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Infants Operated on for Necrotizing Enterocolitis: Towards Evidence-Based Pain Guidelines

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Key Words

Necrotizing enterocolitis · Analgesia · Pain management · Premature infants

Abstract

Background: Necrotizing enterocolitis (NEC) is known as an extremely painful childhood condition. **Objectives:** The objective of this study was to explore pain management around NEC-related surgery in our neonatal intensive care unit (NICU) from a chart review of prospectively collected data on 60 operated NEC patients admitted between 2008 and 2013 with a median (IQR) gestational age of 28.3 (25.5–31.6) weeks. **Methods:** Pain medication data and pain scores (i.e. COMFORTneo and Numerical Rating Scale pain and distress scores) from 72 h before until 72 h after surgery were collected. **Results:** Preoperatively, 95% of the patients received morphine versus 100% postoperatively, with a median dosage of 10.0 (IQR 9.7–14.5) and 16.9 (IQR 10.1–20.0) $\mu\text{g}/\text{kg}/\text{h}$, respectively. Postoperatively, 28 patients (46.7%) received additional fentanyl intermittently and 14 (23.3%) received midazolam, which was part of palliative treatment for 6 patients (42.9%). In patients receiving pain medication, median

COMFORTneo scores were 10 (IQR 10–11) preoperatively and 11 (10–12) postoperatively. The pain scores were comparable with those of other patients admitted to the NICU in the same time period. **Conclusions:** Continuous morphine of 10 $\mu\text{g}/\text{kg}/\text{h}$ preoperatively, with an increase to 15 $\mu\text{g}/\text{kg}/\text{h}$ postoperatively, seems to constitute a good starting dose for further individualized pain management guided by pain scores.

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Introduction

Necrotizing enterocolitis (NEC) is a dreadful and extremely painful complication that is related to very high morbidity and mortality [1, 2]. Research efforts so far have mainly focused on etiology, surgical and conservative treatment and prevention of the disease [3]. It is also important, though, to protect hospitalized neonates from pain, not only for ethical reasons but in view of the possible negative short- and long-term consequences of untreated pain [4, 5]. However, there is surprisingly little research into optimal pain management for NEC [6, 7].

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In contrast to other intestinal diseases, such as an isolated perforation or congenital atresia, NEC is much more painful, both pre- and postoperatively, on account of the ongoing inflammatory and ischemic processes in the intestines as well as the related peritonitis [8, 9]. There is consensus among clinicians that NEC-related pain must be assessed and treated, but how this should be done is unclear and this is usually left to the discretion of the treatment team [10–12]. To our knowledge, there are no guidelines for the assessment and management of NEC-related pain.

While the main focus of current research on neonatal pain assessment is on acute procedural pain, NEC-related pain requires an instrument validated for the assessment of prolonged pain [13]. In our hospital, a modified version of the COMFORT-behavior scale, the COMFORT-neo scale, was designed and validated to assess prolonged pain in premature neonates [14].

Opioids seem the most appropriate for pain management in NEC [15]. For premature infants weighing <1,000 g, 10 µg/kg/h of morphine or 0.5–2 µg/kg/h continuous fentanyl is considered a reasonable dosage to relieve NEC-related pain [16], although there is no evidence for this assumption. Based on the latest population pharmacokinetic/pharmacodynamic (PK/PD) model for morphine, lower postoperative dosages might be more appropriate in neonates undergoing major noncardiac surgery, particularly when they are <10 days of age [17, 18], but the question remains whether this holds for NEC patients as well.

This study describes pain management in neonates before and after NEC-related surgery according to the guidance of validated pain scales. We also aimed to determine if their pain assessment scores were comparable to those of patients admitted to the NICU with other diagnoses.

Materials and Methods

Study Design

This was a retrospective chart review of prospectively collected data in the computerized Patient Data Management System (PDMS).

Patients and Setting

All neonates admitted to the level III neonatal intensive care unit (NICU) of the Erasmus University Medical Center – Sophia Children’s Hospital, Rotterdam, The Netherlands, who underwent a laparotomy for suspected or confirmed NEC (Bell stages 2 and 3) from January 2008 to December 2013 were included. Patients with a focal intestinal perforation were excluded, as this was con-

sidered a separate entity [19]. Because of the different histopathology and possible differences regarding pain, our study concentrated on operated infants with confirmed NEC.

The pain management protocol is described in figure 1. Guided by pain scores, analgesics could be titrated. In case of suspected pain during caregiving, intermittent fentanyl could be added. There is a probable synergistic sedative effect between morphine and midazolam [20]. Midazolam is therefore sometimes given to preterm neonates whose discomfort does not adequately respond to morphine therapy. This pain protocol is used for all NICU patients and not specifically for NEC patients.

Data Collection

The following data were retrieved from the PDMS: sex, date of birth, gestational age at birth, date of surgery, medication data and pain and distress scores. The time of the start and end of surgery and confirmation of the NEC diagnosis were retrieved from surgery reports. The time of the NEC diagnosis is often unclear. Therefore, a time-span of 72 h was chosen for specific data collection. Medication data and COMFORTneo and Numerical Rating Scale (NRS) pain and distress scores were collected for the period from 72 h before the start of surgery until 72 h after the end of surgery, excluding intraoperative medication. For the patients who died within 72 h after surgery, the data collected until the time of death were included in the analysis. The type of surgery was categorized by a surgeon (C.M.G.K.-D.).

In addition, to enable comparison with other patients, the COMFORTneo and NRS pain scores for all other patients, both surgical and nonsurgical, who were admitted to the NICU in the research period, were also retrieved. The advised morphine dosages according to the PK/PD model of Krekels et al. [17], based on the birth weight and postnatal age, were also calculated.

Measurement Instruments

Nurses in our NICU are trained to apply the COMFORTneo scale, an NRS for pain and an NRS for distress. A nurse’s interrater reliability for the COMFORTneo scale was assessed from the weighted Cohen’s kappa [21], calculated from the results of 10 paired assessments with a qualified nurse. The COMFORTneo score has been validated for the use in the NICU [14]. The cut-off score for pain is set at ≥ 14 . The total score ranges from 6 to 30. NRS scores range from 0 to 10; cut-off scores for NRS pain and NRS distress are both set at ≥ 4 . The pain management protocol prescribes that each neonate is assessed while resting at least once during every 8-hour shift. Extra assessment is indicated after the administration of sedatives or analgesics and if pain or over-/undersedation is suspected.

Data Analysis

Data were exported from the PDMS automatically to SPSS v21.0 (SPSS Inc., Chicago, Ill., USA).

Postoperative morphine dosages were compared with the recently advised morphine dosage for postoperative neonates after major noncardiac surgery by Krekels et al. [17]. Median COMFORTneo scores, NRS pain and NRS distress before and after surgery were compared with the Wilcoxon signed-rank test. The institutional ethical review board waived the need for approval because the participants did not have to undergo medical procedures or follow special rules of behavior (MEC-2014-547).

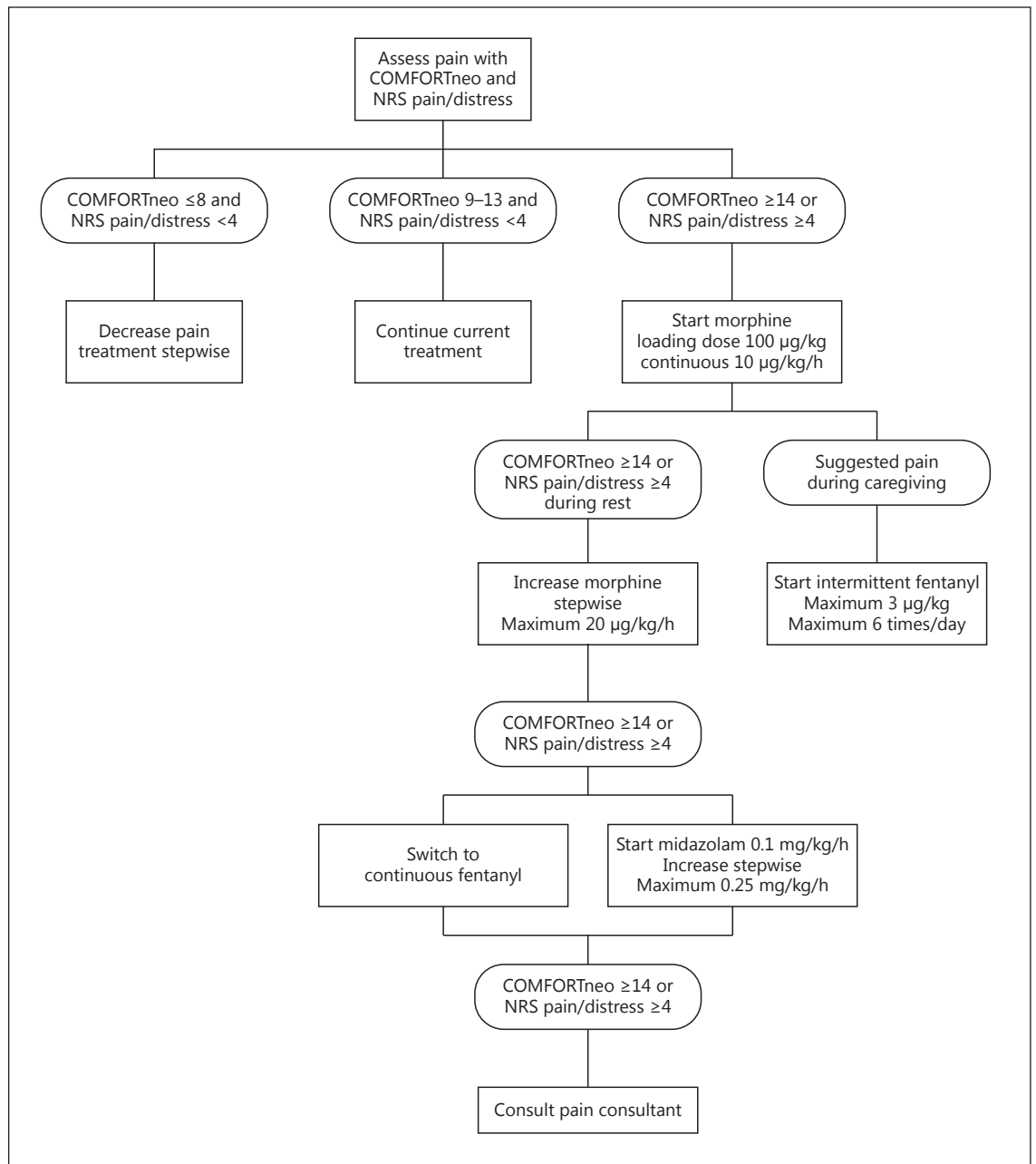


Fig. 1. Pain treatment flow diagram.

Results

Patients

Figure 2 shows the patient flow diagram for this study. Of the 80 neonates operated on due to suspected or proven NEC between 2008 and 2013, 60 were included in this study. Three patients were admitted to the Pediatric ICU

and 1 patient had already undergone a laparotomy in another NICU; these 4 were excluded because of possible differences in pain management.

Table 1 shows patients' background characteristics. The median gestational age was 28 weeks and 3 days and median postnatal age at the time of surgery was 10 days (range 5–57 days). Fourteen patients (23.3%) died

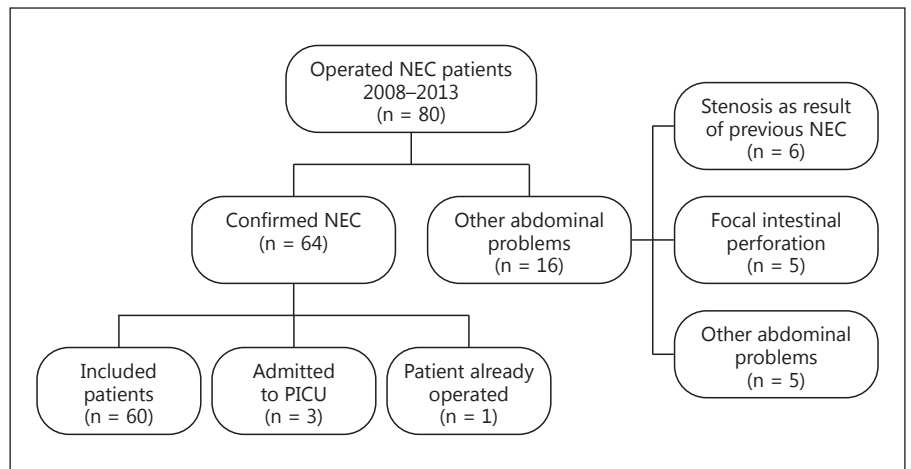


Fig. 2. Patient flow diagram. PICU = Pediatric ICU.

Table 1. Background characteristics of 60 patients

Variables	
Boy/girl	24 (40)/36 (60)
Gestational age, weeks ^{+days}	28 ⁺³ (25 ⁺⁵ –31 ⁺⁶)
Birth weight, g	1,053 (836–1,525)
Postnatal age at surgery, days	10 (8–22)
Death within 72 h after surgery	14 (23.3)
Relaparotomy within 72 h	4 (6.7)
Bell staging ^a	
2B	5 (8.3)
3A	17 (28.3)
3B	38 (63.3)
Preoperative drain	3 (5.0)
Surgery	
(Almost) complete necrotic intestines	10 (16.7)
Partial jejunal/ileal resection	18 (30.0)
Ileocecal resection/hemicolectomy/ partial colon resection	15 (11.7)
Subtotal colectomy	7 (11.7)
Partial jejunal/ileal and partial colon resection	6 (10.0)
Isolated creation of stoma/clip and drop	4 (6.7)

Values are expressed as n (%) or median (IQR).
^a Adapted Bell's criteria [23].

within 72 h after surgery. All of these deaths were related to NEC and were preceded by the decision to withdraw IC treatment; 10 of them had (almost) completely necrotic intestines and the other 4 had undergone a 'second look' operation to evaluate viability of the intestines within 72 h.

Pain Assessment

The COMFORTneo and NRS pain and distress scores were available for 56 patients (93.3%) preoperatively and 52 (86.7%) postoperatively. The patients without preoperative pain scores had been admitted 5–15 h before surgery. The patients without pain scores postoperatively had died within 2–9 h after surgery. COMFORTneo scores 72 h after surgery were significantly higher than those 72 h before surgery (Wilcoxon signed-rank test, $p = 0.012$). Median NRS pain was higher preoperatively than postoperatively, but the difference was not statistically significant (Wilcoxon signed-rank test, $p = 0.117$). Median NRS distress tended to be higher after surgery than before surgery but this was not statistically significant (Wilcoxon signed-rank test, $p = 0.099$).

Table 2 shows the pain scores of the NEC patients in the 72-hour preoperative and postoperative periods and of all other NICU patients admitted in the study period. These results are presented in figure 3 as median COMFORTneo and NRS pain scores per patient.

Thirteen patients received only morphine (21.7%). One, two or three additional analgesic or sedative drugs were administered to 36 patients (60.0%), 10 patients (16.7%) and 1 patient (1.7%), respectively.

Pain Management

All patients received morphine after surgery. Fifty-seven of them (95%) also received morphine before surgery (table 2). The maximum and median doses per patient in $\mu\text{g}/\text{kg}/\text{h}$ were both significantly higher after surgery (both Wilcoxon signed-rank test, $p < 0.001$). After surgery, almost half of the patients (46.7%) were also given intermittent fentanyl before procedures that are pain-

Table 2. Pain assessment results for NEC patients and all other patients admitted to the NICU in 2008–2013 as well as a list of the analgesics and sedatives administered before and after surgery

	72 h before surgery	72 h after surgery	All other NICU patients
Patients assessed	56 (93.3)	52 (86.7)	3,685
Total number of COMFORTneo scores/patient	9 (5–12)	13 (11–16)	8 (3–22)
<i>COMFORTneo</i>			
Score	10 (10–11)	11 (10–12)	10 (10–11)
Patients with at least one score ≥ 14	27 (45.0)	37 (61.7)	1,760 (47.7)
Patients with at least one score ≤ 8	33 (55.0)	33 (55.0)	1,659 (45.0)
<i>NRS pain</i>			
Score	0 (0–2)	0 (0–1)	0 (0–0)
Patients with at least one score ≥ 4	31 (51.7)	23 (38.3)	516 (14.0)
<i>NRS distress</i>			
Score	0 (0–0)	0 (0–0)	0 (0–0)
Patients with at least one score ≥ 4	11 (18.3)	17 (28.3)	1,193 (32.4)
<i>Morphine</i>			
Patients	57 (95.0)	60 (100)	–
Cumulative dose, $\mu\text{g}/\text{kg}/72\text{ h}$	307 (133–626)	895 (459–1177)	–
Dose, $\mu\text{g}/\text{kg}/\text{h}$			
Maximum	14.6 (10.0–19.8)	19.8 (15.0–20.5)	–
Median	10.0 (9.7–14.5)	16.9 (10.1–20.0)	–
<i>Fentanyl</i>			
Patients on intermittent dosage	21 (35.0)	28 (46.7)	–
Patients on continuous dosage	–	2 (3.3)	–
Dose, $\mu\text{g}/\text{kg}$	2.0 (1.7–2.3)	2.0 (1.3–2.2)	–
Number of doses	1.0 (1.0–2.5)	4.0 (2.0–8.0)	–
<i>Acetaminophen</i>			
Patients	1 (1.7)	5 (8.3)	–
<i>Midazolam</i>			
Patients	3 (5.0)	14 (23.3)	–
Cumulative dose, $\text{mg}/\text{kg}/72\text{ h}$	3.5 (0.5–3.6)	1.0 (0.4–1.8)	–
Used for palliative treatment	–	6 (42.9)	–
<i>Clonidine</i>			
Patients	–	1 (1.7)	–

Values are expressed as n (%) or median (IQR).

ful for such patients, such as diaper change. Fourteen patients (23.3%) additionally received midazolam after surgery; for 6 of them, this was part of the palliative treatment. Median doses are presented as median per patient.

Figure 4 shows the relation between postoperative morphine dosages in our research population (except for in those who died within 72 h after surgery) and the morphine dosages calculated according to the PK/PD model of Krekels et al. [17]. This validated model is based on term newborns that undergo major noncardiac surgery and receive a loading dose of 100 $\mu\text{g}/\text{kg}$ in the operating room. Dosage recommendations are based on their post-

natal age (i.e. ≤ 10 days or > 10 days) and weight. It shows that all neonates in our research population required more morphine than the calculated dosages.

Discussion

We found that pain scores for neonates who underwent surgery for NEC were acceptable and comparable to those of all other patients admitted to the NICU in the same period. Median continuous morphine dosages of 10 and 17 $\mu\text{g}/\text{kg}/\text{h}$ before and after surgery were needed, re-

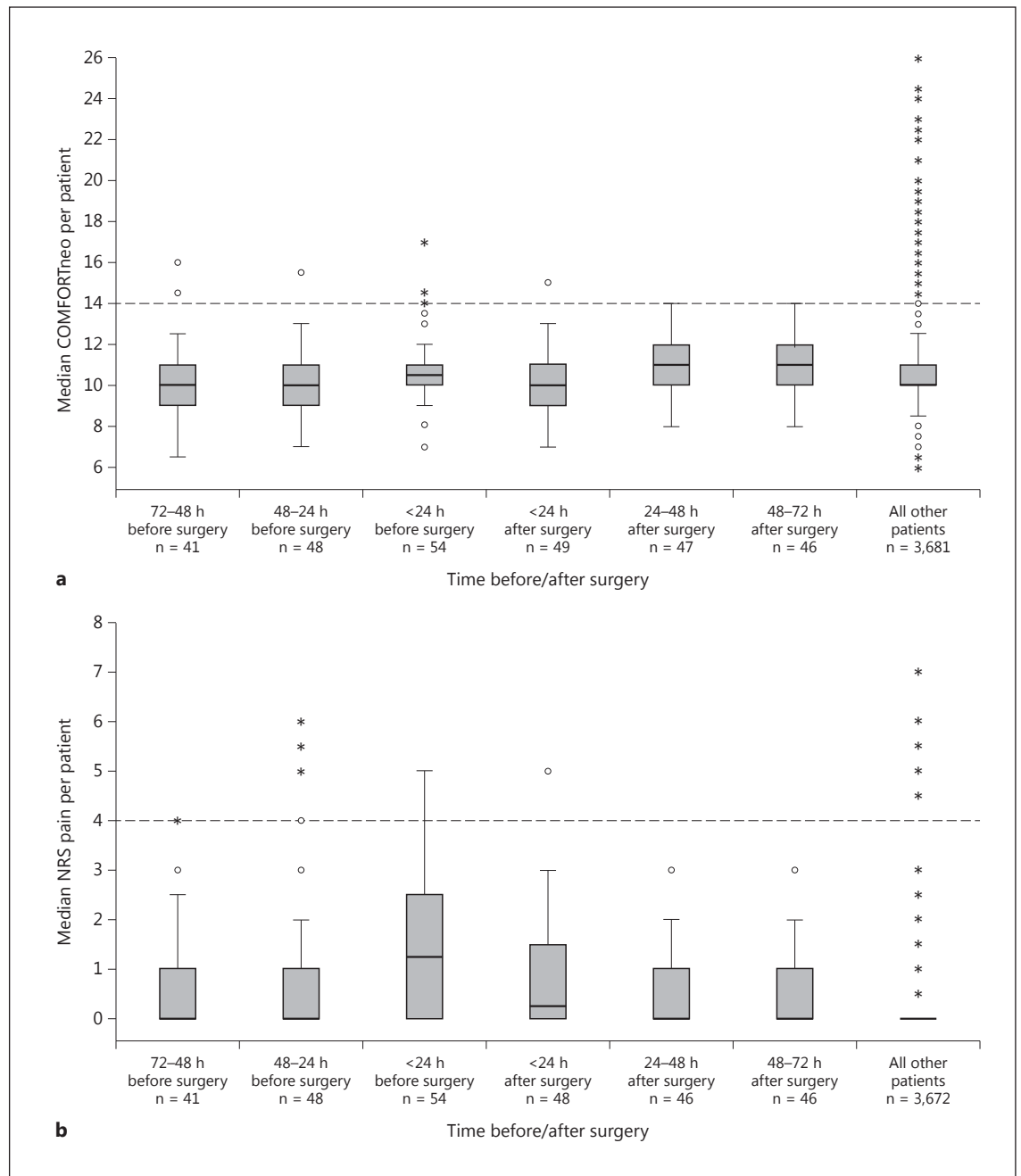


Fig. 3. Box plots showing COMFORTneo scores (a) and NRS pain scores (b) for the patients with NEC. ° = Any score > 1.5 × the IQR from the rest of the scores (mild outliers); * = any score > 3 × the IQR from the rest of the scores (extreme outliers).

spectively, to reach adequate analgesia. One or more additional analgesics, particularly fentanyl, were needed in 88.3% of the patients.

To our knowledge, only one other paper has been published on pain assessment and pharmacological manage-

ment in infants with NEC [22]. This retrospective study included 25 infants with stage II NEC, and pain was assessed with the PIPP (Premature Infant Pain Profile), which is validated for acute painful procedures only. Nurses' compliance with pain assessment was poor and

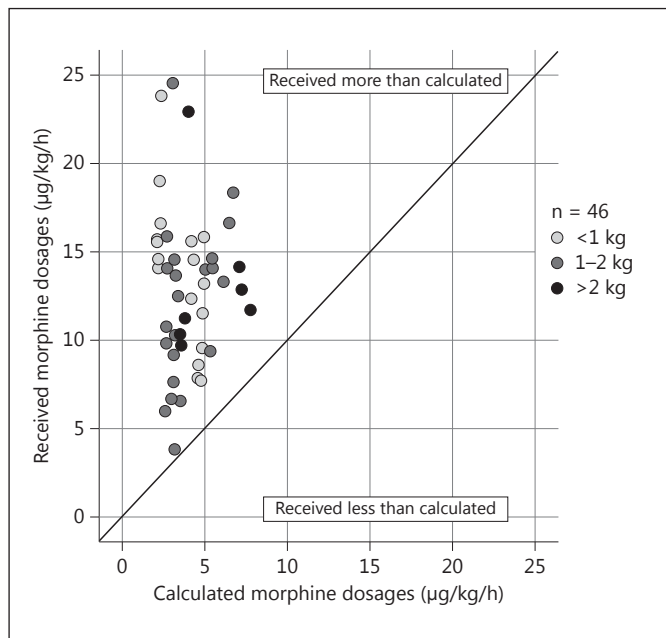


Fig. 4. Calculated PK/PD model-based morphine maintenance doses for neonates after major noncardiac surgery as a follow-up to 100 µg/kg/h loading dose [17] (x-axis) compared to the average received morphine dosages in neonates after NEC surgery over 72 h (y-axis). Doses are provided for different groups of patients based on birth weight.

the PIPP scores were not presented. The mean morphine infusion during 5 days after initial diagnosis was 15 µg/kg/h combined with a mean dose of fentanyl of 3 µg/kg/h. The morphine doses that they used are comparable to ours and slightly higher than those suggested by Thiagarajah and Thiagarajah [16], i.e. 10 µg/kg/h for premature infants weighing <1,000 g in the postoperative period after a laparotomy for NEC.

The recently advised morphine dose for postoperative neonates after major noncardiac surgery by Krekels et al. [17] is much lower than what our patients needed (fig. 4). Even though they did not study preterm neonates weighing <2 kg, it seems that in NEC and NEC-related surgery, separate dosing guidelines are necessary for the administration of morphine and additional analgesics. Postoperatively, neonates received significantly more morphine and also more additional analgesic or sedative drugs than preoperatively. Based on our study, we would advise starting at 10 µg/kg/h of morphine after a loading dose when NEC is diagnosed. Postoperatively, this dose should be increased to 15 µg/kg/h. Intermittent fentanyl can be added if pain assessment during caregiving indicates

pain. If, subsequently, pain scores during rest remain too high, the morphine dosage should be increased to up to 20 µg/kg/h. Continuous fentanyl and the addition of midazolam are alternatives if this maximum dose is still inadequate to achieve sufficient comfort. Although not frequently used in our study, intermittent intravenous paracetamol administration might be beneficial [18] but needs further study in this specific population.

Dosing of analgesics and sedatives needs to be adjusted on the guidance of pain scores to prevent oversedation and undersedation. The assessment of pain should always be made before and after changes in analgesic treatment with, for instance, the COMFORTneo scale or the EDIN (Échelle Douleur Inconfort Nouveau-Né) [13, 14], validated for prolonged pain. We showed that median COMFORTneo scores for patients with NEC were comparable to those of other NICU patients admitted in the same period. Both before and after surgery, 55% of patients in our study population were assigned a COMFORTneo score of ≤8 compared to 45% of the other patients. If oversedation had been a problem in our study population, we would have expected the difference between the groups to have been larger. We do realize, however, that COMFORTneo scores of ≤8 are acceptable in patients who do not receive opioids or sedatives but are simply in a deep sleep. Because of the possibility of unjustifiably low pain scores due to the lack of body movements and blank facial expression which are common in NEC patients [13], it is important that not only the COMFORTneo scores but also the NRS scores are acceptable [13].

The findings of this study offer a first step towards evidence-based guidelines. Because the management of pain in NEC patients is still neglected in the scientific literature, prospective studies are needed to validate pain management guidelines and an adequate pain assessment instrument. Further research is also needed on specific behavioral and physiological item changes related to pain in NEC patients and to search for biomarkers and specific stress responses.

One strength of this study is the relatively large cohort studied, which allowed for reliable insight into the pain management in these very ill patients. The study did, however, have a retrospective design and only described pain management in our NICU during the research period. Furthermore, nonoperated NEC patients were not included, which limits the generalizability of our results.

In conclusion, the pain management based on pain scores for patients with severe NEC in our NICU was acceptable. This assumption is strengthened by the finding that both preoperative and postoperative COMFORTneo

scores were comparable to those of all other patients admitted to the NICU in the same period. The morphine dosages needed were much higher than suggested for pediatric noncardiac surgery in a recent PK/PD model. In patients with severe NEC, continuous morphine of 10 µg/kg/h preoperatively and an increase to 15 µg/kg/h postoperatively seem to constitute a good starting dose for further individualized pain management guided by pain scores.

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Disclosure Statement

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