Original Paper

Neonatology

Neonatology 2016;110:190–197
DOI: 10.1159/000445284

Received: January 16, 2016
Accepted after revision: March 8, 2016
Published online: May 20, 2016

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

Naomi J. Meesters[a] Monique van Dijk[a, b] Catherijne A.J. Knibbe[c]
Claudia M.G. Keyzer-Dekker[b] Dick Tibboel[b] Sinno H.P. Simons[a]

[a]Division of Neonatology, Department of Pediatrics and [b]Intensive Care and Department of Pediatric Surgery, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, [c]Division of Pharmacology, Leiden Academic Center for Drug Research (LACDR), Leiden University, Leiden, The Netherlands

**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) µg/kg/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 µg/kg/h preoperatively, with an increase to 15 µg/kg/h postoperatively, seems to constitute a good starting dose for further individualized pain management guided by pain scores.



## 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].

KARGER

E-Mail karger@karger.com
www.karger.com/neo



Naomi J. Meesters
Division of Neonatology, Department of Pediatrics
Erasmus University Medical Center – Sophia Children's Hospital
Wytemaweg 80, NL–3015 CN Rotterdam (The Netherlands)
E-Mail n.meesters@erasmusmc.nl

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 COMFORTneo 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 considered 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).

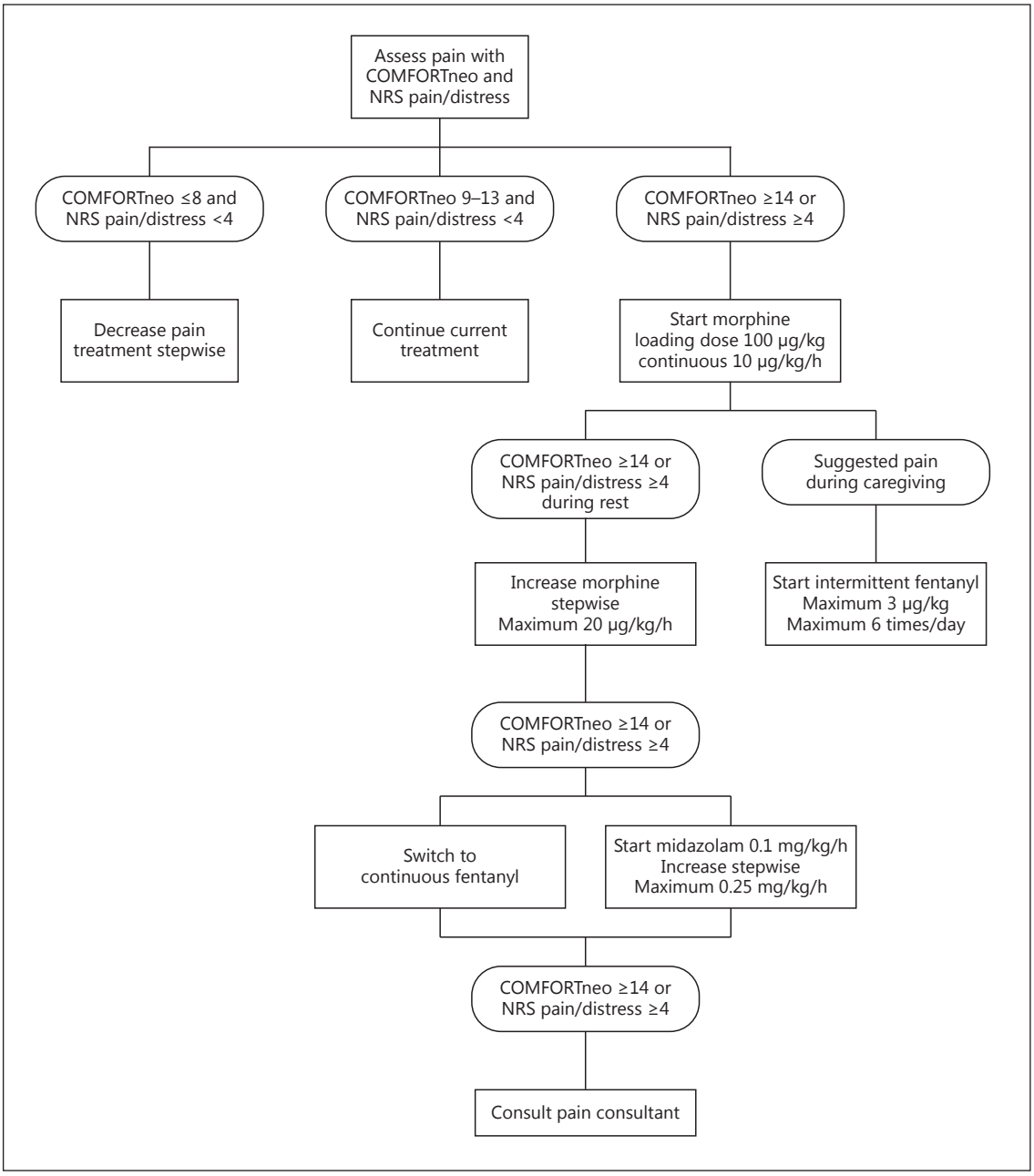


**Fig. 1.** Pain treatment flow diagram.

## 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

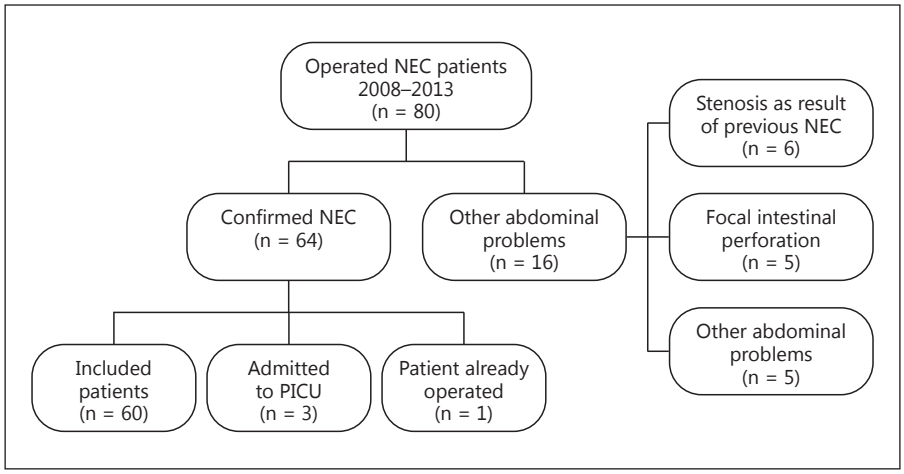


**Fig. 2.** Patient flow diagram. PICU = Pediatric ICU.

**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 μg/kg/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) |
| *COMFORTneo* | | | |
| 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) |
| *NRS pain* | | | |
| 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) |
| *NRS distress* | | | |
| 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) |
| *Morphine* | | | |
| Patients | 57 (95.0) | 60 (100) | – |
| Cumulative dose, μg/kg/72 h | 307 (133–626) | 895 (459–1177) | |
| Dose, μg/kg/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) | |
| *Fentanyl* | | | |
| Patients on intermittent dosage | 21 (35.0) | 28 (46.7) | – |
| Patients on continuous dosage | – | 2 (3.3) | |
| Dose, μg/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) | |
| *Acetaminophen* | | | |
| Patients | 1 (1.7) | 5 (8.3) | – |
| *Midazolam* | | | |
| Patients | 3 (5.0) | 14 (23.3) | – |
| Cumulative dose, mg/kg/72 h | 3.5 (0.5–3.6) | 1.0 (0.4–1.8) | |
| Used for palliative treatment | – | 6 (42.9) | |
| *Clonidine* | | | |
| 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 μg/kg in the operating room. Dosage recommendations are based on their postnatal 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 μg/kg/h before and after surgery were needed, re-

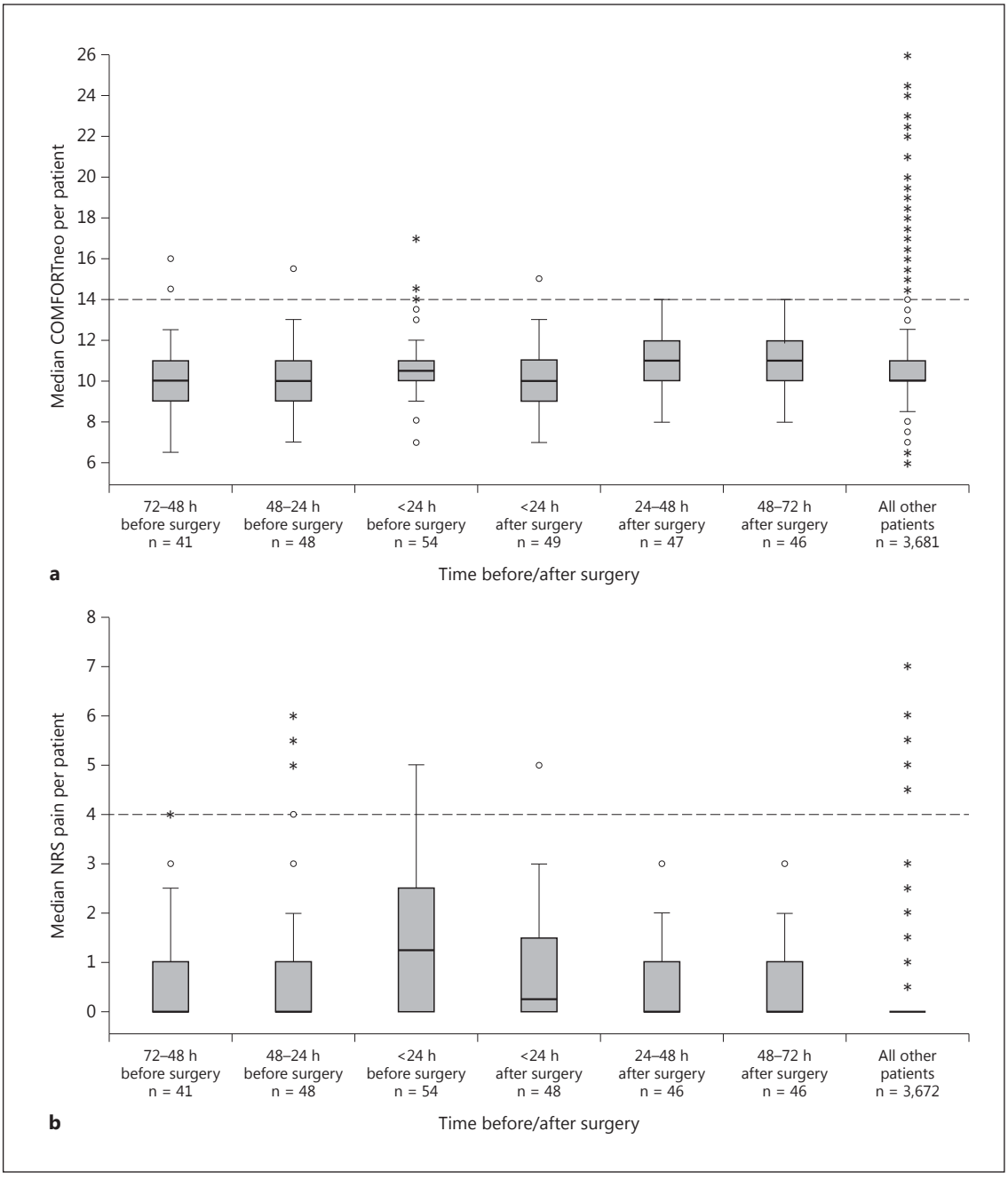


**Fig. 3.** Box plots showing COMFORTneo scores (**a**) and NRS pain scores (**b**) for the patients with NEC. ° = Any score > 1.5 × the IQR from the rest of the scores (mild outliers); * = any score > 3 × the IQR from the rest of the scores (extreme outliers).

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 management 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

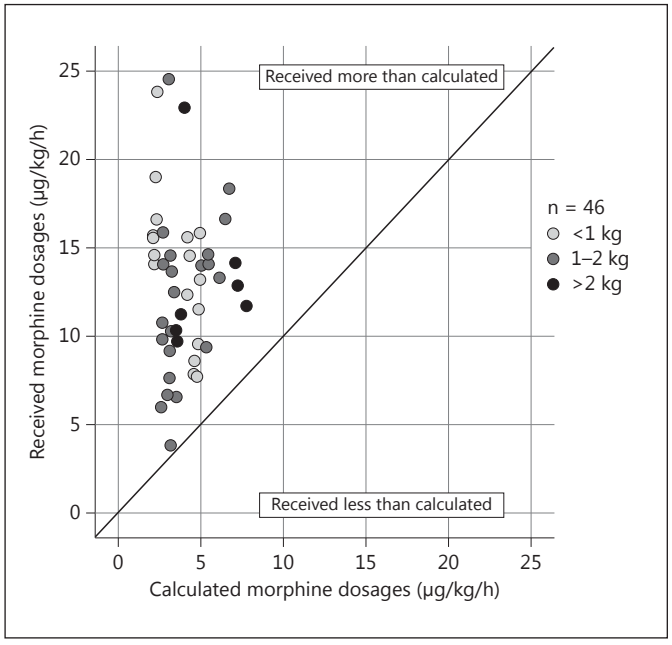


**Fig. 4.** Calculated PK/PD model-based morphine maintenance doses for neonates after major noncardiac surgery as a follow-up to 100 μg/kg/h loading dose [17] (x-axis) compared to the average received morphine doses in neonates after NEC surgery over 72 h (y-axis). Doses are provided for different groups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


## Acknowledgments

We thank Ko Hagoort for editing.


## Disclosure Statement

There were no conflicts of interest.

## References


1 Murthy K, Yanowitz TD, DiGeronimo R, Dykes FD, Zaniletti I, Sharma J, Sullivan KM, Mirpuri J, Evans JR, Wadhawan R, Piazza A, Adams-Chapman I, Asselin JM, Short BL, Padula MA, Durand DJ, Pallotto EK, Reber KM: Short-term outcomes for preterm infants with surgical necrotizing enterocolitis. J Perinatol 2014;34:736–740.

2 Pike K, Brocklehurst P, Jones D, Kenyon S, Salt A, Taylor D, Marlow N: Outcomes at 7 years for babies who developed neonatal necrotising enterocolitis: the ORACLE children study. Arch Dis Child Fetal Neonatal Ed 2012;97:F318–F322.

3 Downard CD, Renaud E, St Peter SD, Abdullah F, Islam S, Saito JM, Blakely ML, Huang EY, Arca MJ, Cassidy L, Aspelund G: Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg 2012;47:2111–2122.

4 Grunau RE, Holsti L, Peters JW: Long-term consequences of pain in human neonates. Semin Fetal Neonatal Med 2006;11:268–275.

5 Grunau RE, Weinberg J, Whitfield MF: Neonatal procedural pain and preterm infant cortisol response to novelty at 8 months. Pediatrics 2004;114:e77–e84.

6 Hall NJ, Eaton S, Pierro A: Royal Australasia of Surgeons Guest Lecture. Necrotizing enterocolitis: prevention, treatment, and outcome. J Pediatr Surg 2013;48:2359–2367.

7 Huda S, Chaudhery S, Ibrahim H, Pramanik A: Neonatal necrotizing enterocolitis: clinical challenges, pathophysiology and management. Pathophysiology 2014;21:3–12.

8 Noerr B: Current controversies in the understanding of necrotizing enterocolitis. Part 1. Adv Neonatal Care 2003;3:107–120.

9 Henry MC, Moss RL: Current issues in the management of necrotizing enterocolitis. Semin Perinatol 2004;28:221–233.

10 Bradshaw WT: Necrotizing enterocolitis: etiology, presentation, management, and outcomes. J Perinat Neonatal Nurs 2009;23:87–94.

11 Coit AK: Necrotizing enterocolitis. J Perinat Neonatal Nurs 1999;12:53–66; quiz 88–59.

12 American Academy of Pediatrics Committee on Fetus and Newborn; American Academy of Pediatrics Section on Surgery; Canadian Paediatric Society Fetus and Newborn Committee, Batton DG, Barrington KJ, Wallman C: Prevention and management of pain in the neonate: an update. Pediatrics 2006;118:2231–2241.

13 Debillon T, Zupan V, Ravault N, Magny JF, Dehan M: Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Arch Dis Child Fetal Neonatal Ed 2001;85:F36–F41.

14 van Dijk M, Roofthooft DW, Anand KJ, Guldemond F, de Graaf J, Simons S, de Jager Y, van Goudoever JB, Tibboel D: Taking up the challenge of measuring prolonged pain in (premature) neonates: the COMFORTneo scale seems promising. Clin J Pain 2009;25:607–616.

15 Schechter N, Berde C, Yaster M (eds): Pain in infants, Children and Adolescents, ed 2. Philadelphia, Lippincot & Wilkins, 2003.

16 Thiagarajah S, Thiagarajah PH: Lesson 259: Preanesthetic Assessment of a Micropremie with Necrotizing Enterocolitis. AnesthesiologyNews.com. 2007 (www.mssm.procampus.net).

17 Krekels EH, Tibboel D, de Wildt SN, Ceelie I, Dahan A, van Dijk M, Danhof M, Knibbe CA: Evidence-based morphine dosing for postoperative neonates and infants. Clin Pharmacokinet 2014;53:553–563.

18 Ceelie I, de Wildt SN, van Dijk M, van den Berg MM, van den Bosch GE, Duivenvoorden HJ, de Leeuw TG, Mathot R, Knibbe CA, Tibboel D: Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial. JAMA 2013;309:149–154.

19 Gordon PV: Understanding intestinal vulnerability to perforation in the extremely low birth weight infant. Pediatr Res 2009;65:138–144.

20 Kissin I, Brown PT, Bradley EL Jr: Sedative and hypnotic midazolam-morphine interactions in rats. Anesth Analg 1990;71:137–143.

21 Cohen J: Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 1968;70:213–220.

22 Gibbins S, Maddalena P, Moulsdale W, Garrard F, jan Mohamed T, Nichols A, Asztalos E: Pain assessment and pharmacologic management for infants with NEC: a retrospective chart audit. Neonatal Netw 2006;25:339–345.

23 Gregory KE, Deforge CE, Natale KM, Phillips M, Van Marter LJ: Necrotizing enterocolitis in the premature infant: neonatal nursing assessment, disease pathogenesis, and clinical presentation. Adv Neonatal Care 2011;11:155–164;quiz 165–156.