Hip Arthroplasties in Patients Up To 50 Years of Age: A 5-24 Years of Follow-Up Study. *J. Arthroplast.* **2019**, *34*, S232–S237. [CrossRef]
20. Vicenti, G.; Solarino, G.; Zaccari, D.; Bizzoca, D.; Delmedico, M.; Carrozzo, M.; Ottaviani, G.; Simone, F.; Zavattini, G.; Moretti, B. Perioperative blood management programme in Jehovah's witnesses undergoing total knee arthroplasty: Clinical results and cost-benefit analysis. *Orthop. Rev.* **2023**, *14*. [CrossRef]
21. Vicenti, G.; Bizzoca, D.; Solarino, G.; Moretti, F.; Ottaviani, G.; Simone, F.; Zavattini, G.; Maccagnano, G.; Noia, G.; Moretti, B. The role of biophysical stimulation with pemfs in fracture healing: From bench to bedside. *J. Biol. Regul. Homeost. Agents* **2020**, *34* (Suppl. S1), 131–135.

22. Cappellini, M.D.; Comin-Colet, J.; de Francisco, A.; Dignass, A.; Doehner, W.; Lam, C.S.; Macdougall, I.C.; Rogler, G.; Camaschella, C.; Kadir, R.; et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis, and management. *Am. J. Hematol.* **2017**, *92*, 1068–1078. [CrossRef] [PubMed]
23. Scott, L.J. Ferric Carboxymaltose: A Review in Iron Deficiency. *Drugs* **2018**, *78*, 479. [CrossRef] [PubMed]
24. Bisbe, E.; Moltó, L.; Arroyo, R.; Muniesa, J.M.; Tejero, M. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for post-operative anaemia after total knee arthroplasty. *Br. J. Anaesth.* **2011**, *107*, 477–478. [CrossRef] [PubMed]
25. Khalafallah, A.A.; Yan, C.; Al-Badri, R.; Robinson, E.; Kirkby, B.E.; Ingram, E.; Gray, Z.; Khelgi, V.; Robertson, I.K.; Kirkby, B.P. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: A prospective, open-label, randomised controlled trial. *Lancet Haematol.* **2016**, *3*, e415–e425. [CrossRef]
26. Bisbe, E.; García-Erce, J.A.; Díez-Lobo, A.I.; Muñoz, M. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. *Br. J. Anaesth.* **2011**, *107*, 477–478. [CrossRef] [PubMed]
27. Onken, J.E.; Bregman, D.B.; Harrington, R.A.; Morris, D.; Acs, P.; Akright, B.; Barish, C.; Bhaskar, B.S.; Smith-Nguyen, G.N.; Butcher, A.; et al. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anaemia. *Transfusion* **2014**, *54*, 306–315. [CrossRef]
28. Theusinger, O.M.; Leyvraz, P.F.; Schanz, U.; Seifert, B.; Spahn, D.R. Treatment of Iron Deficiency Anemia in Orthopedic Surgery with Intravenous Iron: Efficacy and Limits: A Prospective Study. *Anesthesiology* **2007**, *107*, 923–927. [CrossRef]
29. Bartosz, P.; Marczyński, W.; Para, M.; Kogut, M.; Białecki, J. Comparative study of suction drainage placement in cementless hip replacement among patients undergoing extended thromboprophylaxis: A prospective randomized study. *BMC Musculoskelet. Disord.* **2021**, *22*, 688. [CrossRef]
30. Iliopoulou-Kosmadaki, S.; Hadjimichael, A.C.; Kaspiris, A.; Lianou, I.; Kalogridaki, M.; Trikoupis, I.; Touzopoulos, P.; Velivasakis, E.; Sperelakis, I.; Laskaratou, E.D.; et al. Impact of Preoperative Quality of Life and Related Factors on the Development of Surgical Site Infections Following Primary Total Joint Arthroplasty: A Prospective Case-Control Study with a Five-Year Follow-Up. *Adv. Orthop.* **2023**, *2023*, 7010219. [CrossRef]
31. Moretti, L.; Bizzoca, D.; Giancaspro, G.A.; Cassano, G.D.; Moretti, F.; Setti, S.; Moretti, B. Biophysical Stimulation in Athletes' Joint Degeneration: A Narrative Review. *Medicina* **2021**, *57*, 1206. [CrossRef]