Journal of Clinical Anesthesia 97 (2024) 111508

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Current anesthesia practice for preterm infants undergoing surgery for necrotizing enterocolitis: A European survey

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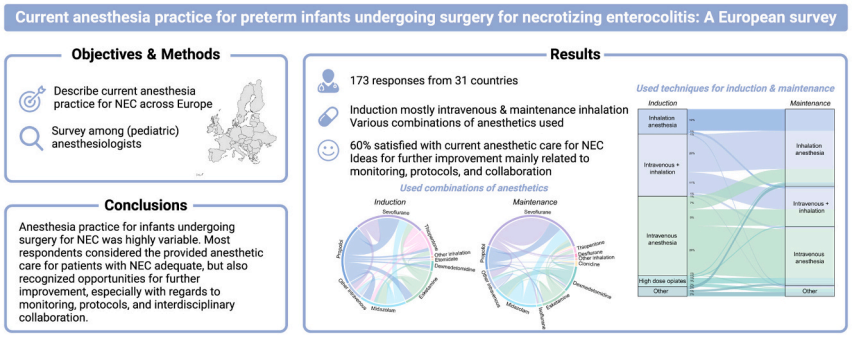
HIGHLIGHTS

- Anesthesia practice for preterm infants with NEC is highly variable.
- Sixty percent of anesthesiologists are satisfied with current anesthetic care for NEC.
- Advances in monitoring, protocols, and collaboration may drive further improvement.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Anesthetics
Laparotomy
Necrotizing enterocolitis
New-born infant
Pediatric anesthesia
Perioperative care
Premature infant

ABSTRACT

Study objective: Necrotizing enterocolitis (NEC) is a life-threatening intestinal illness mostly affecting preterm infants, which commonly requires surgery. Anesthetic care for these patients is challenging, due to their prematurity and critical illness with hemodynamic instability. Currently, there are no guidelines for anesthetic care for these vulnerable patients. Therefore, this study aimed to describe current anesthesia practices across Europe for infants undergoing surgery for NEC.
Design: Cross-sectional survey study.
Participants: Anesthesiologists working in centers where surgery for NEC is performed across Europe.
Measurements: A 46-item questionnaire assessing protocols for anesthesia practice, preoperative care, intraoperative care, postoperative care, and the respondent's opinion on the adequacy of anesthetic care for patients with NEC in their center.
Main results: Out of the 173 responding anesthesiologists from 31 countries, approximately a third had a written standard protocol for anesthetic care in infants. Three quarters of the respondents screened all patients with NEC preoperatively, and a third structurally performed preoperative multidisciplinary consultation. For induction of general anesthesia, most respondents opted for intravenous anesthesia (n = 73, 43%) or a combination of

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https://doi.org/10.1016/j.jclinane.2024.111508
Received 5 April 2024; Received in revised form 15 May 2024; Accepted 31 May 2024
Available online 5 June 2024

intravenous and inhalation anesthesia ($n = 57$, 33%). For intravenous induction, they mostly used propofol ($n = 58$, 44%), followed by midazolam ($n = 43$, 33%) and esketamine ($n = 42$, 32%). For maintenance of anesthesia, inhalation anesthetic agents were more commonly used (solely: $n = 71$, 41%; in combination: $n = 37$, 22%), almost exclusively with sevoflurane. Postoperative analgesics mainly included paracetamol and/or morphine. Sixty percent of the respondents ($n = 104$) considered their anesthetic care for patients with NEC adequate. Suggestions for further improvement mainly revolved around monitoring, protocols, and collaboration.
Conclusions: Anesthesia practice for infants undergoing surgery for NEC was highly variable. Most respondents considered the provided anesthetic care for patients with NEC adequate, but also recognized opportunities for further improvement, especially with regards to monitoring, protocols, and interdisciplinary collaboration.

1. Introduction

Necrotizing enterocolitis (NEC) is a life-threatening illness that mainly affects preterm born infants, with a prevalence of 11% among extremely preterm infants [1]. This condition is marked by progressive intestinal inflammation and ischemia as well as critical illness with respiratory and hemodynamic instability. Its treatment consists of conservative management (e.g., antibiotics and bowel rest) combined with surgery in the most severe cases [2]. Surgical treatment is required in two thirds of infants with confirmed NEC and entails resection of the affected part of the intestine [3], under anesthesia.

Providing adequate anesthetic care is essential but challenging in preterm infants with NEC, since these patients are often extremely premature and suffer from excessive inflammation, respiratory and hemodynamic instability, electrolyte disturbances, and coagulopathy [4–6]. Furthermore, as NEC is a rare disease, anesthesiologists may have limited experience treating these patients, which in turn is related to increased risk of complications [7,8].

Currently, the optimal anesthetic care for infants undergoing surgery for NEC is unknown and practices may vary considerably as there are no international guidelines and evidence regarding the efficacy and safety of many anesthetics in infants is lacking [9]. Therefore, this study aimed to describe current anesthesia practice for preterm infants undergoing surgery for NEC. Ultimately, this study aims to provide a step towards optimizing anesthetic care for these vulnerable infants and thereby improving their outcomes.

2. Methods

2.1. Study design and participants

We conducted a cross-sectional study to describe perioperative anesthetic care provided to preterm infants undergoing surgery across Europe for NEC. For this purpose, we developed a web-based survey. Anesthesiologists working in centers where surgery for NEC is performed, were requested to complete the survey. Participants were informed that completing the survey meant agreeing to participate in this study. This study was deemed exempt from ethical approval in line with the Dutch Medical Research Involving Human Subjects Act (WMO), as it was a voluntary and anonymous survey among clinicians.

2.2. Survey

We developed the survey in LimeSurvey version 2.06 (Limesurvey GmbH, Hamburg, Germany). The included questions were designed based on a literature search and the expert opinion of the multidisciplinary group of authors. To establish the validity of the survey, an international group of six anesthesiologists reviewed its relevance, comprehensiveness, and comprehensibility. Based on their suggestions, we rephrased four questions and added multiple choice answer options for five questions.

The final version of the survey included a total number of 46 questions: eight questions about demographics, two about protocols for anesthesia practice, six about preoperative care, 26 about intraoperative care, two about postoperative care, and two about the respondent's opinion on the adequacy of anesthetic care for patients with NEC in their center and ways it might be improved (Supplementary Table 1).

The survey was distributed with help of the European Society for Pediatric Anesthesiology (ESPA) and several national (pediatric) anesthesiology societies. To maximize the number of responses, societies in countries with a low response rate were requested to send reminders. The survey was open from June 12, 2023 until January 8, 2024.

2.3. Statistical analyses

Descriptive analyses were presented as median (IQR) or number (percentage). Agreement between anesthesiologists' chosen agents for anesthesia, analgesia and muscle relaxation was assessed by calculating Fleiss' Kappa statistic. Analyses were conducted with RStudio version 2021.09.2 and R version 4.1.2 (R Core Team, Vienna, Austria). Responses to the open question about the anesthesiologist's opinion were analyzed with thematic content analysis. These responses were coded in ATLAS.ti Web (version 5.21.1).

3. Results

3.1. Responding anesthesiologists

A total number of 173 anesthesiologists from 31 European countries completed the survey. The majority worked in university hospitals ($n = 93$, 54%) or university affiliated children's hospitals ($n = 61$, 35%). Most respondents were pediatric anesthesiologists ($n = 133$, 77%) with over 15 years of experience ($n = 121$, 70%), and dedicating 80–100% of their working hours to pediatric anesthesiology ($n = 95$, 55%). The yearly number of patients with NEC undergoing surgery in the respondent's center was highly variable, with approximately a quarter of centers treating 5–10 patients and a quarter treating 10–20 patients yearly. Table 1 provides an overview of the respondents' background characteristics. Fig. 1 shows the respondents' distribution across Europe. The 173 respondents worked in 144 different hospitals. In 123 of these hospitals a single anesthesiologist completed the survey and in 21 hospitals multiple anesthesiologists completed the survey (two responses: $n = 16$, three responses: $n = 2$, four responses: $n = 3$).

3.2. Protocols for anesthesia practice

The majority of respondents reported that their center did not have a written standard protocol for anesthetic care in infants ($n = 113$, 65%). Fifty-three respondents (31%) had a written standard protocol and seven respondents (4%) did not know whether their center had one or not. Out of the 53 respondents with a written standard protocol, 45 (26%) had a protocol for both term and preterm born infants, seven (4%) only had a protocol for term born infants, and one (1%) only for preterm born infants. Nineteen respondents (11%) had a specific protocol for anesthetic care in patients with NEC in their center.

Table 1
Background characteristics of the respondents.

	$N = 173$
Type of hospital	
Academic affiliated children's hospital	61 (35%)
University (academic) hospital	93 (54%)
Children's (non-academic) hospital	8 (5%)
General (non-academic) hospital	10 (6%)
Other	1 (1%)
Function of respondent	
Pediatric anesthesiologist	133 (77%)
Pediatric anesthesiology fellow	6 (3%)
Anesthesiologist	26 (15%)
Anesthesiology resident	3 (2%)
Other	5 (3%)
Number of years' experience in anesthesiology	
> 15 years	121 (70%)
10–15 years	24 (14%)
5–10 years	16 (9%)
0–5 years	9 (5%)
Not answered	3 (2%)
Time spent practicing pediatric anesthesiology	
80–100%	95 (55%)
60–80%	25 (14%)
40–60%	29 (17%)
20–40%	13 (8%)
0–10%	4 (2%)
10–20%	4 (2%)
Not answered	3 (2%)
Number of NEC patients undergoing surgery in center yearly	
> 50	7 (4%)
40–50	13 (8%)
30–40	6 (3%)
20–30	26 (15%)
10–20	43 (25%)
5–10	41 (24%)
1–5	36 (21%)
0	1 (1%)
Person giving anesthesia to patients with NEC undergoing surgery	
Pediatric anesthesiologist	144 (83%)
General anesthesiologist	12 (7%)
(Pediatric) anesthesiologist in collaboration with neonatologist	33 (19%)
Neonatologist	3 (2%)
Other	6 (3%)

Values are expressed as number of responses (%).

3.3. Preoperative care

One respondent's center treated zero patients with NEC yearly, and therefore this respondent received no further questions about anesthetic care for patients with NEC. Out of the remaining 172 respondents, three-quarters (n = 128) reported that preoperative evaluation is always performed before surgery in patients with NEC, 19 (11%) that preoperative evaluation is not always performed, and 26 (15%) did not answer this question.

Furthermore, 62 respondents (36%) always, 77 respondents (45%) sometimes, and 24 respondents (14%) never performed multidisciplinary team (MDT) consultation prior to anesthesia in patients with NEC, while 10 respondents (5%) did not answer this question. The attendants of these MDTs usually included a neonatologist (n = 131, 76%), an anesthesiologist (n = 122, 71%), and a pediatric surgeon (n = 121, 70%). During these meetings, decisions were made regarding use and choice of inotropes/vasopressors (n = 86, 50%), ventilator strategy (n = 81, 47%), blood pressure targets (n = 51, 30%), use of anesthetics/analgesics (n = 32, 19%), and/or target end-tidal CO2 concentrations (n = 22, 13%). Lastly, a few respondents reported discussing whether to perform surgery (n = 5, 3%), the location of surgery (operating room vs. neonatal intensive care unit) (n = 5, 3%), postoperative care (n = 5, 3%), the patient's general condition (n = 5, 3%), and the surgical plan (n = 4, 2%).

Almost all respondents (n = 167, 97%) routinely assessed hemoglobin level and the vast majority (n = 136, 79%) routinely ordered blood products before surgery.

3.4. Intraoperative care

3.4.1. Location of surgery

Over half of the respondents (n = 94, 55%) reported that surgery for NEC in their center is generally performed in an operating room (OR), 44 (26%) that it is generally performed in the neonatal intensive care unit (NICU), and 28 (16%) that these locations are both equally common. Factors affecting the choice of location included the condition of the patient (n = 144, 66%), ventilator strategy (n = 55, 32%), common practice (n = 46, 27%), preference of the surgeon (n = 45, 26%), agreements within the hospital (n = 35, 20%), preference of the anesthesiologist (n = 34, 20%), preference of the neonatologist (n = 18, 10%), and the patient's weight (n = 6, 3%).

3.4.2. Monitoring

In order of descending frequency of use, the types of monitoring used during surgery in patients with NEC were pulse oximetry (n = 172, 100%), temperature (n = 170, 99%), heart frequency (n = 165, 96%), end-tidal CO2 concentration (n = 148, 86%), non-invasive blood pressure (NIBP) (n = 144, 84%), electrocardiogram (ECG) 3 lead (n = 141, 82%), blood gas analysis (n = 138, 80%), diuresis quantity (n = 127, 74%), end tidal anesthetic concentration (n = 123, 72%), invasive blood pressure (n = 111, 65%), near-infrared spectroscopy (NIRS) (n = 93, 54%), transcutaneous CO2 concentration (n = 46, 27%), central venous pressure (n = 37, 22%), processed electroencephalogram (EEG) (n = 25, 15%), and ECG 5 lead (n = 10, 6%). Eighty percent of the respondents (n = 138) used all standard monitoring, defined as electrocardiography, blood pressure measurement (invasive and/or non-invasive), pulse oximetry, CO2 measurement (end-tidal and/or transcutaneous), and temperature measurement.

3.4.3. Used techniques for induction and maintenance of anesthesia

The most used technique for induction in patients with NEC was intravenous anesthesia (n = 73, 43%), followed by a combination of intravenous and inhalation anesthesia (n = 57, 33%), inhalation anesthesia (n = 23, 13%), and high dose opiates (n = 10, 6%). Nine respondents chose 'other', with five commenting that these patients have usually already been intubated by the neonatologist, and the remainder that they use a combination of high dose opiates and a (low dose) inhalation anesthetic.

For maintenance, inhalation anesthesia (n = 71, 41%) was most used, followed by intravenous anesthesia (n = 54, 32%), and a combination of intravenous and inhalation anesthesia (n = 37, 22%). Ten respondents chose other and commented that the used technique depends on the location of surgery (n = 4) or that they used other techniques, including high dose opiates (n = 5) or regional anesthesia (n = 1). As illustrated in Fig. 2, switching resulted in a higher use of inhalation anesthesia for maintenance compared with induction.

Chi-square tests revealed that the used techniques for induction ($p <$ 0.0001) and maintenance of anesthesia ($p < 0.0001$) significantly differed depending on the location of surgery, with those performing surgery in the OR also using inhalation anesthesia, while those performing surgery in the NICU almost exclusively used intravenous anesthesia or high dose opiates.

3.4.4. Used anesthetics, analgesics, and muscle relaxants

Respondents using intravenous anesthesia for induction predominantly used propofol (n = 58, 45%), followed by midazolam (n = 43, 33%), esketamine (n = 42, 32%), and thiopentone (n = 27, 21%) (Fig. 3). Among those using inhalation anesthesia, sevoflurane was by far the most used (n = 79, 99%). Fentanyl (n = 130, 76%) and rocuronium (n = 96, 56%) were the most used analgesics and muscle relaxants during induction, respectively.

The most used intravenous and inhalation agents for maintenance of

anesthesia were midazolam (n = 39, 43% of those using intravenous anesthesia) and sevoflurane (n = 105, 97% of those using inhalation anesthesia), respectively (Fig. 3). Similarly to induction, fentanyl was the most used analgesic drug during maintenance (n = 122, 71%). Furthermore, 99 respondents (58%) reported providing continuous or repeated neuromuscular blockade in patients with NEC. For this purpose, rocuronium was the most used muscle relaxant (n = 56, 57%). Fig. 3 shows the number of respondents using the various agents for anesthesia (a and b), analgesia (c), and muscle relaxation (d), during both induction and maintenance.

For induction of anesthesia, respondents usually administered a combination of multiple anesthetics (n = 91, 53%), with sevoflurane and propofol being the most used combination (n = 33, 19%). For maintenance of anesthesia, on the other hand, using a single anesthetic was more common (n = 104, 60%). Fig. 4 illustrates the combinations of agents used for induction (a) and maintenance (b) of anesthesia. For induction, 39 different combinations of anesthetics were used, and for maintenance 25 different combinations were used. Supplementary Fig. 1 provides a more detailed overview of the various combinations of agents used for induction and maintenance of anesthesia.

3.4.5. Regional anesthesia

Sixteen anesthesiologists (9%) used regional anesthesia and 37 (22%) sometimes used regional anesthesia in patients undergoing surgery for NEC. Out of these 53 (31%) respondents applying regional techniques, 28 (53%) used a single shot caudal block and 25 (47%) an abdominal wall block. Other regional techniques mentioned were a caudal catheter (n = 8, 15%), wound infiltration (n = 3, 6%), and an epidural catheter (n = 2, 4%). The most used local anesthetics were levobupivacaine (n = 30, 57%) and ropivacaine (n = 22, 42%), followed by bupivacaine (n = 7, 13%), and lidocaine (n = 1, 2%). Those providing regional anesthesia usually administered this after induction and before the start of the procedure (n = 41, 77%), whilst 17 respondents (32%) (also) provided regional anesthesia at the end of the procedure.

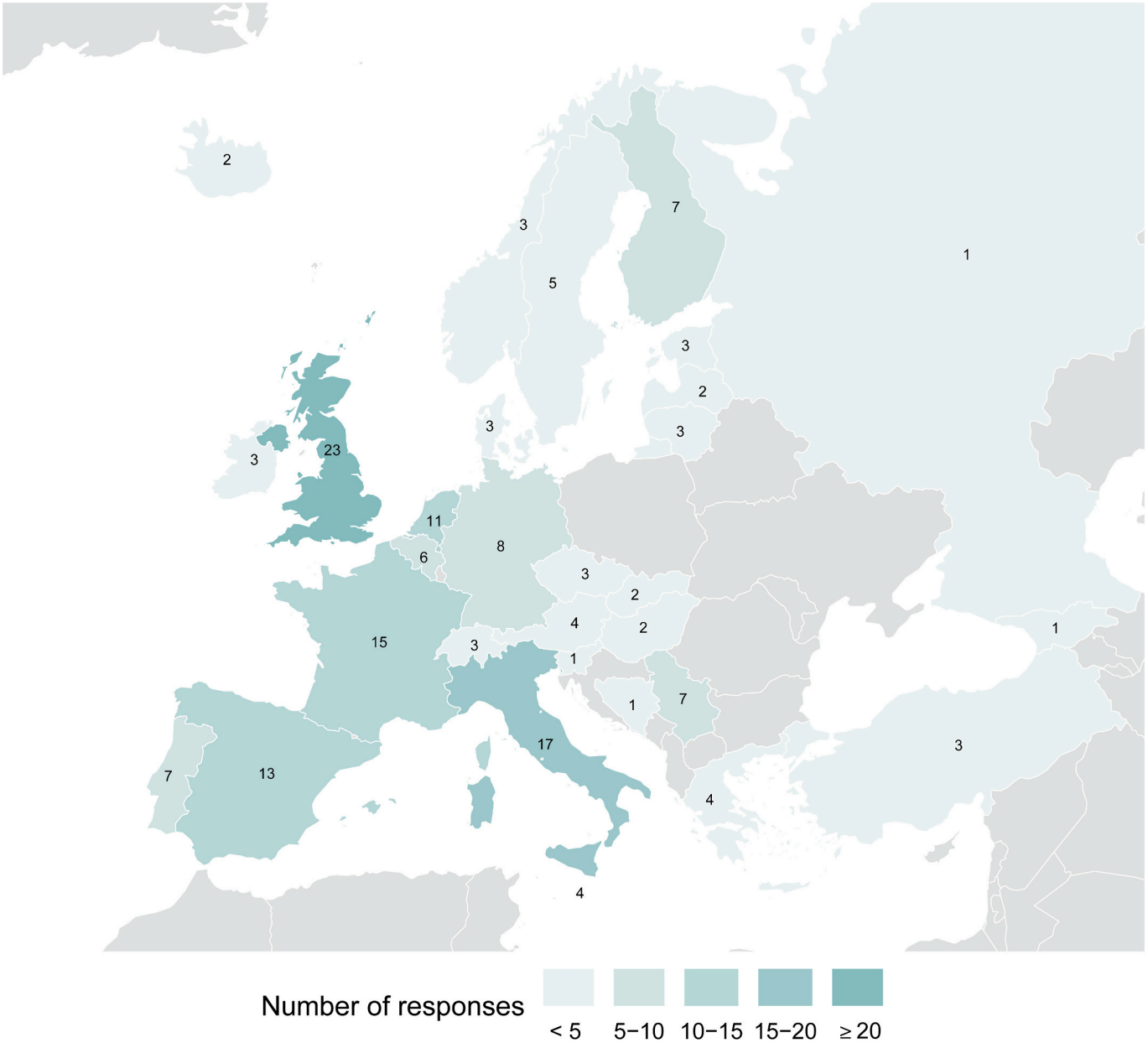

Fig. 1. Number of responses per country.

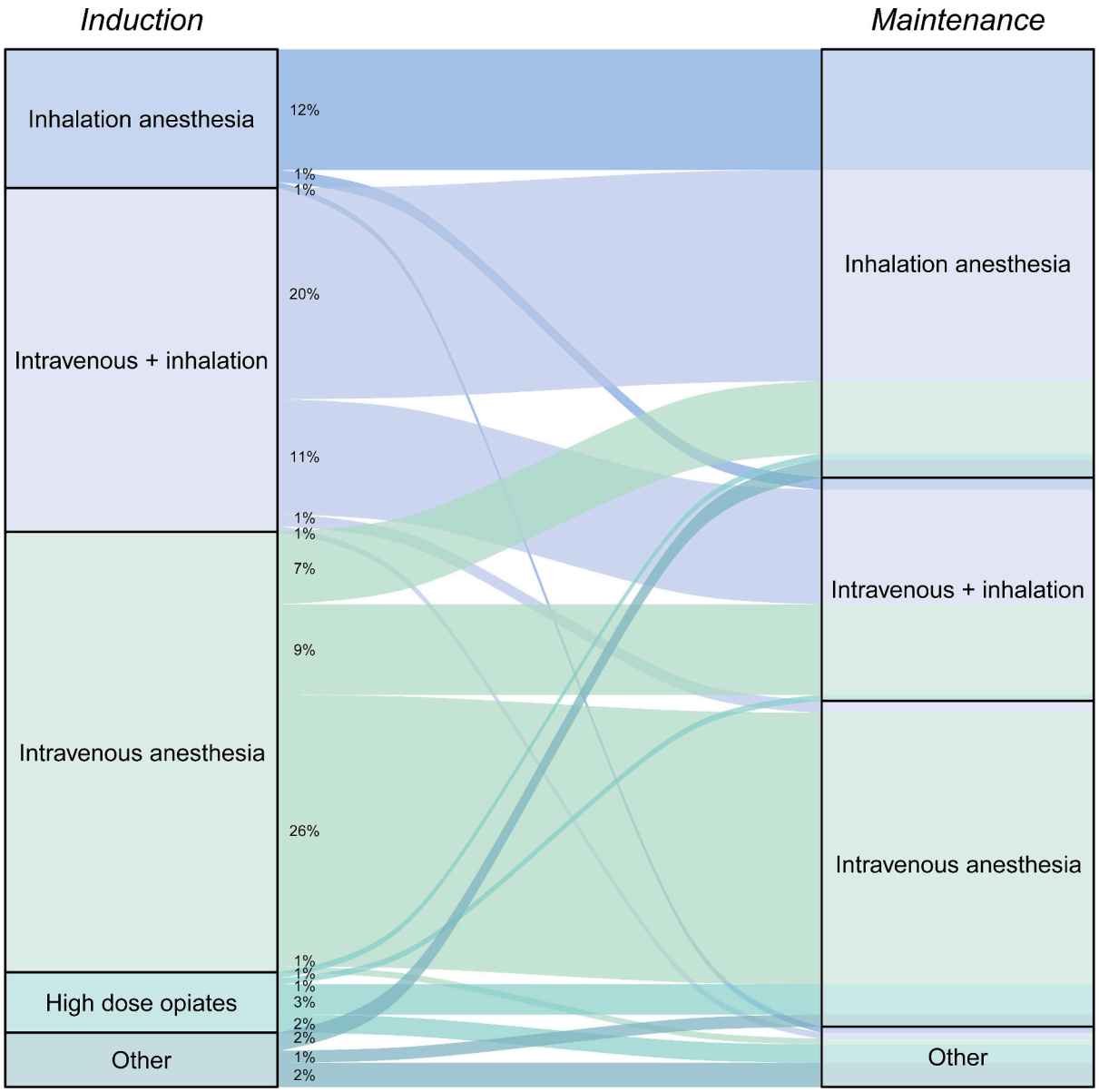

Fig. 2. Combination of techniques used for induction and maintenance of anesthesia. Respondents who chose 'other' mainly commented that their choice of induction technique depends on the location of surgery (OR vs. NICU).

3.4.6. Neurotoxicity

For 67 (39%) respondents, fear for neurotoxicity played a role in their choice of agents for anesthesia, analgesia or muscle relaxation. The most mentioned agent that respondents avoided for fear of neurotoxicity was esketamine ($n = 13$), followed by propofol ($n = 7$), midazolam (n = 4), benzodiazepines ($n = 3$), inhalation anesthetics (n = 3), and nitrous oxide (n = 3). Furthermore, ten respondents mentioned using low doses of inhalation anesthetics due to possible neurotoxicity. Similarly, high doses of esketamine and propofol were avoided by two respondents each.

3.4.7. Parameters guiding intraoperative anesthesia

Fig. 5 illustrates the most important intraoperative parameters guiding the titration of anesthesia and analgesia, as ranked by the respondents. Heart rate was generally deemed the most important parameter affecting their decision-making process, followed by blood pressure, end-tidal anesthetic concentration (ETAC), and near-infrared spectroscopy (NIRS). The majority of the respondents did not select bispectral index (BIS), Narcotrend, electroencephalogram (EEG), or A-line autoregressive index (AAI). A few respondents mentioned other parameters affecting their decision-making, including temperature and muscle tension.

3.4.8. Parental presence

In the majority of respondents' centers ($n = 121$, 70%), parents were not allowed to be present during the induction of anesthesia in patients undergoing surgery for NEC. In 23 (13%) centers, one parent was allowed to be present during induction and in 9 (5%) centers both parents were allowed.

3.4.9. Fluid management

Most respondents chose to administer both vasopressors/inotropes and fluids ($n = 149$, 87%) to maintain tissue perfusion during surgery for NEC, with the remainder choosing for one of these options. Those administering inotropes/vasopressors ($n = 157$, 91%) most commonly used norepinephrine ($n = 85$, 54%), followed by dopamine ($n = 73$, 46%), and epinephrine ($n = 57$, 36%).

Those administering fluids (n = 157, 91%) used a wide range of types

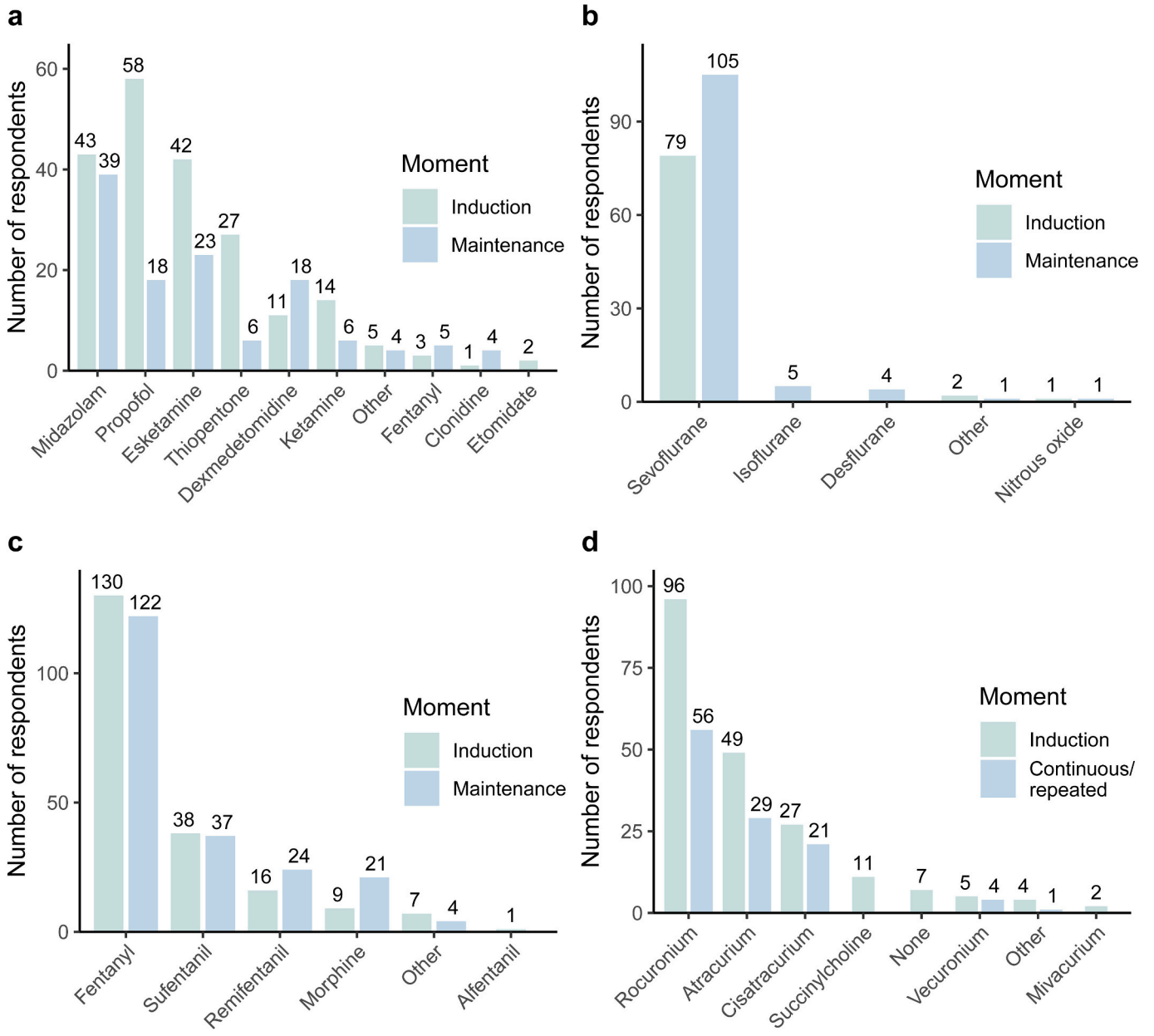

Fig. 3. Used intravenous anesthetics (a), inhalation anesthetics (b), analgesics (c) and muscle relaxants (d) during induction and maintenance.

of fluids. For maintenance fluid therapy, this most often included Ringer's lactate (n = 57, 36%), normal saline (41, 26%), and/or glucose 5% (n = 36, 23%). For replacement fluid therapy, albumin (n = 72, 46%), red blood cells (n = 68, 43%), and Ringer's lactate (n = 65, 41%) were most frequently chosen. Respondents were allowed to choose multiple options. Supplementary Table 2 shows an overview of all vasopressors/inotropes and fluids used.

The median (IQR) target hemoglobin level was 6.21 mmol/L (6.00–7.45), or 10.00 g/dL (9.67–12.00).

3.5. Postoperative care

For treatment of postoperative pain, the most used analgesics and sedatives were morphine (n = 114, 66%), paracetamol (n = 112, 65%), fentanyl (n = 62, 36%), single shot caudal block (n = 22, 13%), midazolam (n = 21, 12%), dexmedetomidine (n = 20, 12%), and abdominal wall block (n = 17, 10%). Supplementary Table 3 shows an overview of all agents used for postoperative analgesic therapy. The most used combination of agents was morphine and paracetamol (n = 21, 12%). A total of 46 (27%) respondents used regional techniques postoperatively, and 17 respondents used multiple regional techniques, with the combination of a single shot caudal block with an abdominal wall block being the most common (n = 7). The most used local anesthetic postoperatively was ropivacaine (n = 27), followed by levobupivacaine (n = 19).

3.6. Variations in anesthetic care

Agreement between respondents in the used agents for anesthesia, analgesia, and muscle relaxation was variable. Agreement in the choices for anesthetics was poor, as indicated by a Fleiss' Kappa statistic of 0.04. Agreement in the choices for analgesics and muscle relaxants was good (Fleiss' Kappa statistics of 0.63 and 0.67, respectively) and for postoperative analgesics fair (Fleiss' Kappa statistic 0.31). Supplementary Fig. 2 shows the used techniques for induction and maintenance per country.

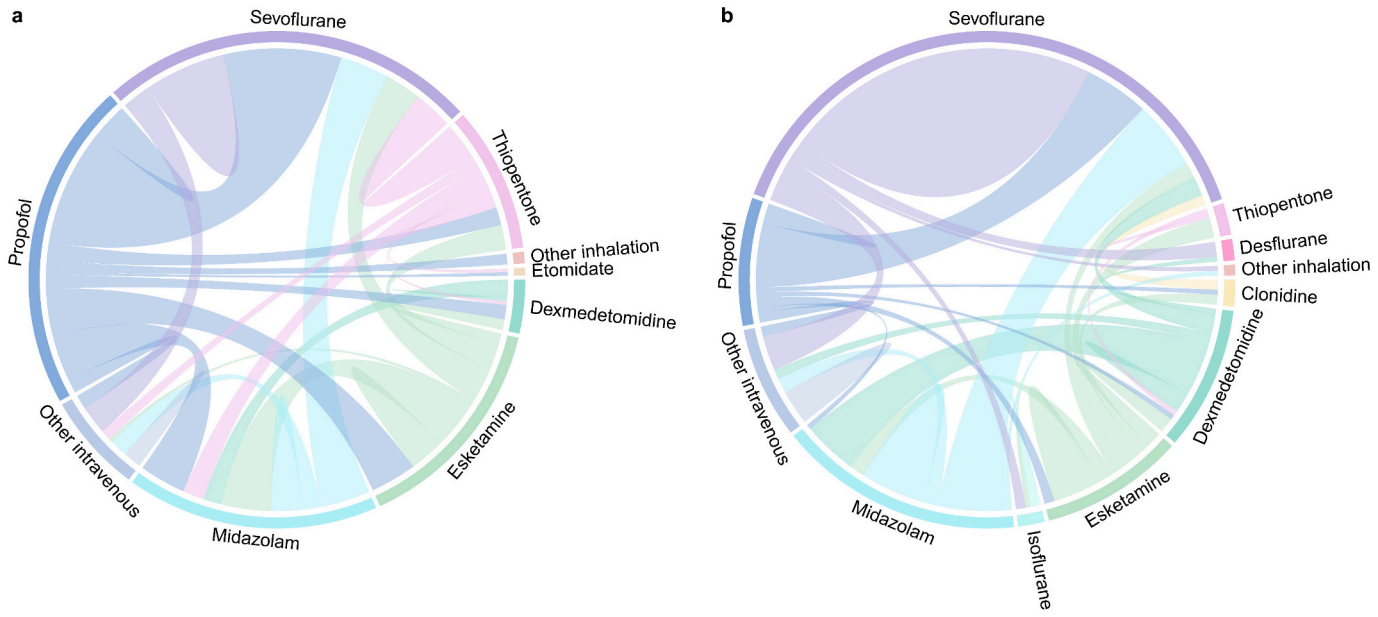

Fig. 4. Used combinations of agents for induction (a) and maintenance (b) of anesthesia.

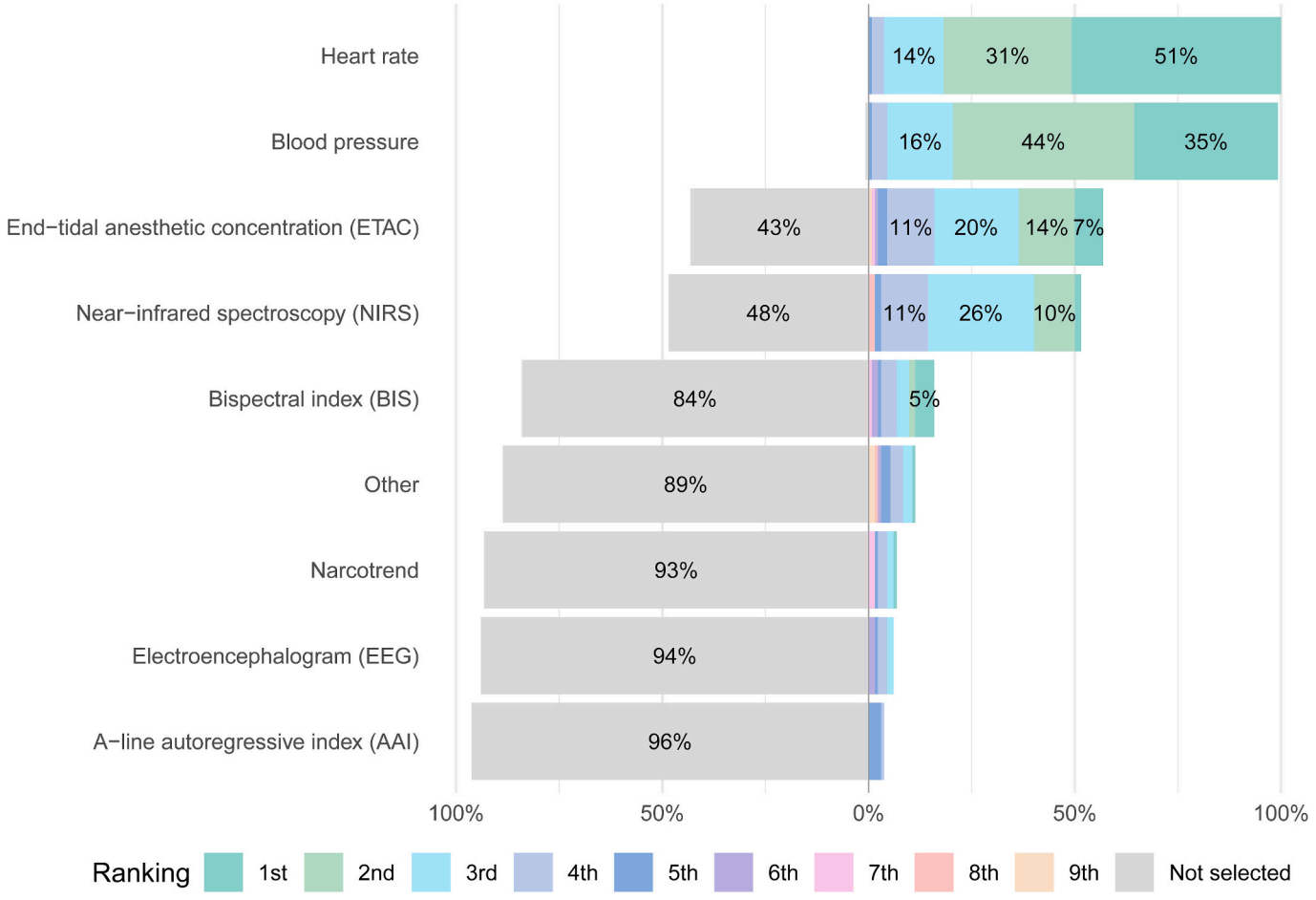

Fig. 5. Intraoperative parameters guiding the titration of anesthesia. On the right side of the y-axis, the percentage of respondents that considered a certain parameter as guiding their titration of anesthesia is shown, as well as their ranking of the importance of this parameter. On the left side of the y-axis, the percentage of respondents that did not select a certain parameter is shown.

In the 21 hospitals with two or more respondents, within-center agreement in the choices for anesthetics, analgesics, and muscle relaxants was also assessed. Compared to the entire respondent group, within-center agreement was generally higher, with a median (IQR) Fleiss' Kappa statistics of 0.79 (0.71–0.92), 0.85 (0.69–1.0), and 0.78 (0.62–1.0) for anesthetics, analgesics, and muscle relaxants, respectively.

3.7. Opinions regarding current anesthetic care for infants with NEC

When asked whether they think current anesthetic care for infants undergoing surgery for NEC in their center is adequate, 104 (60%) respondents chose 'Yes', 22 (13%) chose 'No', and 27 (16%) chose 'I don't know'. Those satisfied with anesthetic care in their center mainly mentioned a good collaboration between anesthesiologists, neonatologists, and surgeons ($n = 7$) and good outcomes (n = 7) as their reasons. Those dissatisfied mainly mentioned the lack of a protocol ($n = 4$), the infrequent use of regional techniques ($n = 2$), inadequate monitoring (n = 2), and a shortage of pediatric anesthesiologists (n = 2).

Furthermore, 98 (57%) respondents provided suggestions for further improvement of anesthetic care for infants undergoing surgery for NEC. The most frequently mentioned opportunities for improvement were monitoring ($n = 30$, 31% of those with suggestions for improvement), introduction of protocols ($n = 26$, 27%), and collaboration ($n = 20$, 20%). Additionally, more frequent use of regional anesthesia ($n = 8$), better teaching ($n = 5$), and a common decision on hemodynamic targets (n = 5) were mentioned. With regards to monitoring, the introduction of NIRS ($n = 10$) was most mentioned, followed by EEG ($n = 4$), end-tidal CO2 (ETCO2) (n = 3), and thromboelastography (TEG) (n = 2). With regards to collaboration, thirteen respondents mentioned preoperative multidisciplinary team consultations and eight mentioned the need for better communication between anesthesiologists, neonatologists, and surgeons as suggestions for improvement.

4. Discussion

This survey among 173 anesthesiologists across 31 European countries identified a large variability in anesthetic care for preterm infants undergoing surgery for NEC, particularly in the chosen agents for anesthesia and their combinations. Intravenous anesthesia was most used for induction, while inhalation anesthesia was favored for maintenance. For both induction and maintenance, the choice of technique strongly correlated with the location of surgery (OR vs. NICU). Propofol and midazolam were the preferred intravenous anesthetics for induction and maintenance, respectively, and sevoflurane the preferred inhalation anesthetic for either. Compared with the variety of anesthetics used, there was more consensus on the choices for analgesics and muscle relaxants, with fentanyl and rocuronium being the most commonly used. Approximately a third of respondents used regional techniques intraoperatively and approximately a quarter postoperatively. Postoperative pain management mainly included paracetamol and/or morphine. The majority of respondents regarded current anesthetic care for patients with NEC in their center as adequate, but many ideas were shared for further improvement. These suggestions mostly revolved around enhanced monitoring, implementation of protocols, and improved collaboration.

To our knowledge, anesthetic care for patients undergoing surgery for NEC has not been studied on a European scale before. Two recent multicenter cohort studies, the APRICOT study and the NECTARINE study, have assessed anesthetic care for various surgical and nonsurgical procedures in the pediatric and neonatal population, respectively [8,10]. Similarly to our study, the APRICOT study found a large variation in the used anesthetics, with sevoflurane and propofol being the most used inhalation and intravenous anesthetics for induction and fentanyl the most used analgesic [8]. The use of regional anesthesia in our study was also comparable with that reported in the APRICOT study and the NECTARINE study [10,11]. However, preterm infants with NEC may exhibit thrombocytopenia, which is a contraindication for neuraxial analgesia techniques, possibly explaining the low reported use of epidural or caudal catheter techniques. A notable difference with the APRICOT study and the NECTARINE study was the far higher use of invasive blood pressure monitoring and NIRS in our study [8,10]. This may be explained by differences in study population, with the APRICOT and NECTARINE study not only including critically ill children admitted to the intensive care unit but also ASA I-II children undergoing minor surgical procedures that require less intensive monitoring. The postoperative pain treatment observed in this study seems to resemble the pain treatment provided by neonatologists, which has been evaluated in a previous European survey [12]. This survey among neonatologists found that initial pain treatment for patients with NEC usually includes paracetamol, fentanyl and/or morphine, and that in case of persisting pain, pain treatment is intensified by increasing the dose of the administered opiate and/or adding agents such as midazolam, ketamine or dexmedetomidine [12].

The heterogeneity in anesthetic care for patients with NEC identified in this study may be explained by the lack of (international) guidelines. Existing Enhanced Recovery After Surgery (ERAS) consensus guidelines for perioperative care in neonatal intestinal surgery offer limited recommendations regarding choice of anesthetics, and do not apply to preterm infants and infants with complex surgical conditions such as NEC [13]. Furthermore, this survey found that only a third of centers had written standard protocols for anesthesia in infants, and even fewer had specific protocols for patients with NEC. This lack of protocols is probably attributed to the paucity of evidence on this topic, with various anesthetics being used off-label [9]. Consequently, the anesthetic care provided to patients with NEC likely varies depending on the anesthesiologist's preferences, availability of medication in the center, and local habits. This practice variability highlights the lack of evidence on what is the most optimal anesthetic care for this patient group, although it may also reflect multiple treatments being equally effective [14]. Nonetheless, the implementation of protocols was frequently mentioned as an opportunity to improve anesthetic care for patients with NEC. The results of this survey may provide a first step towards developing a guideline for perioperative anesthetic care for preterm infants with NEC. Alternatively, individualized anesthetic plans could be developed according to the 10-Ns principle proposed by the SAFETOTS initiative, focusing on physiological targets rather than choice of anesthetics [15].

In addition to the implementation of protocols, respondents suggested collaboration within the surgical team as a target to improve anesthetic care for infants with NEC. Collaboration may be improved by performing preoperative multidisciplinary consultation, which four in five respondents of this survey reported doing structurally or occasionally. Additionally, this survey showed that preoperative evaluation is not always performed prior to surgery in patients with NEC, which may reflect the urgency of surgery in the most severely ill patients. The ERAS guidelines for neonatal intestinal surgery strongly recommend standardized perioperative communication with multidisciplinary teams [13]. Preoperative briefings have been shown to improve team work and communication in the operating room and may thereby improve patient outcomes [16].

Respondents also frequently mentioned monitoring as an area for improvement, for instance through increased use of NIRS monitoring. NIRS is not part of standard intraoperative monitoring yet, but may be a valuable addition as it enables swifter detection of tissue hypoxia [17]. Moreover, in infants with (suspected) NEC, cerebral and splanchnic NIRS measurements may be used diagnostically or predictively [18]. In addition, respondents suggested incorporation of EEG to monitor depth of anesthesia. However, young infants often do not yet have differentiated EEGs, hampering the use of EEG-based monitoring devices [19].

Maintaining tissue perfusion in infants undergoing surgery is of the utmost importance, since impaired tissue oxygenation, indicated by the presence of hypotension, hypoxemia, and anemia, is associated with an

approximately 20-fold higher postoperative morbidity and mortality [10,20]. In addition, the risk of morbidity and mortality is increased in the most preterm born infants and in those requiring intensive support prior to surgery [10]. These risk factors are all highly relevant for infants with NEC, who are often extremely preterm and require admission to a neonatal intensive care unit. Furthermore, infants with NEC are frequently hemodynamically unstable and exhibit impaired tissue oxygenation, both cerebrally and intestinally [21–24]. Given their hemodynamic instability, the high use of propofol observed in this study is surprising, as propofol may induce hypotension in critically ill neonates [25]. Anesthetic strategies for infants with NEC should focus on optimal analgosedation while safeguarding cerebral and intestinal perfusion, and anesthesia should be provided by an experienced pediatric anesthesiologist to mitigate the risks of severe critical events [8,26].

Decreases in cerebral perfusion during surgery may contribute to the increased risk of neurodevelopmental impairment in infants with surgical NEC [27,28]. Other factors that may contribute to this increased risk include the greater disease severity and inflammation in infants with surgical NEC and possibly anesthetics-related neurotoxicity [29,30]. Studies in rodents have demonstrated that neonatal exposure to various anesthetics, including ketamine, midazolam, and inhalation anesthetics, causes neuronal apoptosis and cognitive impairment [31]. Human studies, on the other hand, have not identified clear neurotoxic effects of anesthesia in infants, although high quality and well-powered safety trials are generally missing, especially in preterm infants. While some observational studies suggest an association between neonatal anesthesia exposure and adverse neurodevelopmental outcomes [32–38], a twin study and a sibling-matched cohort study (PANDA study) found no differences in neurodevelopmental outcomes between the exposed and unexposed sibling [39,40], suggesting an underlying vulnerability may confound the association between anesthesia and neurodevelopmental outcomes. This was supported by the General Anesthesia compared to Spinal anesthesia (GAS) trial, which found that infants receiving awake regional anesthesia and infants receiving sevoflurane-based general anesthesia did not differ in cognitive outcomes at 2 years and 5 years [41,42]. However, these prospective studies did not involve critically ill, preterm infants. As shown in this survey, pediatric anesthesiologists remain cautious in patients with NEC, with over a third of the respondents of this survey avoiding certain anesthetics due to concerns about neurotoxicity.

A strength of this study is that it addresses a previously unexplored topic in our most vulnerable patients, namely anesthesia practice for preterm infants with NEC, on a European scale. Furthermore, this study provides a comprehensive overview of anesthetic care for these patients, entailing preoperative, intraoperative, and postoperative care. A limitation inherent to survey research is the fact that only a subset of (pediatric) anesthesiologists completed the survey. Due to the technique used for the dissemination of our survey, the number of anesthesiologists who received the invitation to our survey is unknown and we thus cannot determine the response percentage. Possibly those who completed the survey had a special interest in this topic, limiting the generalizability of our results. In addition, Eastern European countries were underrepresented. Another limitation is that we did not specify the type of surgery for NEC, and therefore respondents may have had different types of surgery (e.g., laparotomy, peritoneal drainage) in mind while completing the questionnaire. This may have affected their responses. Furthermore, to limit the time burden of completing the questionnaire, no questions were included regarding the used anesthetic doses. Given the potential adverse effects related with anesthetics, this could be interesting to assess in future studies. Moreover, qualitative studies may delve into the reasons for prescribing certain anesthetics.

5. Conclusions

Anesthesia practice for infants undergoing surgery for NEC in centers across Europe was highly variable, with over 30 different combinations of anesthetics being used, highlighting the lack of consensus. In general, responding anesthesiologists considered the anesthetic care provided to patients with NEC adequate, but they also offered suggestions for further improvement, mainly pertaining to monitoring, protocols, and multidisciplinary collaboration. These results may serve as a first step towards (consensus) guidelines for anesthetic care for infants with NEC.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Judith A. ten Barge: Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Alexandra J.M. Zwiers:** Conceptualization, Methodology, Writing – review & editing. **Marijn J. Vermeulen:** Methodology, Writing – review & editing. **Claudia M.G. Keyzer-Dekker:** Methodology, Writing – review & editing. **Sinno H.P. Simons:** Methodology, Writing – review & editing. **Lonneke M. Staals:** Conceptualization, Methodology, Writing – review & editing. **Gerbrich E. van den Bosch:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

LS received departmental funding for research from Merck / MSD. The other authors declare no conflict of interest.

Acknowledgements

We are thankful to the anesthesiologists who aided in the distribution of our survey and those who took the time to complete our survey.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2024.111508.

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