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Review

Optimizing Organ Donation After Euthanasia: A Critical Appraisal

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Abstract: This Critical Appraisal aims to explore the pharmacokinetics and pharmacodynamics of medications used in organ donors after euthanasia (ODE) and their impact on abdominal organ quality. With the legalization of ODE, the donor pool has expanded, but it has introduced complexities regarding organ quality. This study evaluates existing euthanasia protocols in the Netherlands, Belgium, Spain, and Canada, focusing on differences in the medication types and dosages. Additionally, a literature review assessed the potential hepatotoxic effects of high-dose medications like thiopental, propofol, and non-depolarizing neuromuscular blocking agents. High doses of non-depolarizing neuromuscular blocking agents, particularly rocuronium, are associated with hepatotoxic effects in vitro. Furthermore, thiopental doses exceeding 750 mg significantly increase the risk of liver dysfunction. Recent findings also indicate that high-dose propofol and lidocaine can slightly prolong the time to death, which is crucial for optimizing organ viability in ODE. This study highlights the need to optimize organ donation procedures after euthanasia. Further research is needed to achieve this balance, maintaining the integrity and ethical standards of the euthanasia process while enhancing the outcomes of organ donation.

Keywords: euthanasia; organ donation; organ transplantation; pharmacokinetics; pharmacodynamics; hepatotoxicity

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1. Introduction

Euthanasia is performed in patients experiencing unbearable suffering with no chance of recovery and when no alternative treatment options remain, only at the patient's request. Most of these patients have illnesses such as end-stage cancer or a combination of somatic disorders. However, euthanasia is also performed in patients with other conditions. A small group of euthanasia patients have severe psychiatric disorders, such as depression, post-traumatic stress disorder, or personality disorders [1,2]. In recent years, more patients have expressed a desire to donate their organs after euthanasia. Since 2012, when the first ODE occurred, approximately 13 organ donors have successfully donated organs through ODE annually in the Netherlands [3,4].

Typically, euthanasia is performed by the intravenous administration of multiple different types of drugs by a physician, thereby ending the patient's life. The drugs are

administered intravenously to facilitate the rapid induction of coma and subsequent death. Oral administration necessitates the ingestion of a relatively large volume of bitter-tasting liquid, which can be problematic for weakened patients in the terminal phase of life. Furthermore, orally administered euthanistic drugs may induce vomiting as an adverse effect, potentially leading to insufficiently deep coma induction, longer time to onset of death, or the absorption of a dose that is insufficient to cause death [5].

A physician performing euthanasia will administer a high dose of a coma-inducing agent. The coma-inducer can be preceded by benzodiazepine as pre-medication to bring the patient to a more relaxed state. In addition, a local anesthetic can be administered intravenously to minimize the discomfort of the coma-inducer. To ensure the rapid onset of death, after coma is achieved, a non-depolarizing neuromuscular blocking agent (nNMBA) will be administered, causing respiratory arrest [6].

Different Countries and Different Protocols for Carrying out Euthanasia

In the Netherlands, euthanasia became legal in 2002 under strict conditions, and subsequently, ODE has become an option [5,7]. Aside from the Netherlands, ODE is legal and morally justified in Belgium, Spain, and Canada. Although these countries have legalized the procedure, they do not use the same protocol for euthanasia. While the general structure of the protocols is similar, differences can be observed in the types and dosages of the medications administered. Table 1 provides a comprehensive summary of the different types of medications and the usual dosages used during euthanasia. In Appendix A, a complete overview of the different protocols is provided for all four countries.

Table 1. Summary of the medication and dosages used during euthanasia in four different countries: the Netherlands, Belgium, Canada, and Spain.

	The Netherlands [5]	**Belgium [8]**	**Canada [9]**	**Spain [10]**
Benzodiazepine	Midazolam 5–15 mg (optional)	Midazolam 5–15 mg (optional)	Midazolam 10–20 mg	Midazolam 5–20 mg
Local anesthetics	Lidocaine 1% 20 mg	Not used	Lidocaine 1% 40 mg	Lidocaine 1% 40 mg
Coma-inducer	Thiopental 2000 mg or Propofol 1000 mg (almost never used)	Thiopental 2000 mg (54%) or Propofol 1000 mg (45%)	Propofol 1000 mg	Propofol 1000 mg (100%) or Thiopental 2000 mg (0%)
Neuromuscular blocking agents (nNMBA)	Rocuronium 150 mg or Atracurium 100 mg or Cisatracurium 30 mg	Atracurium 100 mg or Cisatracurium 20 mg or Mivacurium 20 mg or Rocuronium 100 mg	Rocuronium 200 mg Cisatracurium 40 mg	Atracurium 100 mg or Cisatracurium 30 mg or Rocuronium 150 mg

These variations in medication protocols are not limited to the choice of drugs but also extend to the dosages administered. Euthanasia medication dosages often exceed those used in general anesthesia. A detailed overview of these medications, including their maximum recommended dosages, specific indications, and known side effects, is provided in Table 2. Except for lidocaine, every medication used during euthanasia has a higher dosage than the recommended dosage for the induction of general anesthesia [11,12].

By legalizing ODE, the number of potential organ donors has also increased, but this has potentially introduced complexities regarding the organ quality. Organ transplantation is a delicate procedure in which the quality of the donated organs plays a central role [13,14]. An important factor influencing organ quality is the donor first warm ischemic time (DFWIT), defined as the interval between the withdrawal of life support and the initiation of organ cooling. A prolonged DFWIT is associated with ischemic damage and reduced graft survival. Donation after circulatory death (DCD), such as in ODE (DCD category V),

presents an additional challenge due to a prolonged DFWIT for donors as compared to donation after brain death (DBD). ODE has a shorter DFWIT than that with other DCD categories due to the optimized location and facilitated distal monitoring possible, thereby minimizing ischemic damage [3,15–18].

Table 2. Summary of calculations for each medication used during euthanasia, contrasted with the dosage used in general anesthesia. All calculations are based on a 70 kg individual and are applicable only to the Dutch guidelines. Only side effects relevant to the analysis are noted.

Medication	Euthanasia [5]	Recommended Dose for Induction of General Anesthesia [11]	Side Effects [11,12]
Thiopental	2000 mg	560–1120 mg	Arterial spasm, thrombosis, hypotension
Propofol	1000 mg	175.0 mg	Hypotension, toxic pancreatitis, acute kidney injury, propofol infusion syndrome
Rocuronium	150 mg	42 mg	Hypotension
Atracurium	100 mg	21.0–42.0 mg	Histamine reaction, hypotension
Cisatracurium	30 mg	12.6 mg	Histamine reaction, hypotension
Mivacurium	20 mg	4.9–17.5 mg	Histamine reaction, hypotension

This optimized procedure helps reduce ischemic damage, yet the role of medication dosages in organ quality remains insufficiently understood. Therefore, this study aims to investigate whether the doses of medications administered during euthanasia may impact the quality of abdominal organs, influencing transplant outcomes. To address this, the different euthanasia protocols used in The Netherlands, Belgium, Spain, and Canada will be analyzed for their potential effects on abdominal organ quality in eligible organ donors. During this Critical Appraisal of a Topic (CAT), it is important to understand the different pharmacokinetics and -dynamics of these agents and also to determine if different dosages can have different effects on organ quality. This will be examined by analyzing articles on medication and organ quality.

2. Materials and Methods

Critical Appraisal of a Topic: Literature Search.

Research Strategy

The primary literature search was conducted in February 2024 using PubMed, yielding 51 articles [19]. During the examination of protocols across countries, several differences became apparent. The use of nNMBAs and coma-inducing agents varies across countries. The existing literature shows a gap regarding the potential side effects of these medications and their impact on abdominal organ function.

As a result, this research strategy required a broader scope to evaluate relevant studies on this topic. Therefore, the literature search included studies analyzing euthanasia or medically assisted dying (MAiD) in the Netherlands, Belgium, Canada, and Spain. Additionally, we included studies examining nNMBAs and coma-inducing agents administered in high doses in vivo, in vitro, and in animal models. Studies focusing on non-abdominal organ transplants, such as heart and lung transplantation, were excluded. The search strategy for the PubMed database is presented in Appendix B.

This study was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards where applicable [20]. However, as a CAT, it focuses on a targeted evaluation of the literature to address a specific clinical question, rather than providing a systematic synthesis of the available evidence.

3. Results

Evaluation and analysis of the relevant literature.

In the following section, the articles are evaluated in accordance with the JAMA guidelines for the medical literature [21]. During this evaluation, each study's validity, results, and relevance were assessed.

1. *Van Reeven M et al.*

The article "Evaluation of Liver Graft Donation After Euthanasia" by Van Reeven et al. [22], published in 2020, investigates the quality of liver transplantation (LT) via donation after circulatory death after the withdrawal of life support (DCD-III) compared to that from DCD-V donors [23]. The DCD-III cohort included 542 grafts, whereas the DCD-V cohort included 59 grafts. The primary endpoints were the patient and graft survival rates at 1, 3, and 5 years after LT. The secondary endpoints were postoperative complications. All patients were followed for one year after the LT. In the DCD-V group, 12 grafts were excluded from the analysis because they underwent machine preservation.

The study demonstrates that the donor demographic characteristics reveal a shorter DFWIT in the DCD-V cohort. A shorter DFWIT is directly correlated with fewer post-operative complications. In the DCD-V grafts, the agonal phase was defined as the time between euthanasia and circulatory arrest. For the DCD-III grafts, the agonal phase was defined as the withdrawal of life support. The patient and graft survival rates did not statistically differ from each other. At 1, 3, and 5 years, the DCD-III group had survival rates of 83%, 72%, and 68%, respectively. The DCD-V cohort had survival rates of 74%, 61%, and 57% at 1, 3, and 5 years, respectively. The analysis of the patient and graft survival via a log-rank test resulted in a p-value of 0.11. However, the data analysis indicated that the graft survival was consistently lower at all evaluation points in the DCD-V group. Additionally, the DCD-V cohort consisted of only 59 grafts, which could have impacted the statistical significance of the findings. The researchers suggested that the lower graft survival could be attributed to various factors, including the physical weakness of the patients and the potential influence of euthanasia.

The researchers suspected that the DCD-V cohort would have better outcomes because of the shorter agonal phase of these grafts. However, the graft survival rates did not improve in this cohort. In this study, the researchers speculated that the euthanasia could influence the quality of the liver graft. They hypothesized that the high dose of nNMBA during euthanasia could result in hepatotoxicity, considering that the medication is eliminated by the liver (through bile) and to a lesser extent via the kidneys. The postoperative characteristics and complications showed that the DCD-V group had a higher bilirubin level on day 7, compared to that in the DCD-III group (p = 0.16). An increasing bilirubin level could be a manifestation of primary non-function of the graft [24].

2. *Gilbo et al.*

Gilbo et al. (2019) [18] conducted a retrospective cohort study in Belgium to compare the survival outcomes in patients who received liver transplants from ODE with those from DCD and DBD. The study analyzed 575 LTs performed between January 2005 and December 2018, of which 8 grafts originated from ODE donors, 48 from DCD donors, and 519 from DBD donors. The primary outcome was the patient survival at one year post-transplantation. The results showed an 87.5% survival in the ODE group, 85.4% in the DCD group, and 84.8% in the DBD group, indicating no statistically significant difference between the donor types. Similarly, the graft survival at one year was 87.5% for ODE, 79.2% for DCD, and 82.1% for DBD, again showing comparable outcomes. The donor cold ischemia time was comparable for ODE (4.84 h) and DCD (5.30 h), but shorter than that for

the DBD cohort (7.75 h) (p = 0.02). However, the DCD and ODE donors were also exposed to additional DWIFT, where no differences were observed.

While the sample size for the ODE donors was very small, the results show similar outcomes with the DCD grafts. ODE grafts may therefore be a valuable resource in transplantation programs, requiring further investigation.

3. *Lighthall GK et al.*

The study by Lighthall GK et al. [25] was an open-label randomized control trial to evaluate the pharmacodynamics of nNMBAs. During the study period, 59 people were included, and 40 people were included in the final analysis. The four groups consisted of ten people. One group received cisatracurium 0.15 mg/kg or 0.2 mg/kg and the other groups received rocuronium 0.9 mg/kg or 1.2 mg/kg. There were two primary endpoints: the time to onset of neuromuscular block and clinical recovery from neuromuscular blockade.

This study reveals a few findings. First, the time to 25% recovery of the neuromuscular blockade was highest with rocuronium 1.2 mg/kg. The mean recovery time was 80 min. With cisatracurium 0.2 mg/kg, the mean recovery time was 69 min. The onset of neuromuscular blockade was the highest with cisatracurium 0.15 mg/kg (220 s), and in comparison, the rocuronium 0.9 mg/kg blockade onset time was 134 s. Scientists suggest that the difference in time to equilibrium is due to the different molecular weights of rocuronium and cisatracurium. Understanding the differences in variability is important in the use of NMBAs, in addition to accounting for the patient age, cardiac output, and anesthetic technique.

4. *Sauer M et al.*

These researchers (2019) [26] conducted a study to investigate the hepatotoxicity of succinylcholine versus rocuronium, both of which are nNMBAs. These are used in rapid sequence induction, for instance, during intubation, because of them being short-onset temporal muscle paralyzers. To gain insights into the hepatotoxicity of rocuronium and succinylcholine in vitro, the researchers used the human hepatocyte cell line HepG2/C3A. These cells were obtained from the American Type Culture Collection (ATCC CRL-10741) and used to measure adverse effects on human cells. The primary outcomes were the pH, vitality of cells (via lactate dehydrogenase activity (LDH) and cell count), synthesis of microalbumin, and cytochrome 1A2 activity. The testing was performed in a dose-dependent manner. For rocuronium, the dosage was 1.9×10^{-5}, 6.5×10^{-5}, and 1.9×10^{-4} mol L^{-1}, and for succinylcholine, it was 1.7×10^{-4}, 8.6×10^{-4}, and 1.7×10^{-3} mol L^{-1}. In all the tested parameters, rocuronium was more hepatotoxic than succinylcholine. Tryptan blue staining was used to test the cell vitality. These results show that upon increasing the doses for rocuronium, fewer cells were counted ($p < 0.05$). This was not the case for increased doses of succinylcholine, where the number of cells remained the same. In addition, an increasing dose of rocuronium was associated with a decreased cell viability ($p < 0.05$). The release of LDH was used to assess the damage to in vitro cells, which was significantly increased ($p < 0.05$). In conclusion, rocuronium, but not succinylcholine, decreased the cell viability in vitro.

5. *Dundee J.W.*

Dundee J.W. investigated the effects of thiopental on liver function, which provides valuable insights into the potential hepatotoxicity of the coma-inducer thiopental. In his study "Thiopentone as a Factor in the Production of Liver Dysfunction [27]", 464 patients were analyzed. The primary endpoint was urinary urobilinogen excretion to detect liver dysfunction. He measured the concentration of urobilinogen in urine three days postoperation to investigate the breakdown of thiopental in the liver, and its potential to cause

liver damage. The study had two cohorts: one receiving thiopental as the main anesthetic agent, and the other receiving it only for the induction of anesthesia, supplemented by other agents. This approach allowed for a comparative analysis of liver function based on the dosage and administration of thiopental.

The study excluded patients who developed postoperative fever or other complications, which could increase the urobilinogen levels. Fever can independently increase urobilinogen excretion because of temporary liver swelling, confounding the results related to the anesthetic agent. By excluding these patients, the study ensured that the observed liver dysfunction was directly attributable to the effects of thiopental. This is particularly relevant for abdominal surgeries, where blood extravasation and its subsequent absorption by the liver could increase bilirubin levels. The results showed a significant increase in urinary urobilinogen excretion in patients who received high doses of thiopental, suggesting a direct correlation between dosage and liver dysfunction. Liver dysfunction was observed to occur more frequently in cases where thiopental was used as the main anesthetic, particularly at doses > 750 mg.

6. *Shingu et al.*

The study by Shingu et al. [28] aimed to investigate the impact of various oxygen concentrations, hyperthermia, and vendor choice on anesthetic-induced hepatic injury in rats. The researchers used male Sprague Dawley rats from two vendors: Zivic-Miller and Charles River. These rats were pre-treated with phenobarbital for four days before being exposed to 2 h of hypoxia combined with different anesthetics (halothane, enflurane, isoflurane, thiopental, and fentanyl) at various oxygen concentrations (10%, 12%, 14%, 20%, and 100%). The rectal temperature was controlled between 36.5 °C and 38.5 °C, except for a group that was hypothermic (32–34 °C). The primary outcomes measured were the presence of centrilobular necrosis, the effects of hypoxia at different oxygen concentrations, the influence of hyperthermia and hypothermia on hepatic injury, and a comparison between the rats from different vendors. This analysis solely focused on the effects of thiopental.

The thiopental treatment with 10% oxygen caused significant hepatic injury. The rats exposed to thiopental and 10% oxygen showed higher liver damage than the control rats exposed to 10% oxygen alone. Thiopental did not cause hepatic injury at 20% or 100% oxygen, indicating that the hepatotoxic effects were associated with hypoxia. Hypothermia (32–34 °C) did not protect against thiopental-induced hepatic injury under hypoxia, unlike enflurane and isoflurane, where hypothermia provided protection. These findings suggest that hypoxia combined with anesthetics can cause hepatic injury by depressing ventilation and reducing hepatic blood flow, possibly through metabolic effects. Hypothermia provides protection against hepatic injury by reducing the oxygen consumption and increasing the arterial oxygen saturation, suggesting that controlled hypothermia during anesthesia and surgery could limit hepatic injury.

An attempt to confirm the harmfulness of drugs administered in euthanasia in relation to abdominal organs.

The study conducted by Van Reeven M et al. included two cohorts: one cohort consisting of patients receiving LT via DCD-III and the other cohort via DCD-V. There were no statistically significant differences between the two groups in terms of the patient and graft survival. This is in line with the study group of Gilbo et al., where they also observed no differences in the DCD-V versus DCD-III cohorts. Van Reeven et al. suggested that the effects of nNMBAs on graft function should be further investigated because they are administered at a high dosage [22]. The hepatotoxic effects of nNMBAs have been investigated by Sauer M et al. Their research found more hepatotoxic effects in vitro with increasing doses of rocuronium. Cell cultures, composed of human hepatocytes, showed lower cell counts

and less cell viability [26]. Lighthall et al. demonstrated that with an increasing dosage of rocuronium, the recovery from neuromuscular blockade took longer, and the onset of the neuromuscular blockage took more time [25]. Dundee J.W. demonstrated that high doses of thiopentone (>750 mg) were associated with a significant risk of liver dysfunction. This was evidenced by the increased urinary excretion of urobilinogen postoperation, indicating hepatic impairment [27]. The study by Shingu et al. investigated the effects of different oxygen concentrations, hyperthermia, and vendor choice on anesthetic-induced liver injury in rats. Thiopental caused significant liver damage at 10% oxygen but not at higher oxygen levels, indicating that its hepatotoxic effects are linked to hypoxia. Unlike enflurane and isoflurane, hypothermia does not protect against thiopental-induced liver injury under hypoxic conditions [28]. Table 3 provides a detailed summary of the results of the analyzed studies.

Table 3. Summary of the main results in five studies.

Study	Population	Intervention	Outcome	Results
Van Reeven M et al. Evaluation of Liver Graft Donation After Euthanasia. JAMA Surg, 2020 [22].	2 cohorts: DCD-III: 542 liver grafts DCD-V: 47 liver grafts	The function of liver grafts in DCD-III vs. DCD-V donors.	Primary outcomes: patient and graft survival at years 1, 3, and 5. Secondary outcomes are postoperative complications.	No statistical differences between DCD-III and DCD-V in graft and patient survival. The postoperative complications were the same.
Gilbo et al. Survival of Patients With Liver Transplants Donated After Euthanasia, Circulatory Death, or Brain Death at a Single Center in Belgium. JAMA 2019 [18].	3 cohorts: DCD-III: 48 liver grafts DCD-V: 8 liver grafts DBD: 519 liver grafts	The function of liver grafts in DCD-III, DCD-V, and DBD donors.	The primary outcome was patient survival at one year post-transplantation.	No statistical differences between DCD-III, DCD-V, and DBD in graft and patient survival.
Lighthall GK et al. A comparison of the onset and clinical duration of high doses of cisatracurium and rocuronium. J Clin Anesth 1999 [25].	4 cohorts: Cisatracurium 0.15 mg/kg (n = 10) Cisatracurium 0.2 mg/kg (n = 10) Rocuronium 0.9 mg/kg (n = 10) Rocuronium 1.2 mg/kg (n = 10)	Patients undergoing anesthesia receiving either cisatracurium or rocuronium.	Rocuronium had a quicker onset than cisatracurium at equivalent doses, and recovery tended to be faster for cisatracurium. However, this was not statistically significant.	The data indicate a tendency for cisatracurium to lead to faster clinical recovery compared to equivalent doses of rocuronium.
Sauer M et al. Rocuronium is more hepatotoxic than succinylcholine in vitro. Eur J Anesthesiology 2017 [26].	Human liver cell line HepG2/C3A in vitro	Toxicity of different concentrations of rocuronium and succinylcholine.	Rocuronium demonstrated a reduction in cell viability and cytochrome 1A2 activity, in a dose-dependent pattern.	For all tested parameters, rocuronium was scored as being more hepatotoxic than succinylcholine.
Dundee J.W. Thiopentone as a factor in the production of liver dysfunction. Br J Anaesth 1955 [27].	464 patients, divided into two cohorts of 232 each	Administration of thiopentone as the main anesthetic or only for induction of anesthesia.	Liver dysfunction, measured by the excretion of urobilinogen in urine 3 days postoperation.	High doses of thiopentone (>750 mg) significantly increase liver dysfunction. Using thiopentone only for induction reduces this risk.
Shingu et al. Effect of Oxygen Concentration, Hyperthermia, and Choice of Vendor on Anesthetic-Induced Hepatic Injury in Rat. 1983 [28].	Male Sprague-Dawley rats (approx. 300 g), from Zivic-Miller and Charles River	Phenobarbital pre-treatment, 2 h of hypoxia with anesthetics (halothane, enflurane, isoflurane, thiopental, fentanyl).	Hepatic injury (centrilobular necrosis), effects of hypoxia, hyperthermia, hypothermia, and vendor differences.	Thiopental caused significant hepatic injury at 10% oxygen, not at 20% or 100% oxygen. Hypothermia did not protect. Differences noted between vendors.

4. Discussion

Based on the articles, it became apparent that understanding the different pharmacodynamics and -kinetics is difficult when there is little to almost no information on the high dosages of medication administered during euthanasia. Therefore, this investigation aimed to assess whether varying dosages have different effects on the quality of abdominal organs. To answer this, euthanasia protocols per country were analyzed, and it became apparent that the use of the nNMBAs and coma-inducers differed per protocol. Six articles were included in this analysis, comparing DCD-V donors with DCD-III donors or examining the metabolism and elimination of medications administered during euthanasia.

M et al. [22] were the first to analyze DCD donors with ODE in liver transplantation. The study was conducted in The Netherlands and Belgium; however, they did not differentiate between the countries for the analysis. In this study, the main difference between

the protocols was the use of 150 mg rocuronium in The Netherlands, whereas in Belgium, atracurium (100 mg) was used as the nNMBA. Differentiating between the protocols in terms of graft and patient survival might have provided more insight into the potential side effects associated with the medications used. The findings of Van Reeven et al. were consistent with those reported by Gilbo et al. [18], where the DCD-V cohort showed no significant differences in the post-transplant outcomes at one year. However, the DCD-V cohort in their study included only eight grafts, limiting the statistical power. Additionally, the patient follow-up was restricted to one year post-transplant, and key clinical parameters such as the bilirubin levels, ASAT/ALAT values, and surgical complications were not documented, further restricting the ability to draw definitive conclusions.

Van Reeven et al. hypothesized the potential hepatotoxic effects due to high doses of nNMBAs. Thiopental and propofol are metabolized by the liver; therefore, further investigation is needed to assess the potential impact on the liver. Research conducted by Dundee J.W. demonstrated that higher levels of thiopental increase the postoperative excretion of urobilinogen, indicating liver dysfunction [27]. Propofol can also induce toxic pancreatitis and, in rare cases, propofol infusion syndrome (PRIS). Mirrakhimov et al. identified the dose as a significant risk factor for PRIS, recommending that dosages should not exceed 4 mg/kg [29]. Although this dosage is typical in euthanasia protocols, it remains uncertain whether there is sufficient time for the syndrome to develop under these conditions. Moreover, Murayama et al. (2005) [30] showed that, in minipigs with continued infusion of propofol, the pharmacokinetics did not change. This might indicate that there is also extrahepatic metabolism of propofol, thereby limiting the damage caused by continued propofol infusion [30].

Recent studies from Stukalin et al. [31] provide important insights into the variability in the time to death in euthanasia protocols, which influence the duration of the DFWIT, and, thereby, the organ viability. Their study indicated a median time from the initiation of euthanasia to death of 9 min, with a range from 1 to 127 min. The administration of high-dose propofol and lidocaine was associated with a slightly prolonged time to death. Specifically, high-dose propofol (>1000 mg) increased the median time to death by 3 min, while standard-dose lidocaine (40–60 mg) prolonged it by 1 min. These findings suggest that, while most euthanasia deaths occur within a predictable timeframe, certain medications can extend the process. This prolonged time to death, although minor in most cases, can have significant implications. In scenarios such as ODE, a swift and predictable time to death is crucial to ensure the viability of organs. The study's findings underscore the need to carefully consider medication dosages and combinations to optimize the euthanasia process.

Sauer M et al. [26] demonstrated that rocuronium is more hepatotoxic than succinylcholine in vitro using the human liver cell line HepG2/C3A. Table 2 shows that the dosage administered during general anesthesia was approximately 14 times higher during euthanasia [5,11]. As this has not been tested in vivo, hepatoxicity is not mentioned as a side effect of nNMBAs [11]. Concerning the possible toxic side effects of other medications used for euthanasia, nephrotoxicity is mentioned in midazolam, lidocaine, and propofol use [12]. Lighthall et al. [25] showed that rocuronium has a quicker onset of neuromuscular block than cisatracurium at equivalent doses. Additionally, the recovery tended to be faster for cisatracurium. However, the highest doses for cisatracurium and rocuronium in this calculation were 0.2 mg/kg for cisatracurium and 1.2 mg/kg for rocuronium. When calculating this dosage for someone weighing 85 kg opting for euthanasia, this results in 17 mg of cisatracurium or 102 mg rocuronium. For euthanasia, the highest doses of cisatracurium and rocuronium were 30 mg and 150 mg, respectively. Based on this information, it appears that the time to neuromuscular block is longer with high doses of cisatracurium. This

could result in more time before the drug reaches equilibrium, allowing the organs to be hypo-perfused for a longer period. However, this has never been investigated and therefore needs to be tested in the future.

The study by Shingu et al. [28] underscores the critical need for standardized conditions in toxicological research. For both preclinical studies and clinical anesthesia practice, the precise management of oxygen levels and body temperature and the selection of animal models are essential to minimize hepatic injury. These findings demonstrate that thiopental, in combination with hypoxia, induces significant liver damage, whereas hypoxia alone or thiopental with 100% oxygen does not. This is analogous to the scenario in post-euthanasia liver transplantation, where hypoxia and thiopental contribute to ischemia/reperfusion injury. Understanding the specific conditions under which thiopental causes hepatic injury can enhance its safe application in clinical settings, particularly in situations which hypoxia may occur.

These factors highlight the difficulties in choosing the appropriate protocol for euthanasia for a patient opting for organ donation. Considering these facts and the gap in research on the subject, it may be interesting to conduct research with the following factors: drug-to-drug interactions; the time to neuromuscular block; the hepatotoxicity of rocuronium, propofol, and thiopental; and postoperative complications. Combining all the information on donated organs and drugs used during euthanasia in the four different countries studied could yield more reliable results in terms of organ quality.

5. Conclusions

In conclusion, there is limited evidence on the effects of high-dose nNMBAs and coma-inducing drugs administered during euthanasia on organ quality. The choice of medications primarily depends on those routinely used in each hospital, and given the current lack of data, it remains premature to recommend specific drugs or dosages. Further research is required to determine the potential impact of these medications on organ function and transplant outcomes. Our findings highlight the need for practitioners to document drug dosages systematically, enabling cross-country comparisons.

To further assess the potential effects of euthanasia-related medications, studies should examine organ quality, post-transplant survival, complication rates, and recipient outcomes. While expanding the donor pool through organ donation after euthanasia presents a potential benefit, this should never come at the expense of patient comfort and well-being. Therefore, we do not advocate for adjustments to euthanasia protocols solely to facilitate organ transplantation.

Given the increasing interest in ODE, we encourage international collaboration among the Netherlands, Belgium, Spain, and Canada to conduct extensive research on the effects of euthanasia-related medications on abdominal organ viability and transplantation success.

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Abbreviations

ODE	organ donation after euthanasia
nNMBs	non-depolarizing neuromuscular blocking agent

DCD-III	donation after circulatory death with withdrawal of life support
LT	liver transplantation
DCD-V	donation after circulatory death because of euthanasia
DFWIT	donor first warm ischemia time
LDH	lactate dehydrogenase

Appendix A

Legal aspects, statistics, and euthanasia protocol per country.

The Netherlands' euthanasia protocol:

In 1985, euthanasia was accepted in The Netherlands. However, euthanasia has not yet been legalized. In a famous case concerning Mrs. Bosscher, known as the Chabot case, in 1991, the practice of euthanasia on patients that were not terminally ill was attempted. Following this case and other cases, a law was enacted, known as the Termination of Life Request and Assistant Suicide Act [32,33]. Since the official legalization of euthanasia in The Netherlands in 2002, the number of euthanasia cases has increased. In the first year of legalization, there were 1882 cases. In 2022, however, 8720 cases of euthanasia were reported, accounting for 5.1% of all deaths in The Netherlands [34]. The euthanasia medication protocol in The Netherlands is as follows:

Protocol with dosages: [5]

1. Midazolam 5–15 mg (optional).
2. Lidocaine 1% 2 mL in 30 s.
3. Thiopental 2000 mg or propofol 1000 mg, maximum of 5 min.
4. Rocuronium 150 mg, atracurium 100 mg, or cisatracurium 30 mg.

Belgium's euthanasia protocol:

After its legalization in The Netherlands, Belgium also legalized euthanasia in 2002 through the "Law Concerning Euthanasia". The legal aspects in Belgium are more or less the same as those in The Netherlands [35]. In 2021, there were 2700 cases of euthanasia in Belgium, which accounted for 2.4% of all deaths in Belgium. Approximately 75% of all euthanasia cases were in Flanders, the northern and Dutch-speaking part of Belgium. Belgium's euthanasia medication protocol is as follows.

Protocol with dosages: [8]

1. Midazolam 5–15 mg (this is optional and only given to restless patients).
2. Thiopental 2000 mg of Propofol 1000 mg.
3. Atracurium 100 mg, Cisatracurium 20 mg, Mivacurium 20 mg, or Rocuronium 100 mg.

Canadian euthanasia protocol:

In 2015, euthanasia was legalized in Canada. In the case of Carter v Canada (AG), it became apparent that Kay Carter no longer wished to live because of her uncurable spinal stenosis. Since the verdict of that particular case, the law has changed [36–38]. In Canada, euthanasia is referred to as Medical Assistance in Dying (MAiD). In 2022, there were 13,241 cases of MAID, accounting for 4.1% of all deaths in Canada. The Canadian euthanasia medication protocol is as follows.

Protocol with dosages: [9]

1. Midazolam 10–20 mg.
2. Lidocaine 1% 40 mg.
3. Propofol 1000 mg.
4. Rocuronium 200 mg.

Spain's euthanasia protocol:

Spain was the sixth country in the world to legalize euthanasia. It did so in 2021. The Organic Law for the Regulation of Euthanasia became active after long debates on numerous cases in which people were assisted in their suicide [39,40]. Since the legalization, 370 people have been assisted in dying in Spain. This accounts for 0.07% of all deaths. Since the legalization was very recent, it is not unlikely that these numbers will increase in the coming years. [41] Spain's euthanasia medication protocol is as follows.

Protocol with dosages: [10,41]

1. Midazolam 5–20 mg.
2. Lidocaïne 1% 40 mg.
3. Propofol 1000 mg or Thiopental 2000 mg.
4. Atracurium 100 mg, Cisatracurium 30 mg, or Rocuronium 150 mg.

Appendix B

1. Research strategy

Concept	PICO
Population	Patients who are eligible for organ donation
Intervention	Administration of euthanasia medication
Comparison	Different countries that permit organ donation (Netherlands, Belgium, Spain, and Canada)
Outcome	Variance in the quality of abdominal organs

2. PubMed search

Concept 1:

((("Tissue Donors"[MeSH Terms] OR "organ donor*"[Title/Abstract] OR "tissue donor*"[Title/Abstract] OR "cadaveric donor*"[Title/Abstract] OR "deceased donor*"[Title/Abstract] OR "donor eligibility"[Title/Abstract] OR "donation criteria"[Title/Abstract]) OR "Organ Transplantation"[MeSH Terms]) OR "Liver Transplantation"[MeSH Terms] OR "Kidney Transplantation"[MeSH Terms] OR ("Organ Transplantation"[Title/Abstract] OR "Liver Transplantation"[Title/Abstract] OR "Kidney Transplantation"[Title/Abstract])) AND ("Euthanasia"[MeSH Terms] OR "Euthanasia"[Title/Abstract] OR "assisted suicide"[Title/Abstract] OR "physician-assisted suicide"[Title/Abstract] OR "end-of-life care"[Title/Abstract] OR "right to die"[Title/Abstract]).

Results = 953 articles.

Concept 2:

("Tissue Donors"[MeSH Terms] OR "organ donor*"[Title/Abstract] OR "tissue donor*"[Title/Abstract] OR "cadaveric donor*"[Title/Abstract] OR "deceased donor*"[Title/Abstract] OR "donor eligibility"[Title/Abstract] OR "donation criteria"[Title/Abstract] OR "Organ Transplantation"[MeSH Terms] OR "Liver Transplantation"[MeSH Terms] OR "Kidney Transplantation"[MeSH Terms] OR ("Organ Transplantation"[Title/Abstract] OR "Liver Transplantation"[Title/Abstract] OR "Kidney Transplantation"[Title/Abstract])) AND ("Euthanasia"[MeSH Terms] OR "Euthanasia"[Title/Abstract] OR "assisted suicide"[Title/Abstract] OR "physician-assisted suicide"[Title/Abstract] OR "end-of-life care"[Title/Abstract] OR "right to die"[Title/Abstract]) AND ("Netherlands"[Title/Abstract] OR "Belgium"[Title/Abstract] OR "Spain"[Title/Abstract] OR "Canada"[Title/Abstract]).

Results = 47 articles.

Concept 3:

((("Tissue Donors"[MeSH Terms] OR "organ donor*"[Title/Abstract] OR "tissue donor*"[Title/Abstract] OR "cadaveric donor*"[Title/Abstract] OR "deceased donor*"[Title/Abstract] OR "donor eligibility"[Title/Abstract] OR "donation criteria"[Title/Abstract] OR "Organ Transplantation"[MeSH Terms] OR "Liver Transplantation"[MeSH Terms] OR "Kidney Transplantation"[MeSH Terms] OR ("Organ Transplantation"[Title/Abstract] OR "Liver Transplantation"[Title/Abstract] OR "Kidney Transplantation"[Title/Abstract])) AND ("Euthanasia"[MeSH Terms] OR "Euthanasia"[Title/Abstract] OR "assisted suicide"[Title/Abstract] OR "end-of-life care"[Title/Abstract] OR "right to die"[Title/Abstract])) OR "MAiD"[Title/Abstract] OR "physician assisted suicide"[Title/Abstract]) AND ("Netherlands"[Title/Abstract] OR "Belgium"[Title/Abstract] OR "Spain"[Title/Abstract] OR "Canada"[Title/Abstract]).

Results = 452 articles.

Concept 4:

("Tissue Donors"[MeSH Terms] OR "organ donor*"[Title/Abstract] OR "tissue donor*"[Title/Abstract] OR "deceased donor*"[Title/Abstract] OR "donor eligibility"[Title/Abstract] OR "donation criteria"[Title/Abstract] OR "cadaveric donor*"[Title/Abstract] OR "Organ Transplantation"[MeSH Terms] OR "Liver Transplantation"[Title/Abstract] OR "Kidney Transplantation"[Title/Abstract] OR ("Organ Transplantation"[Title/Abstract] OR "Liver Transplantation"[Title/Abstract] OR "Kidney Transplantation"[Title/Abstract])) AND (("Euthanasia"[MeSH Terms] OR "Euthanasia"[Title/Abstract] OR "assisted suicide"[Title/Abstract] OR "end-of-life care"[Title/Abstract] OR "MAiD"[Title/Abstract] OR "physician assisted suicide"[Title/Abstract]) AND ("Netherlands"[Title/Abstract] OR "Belgium"[Title/Abstract] OR "Spain"[Title/Abstract] OR "Canada"[Title/Abstract])).

Results = 51 articles.

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