Do We Still Hurt Newborn Babies?

A Prospective Study of Procedural Pain and Analgesia in Neonates

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Background: Despite an increasing awareness regarding pain management in neonates and the availability of published guidelines for the treatment of procedural pain, preterm neonates experience pain leading to short- and long-term detrimental effects.

Objective: To assess the frequency of use of analgesics in invasive procedures in neonates and the associated pain burden in this population.

Methods: For 151 neonates, we prospectively recorded all painful procedures, including the number of attempts required, and analgesic therapy used during the first 14 days of neonatal intensive care unit admission. These data were linked to estimates of the pain of each procedure, obtained from the opinions of experienced clinicians.

Results: On average, each neonate was subjected to a mean ± SD of 14 ± 4 procedures per day. The highest exposure to painful procedures occurred during the first day of admission, and most procedures (63.6%) consisted of suctioning. Many procedures (26 of 31 listed on a questionnaire) were estimated to be painful (pain scores > 4 on a 10-point scale). Preemptive analgesic therapy was provided to fewer than 35% of neonates per study day, while 39.7% of the neonates did not receive any analgesic therapy in the neonatal intensive care unit.

Conclusions: Clinicians estimated that most neonatal intensive care unit procedures are painful, but only a third of the neonates received appropriate analgesic therapy. Despite the accumulating evidence that neonatal procedural pain is harmful, analgesic treatment for painful procedures is limited. Systematic approaches are required to reduce the occurrence of pain and to improve the analgesic treatment of repetitive pain in neonates.
neonatal pain management led to the discussion whether analgesia should be given to all ventilated newborns.33,36 Although there is controversy about the risks and benefits of continuous opioid administration (and as a consequence neonatologists are reluctant to prescribe them), recently published international consensus statements37,38 have provided neonatal pain management guidelines, including those for procedural interventions. Therefore, we hypothesized that analgesic therapy is frequently used and that procedural pain is minimal in neonates admitted to the NICU. Prospectively, we collected bedside data on the number and type of daily painful procedures performed in 151 neonates during their stay in a tertiary care NICU, including failed procedures (eg, multiple attempts to insert peripheral venous catheters). These data were integrated with the results of a questionnaire evaluating the opinions of experienced clinicians about the pain of different procedures. Furthermore, the analgesic therapy used was evaluated and compared with current guidelines.

### METHODS

#### PROCEDURES

A pain research team (including a neonatologist [D.R.], pediatric intensivist [D.T.], research nurse, and psychologist [M. van D.]) with extensive research39-50 and clinical experience51 was scored as a measure of severity of illness.

To estimate the pain of NICU procedures, we developed a questionnaire listing all invasive procedures from our checklist, with 2 noninvasive procedures (diaper change and cranial ultrasound) included as control variables. The questionnaire was distributed among the nurses and physicians of (1) the NICU, where the procedures were also counted, (2) a pediatric surgical intensive care unit present in the same hospital where newborns with major congenital anomalies are admitted, and (3) the level III NICU of another, nonuniversity, hospital (Isala Clinics). Participants were asked to estimate a rating from 0 (not painful) to 10 (most painful) for each procedure, without taking specific circumstances into account.

#### STATISTICAL ANALYSIS

Procedures were counted per calendar day. Because the first and last study days are usually shorter than 24 hours, the numbers of procedures were corrected for the actual length of stay on these days.

Random regression modeling (PROC MIXED; SAS Institute, Cary, NC) was used to simultaneously estimate the effect of the time-varying covariates respiratory support (no support, nasal oxygen, continuous positive airway pressure, and mechanical ventilation), postnatal age, gestational age, and length of study on the number of procedures performed. Because a procedural volume difference on the first study day compared with the other days was expected, the study days were dichotomized into 2 variables: 0 (1 day) and 1 (2-14 days). The outcome variable, ie, frequency of procedures, was log-transformed (base 10) to achieve a normal distribution. The model incorporated random intercepts and random slopes.

Multiple regression analysis was performed to estimate the effect of background variables (profession, sex, age, unit, hospital [Erasmus MC–Sophia Children’s Hospital or Isala Clinics], parent [yes or no], and years of NICU experience) on the pain scoring of the participants.

Data are presented as mean±SD.

#### PATIENTS

One hundred fifty-one neonates were included in the study; 89 other newborns who were discharged within 24 hours were excluded. Table 2 lists the study subjects’ background characteristics and primary diagnoses. Most neonates (n=129) were admitted and enrolled on the first postnatal day. Gestational ages ranged from 25.3 to 42.0 weeks, with a mean age of 32.4±4.5 weeks. The CRIB34 scores ranged from 2 to 16, with a mean score of 3.8±3.3. Study subjects required respiratory support consisting of mechanical ventilation on 49.6% of study days (one third high-frequency oscillation and two thirds conventional ven-
tilation), continuous positive airway pressure on 22.5% of study days, nasal oxygen on 15.6% of study days, and subjects required no respiratory support on 12.2% of study days. During 55.2% of the study days, patients had an arterial line (42.8% peripheral arterial lines and 12.3% umbilical arterial lines).

FREQUENCY

During 1375 patient-days, 19674 procedures were performed, with a mean NICU stay of 9.1±4.4 days per patient. Table 3 gives the procedures rank-ordered by their frequency. Suctioning of nasal, endotracheal, and nasopharyngeal tubes constituted 63.6% of the performed procedures. The mean number of procedures per neonate per day was 14.3±4, with a range of 0 to 53 procedures per day. Almost one third (30.9%) of the 1076 insertions of intravenous cannulae were not successful. Procedures for placement of central venous catheters, peripheral arterial catheters, and umbilical catheters were not successful in 45.6%, 37.5%, and 34.6% of attempts, respectively. Failure rates for venipunctures and lumbar punctures were 21.0% and 17.5%, respectively (Figure 1).

Random regression modeling (Table 4) showed significantly higher frequencies of procedures during the

<table>
<thead>
<tr>
<th>Table 2. Background Characteristics and Primary Diagnoses in 151 Infants</th>
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<tbody>
<tr>
<td>Background Characteristic</td>
</tr>
<tr>
<td>Male/female</td>
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<tr>
<td>Gestational age, mean ± SD (range), wk</td>
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<td>Birth weight, mean ± SD, g</td>
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<td>Clinical Risk Index for Babies score, mean ± SD (range)</td>
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<td>Duration of admission, mean ± SD, d</td>
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<tr>
<td>No support</td>
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<tr>
<td>Nasal oxygen</td>
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<tr>
<td>Continuous positive airway pressure</td>
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<td>Conventional ventilation</td>
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<td>High-frequency oscillation ventilation</td>
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<tr>
<td>Primary diagnosis, No.</td>
</tr>
<tr>
<td>Prematurity</td>
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<tr>
<td>Small for gestational age (&gt;2 SDs under mean birth weight)</td>
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<tr>
<td>Asphyxia</td>
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<tr>
<td>Respiratory distress syndrome</td>
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<tr>
<td>Wet lung</td>
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<tr>
<td>Meconium aspiration syndrome</td>
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<tr>
<td>Pneumothorax</td>
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<td>Persistent pulmonary hypertension</td>
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<tr>
<td>Infections</td>
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<td>Sepsis</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Necrotizing enterocolitis</td>
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<tr>
<td>Hyperbilirubinemia</td>
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<tr>
<td>Intraventricular hemorrhage</td>
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<tr>
<td>Other cerebral abnormalities</td>
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<tr>
<td>Patent ductus arteriosus</td>
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<tr>
<td>Indomethacin sodium therapy</td>
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<tr>
<td>Surgical closure</td>
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<tr>
<td>No therapy</td>
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<tr>
<td>Congenital cardiac defects</td>
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<tr>
<th>Table 3. Incidence of Procedures, With Frequencies per Infant per Day</th>
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<tr>
<td>Procedure</td>
</tr>
<tr>
<td>Nasal succioning</td>
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<tr>
<td>Endotracheal succioning</td>
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<tr>
<td>NPT succioning</td>
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<tr>
<td>Heelstick</td>
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<tr>
<td>IV cannula insertion</td>
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<tr>
<td>Nasogastric tube insertion</td>
</tr>
<tr>
<td>IV cannula removal</td>
</tr>
<tr>
<td>Nasogastric tube removal</td>
</tr>
<tr>
<td>X-ray</td>
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<tr>
<td>NPT insertion</td>
</tr>
<tr>
<td>Attempt IV cannula insertion</td>
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<tr>
<td>Laxative or enema</td>
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<tr>
<td>Nasal oxygen cannula insertion</td>
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<tr>
<td>Intubation</td>
</tr>
<tr>
<td>Peripheral arterial line insertion</td>
</tr>
<tr>
<td>TCP02 sticker removal</td>
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<tr>
<td>Exstubation</td>
</tr>
<tr>
<td>Peripheral arterial line removal</td>
</tr>
<tr>
<td>Attempt arterial line insertion</td>
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<tr>
<td>Venipuncture</td>
</tr>
<tr>
<td>Insertion umbilical line</td>
</tr>
<tr>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Changing central line sticker</td>
</tr>
<tr>
<td>Removal umbilical line</td>
</tr>
<tr>
<td>Bladder puncture</td>
</tr>
<tr>
<td>Attempt umbilical line insertion</td>
</tr>
<tr>
<td>Insertion central line</td>
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<tr>
<td>Insertion chest tube</td>
</tr>
<tr>
<td>Attempt central line insertion</td>
</tr>
<tr>
<td>Venipuncture attempt</td>
</tr>
<tr>
<td>Removal central line</td>
</tr>
<tr>
<td>Removal chest tube</td>
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<tr>
<td>Lumbar puncture attempt</td>
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<tr>
<td>Intramuscular injection</td>
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Abbreviations: IV, intravenous; NPT, nasopharyngeal tube; TCP02 sticker, transcutaneous oxygen pressure sticker.
first study day compared with days 2 to 14 \((P < .001)\). The frequency of procedures was not predicted by gestational age \((P = .51)\), day of admission \((P = .50)\), or postnatal age \((P = .72)\).

Procedures were performed with significantly higher frequencies in patients receiving nasal oxygen, continuous positive airway pressure, and ventilation \((P < .001 \text{ for all})\) compared with those without respiratory support.

**PAIN OF PROCEDURES**

Two hundred forty-seven questionnaires were distributed, with a response rate of 59.9\% \((n = 148)\), which was similar for nurses and physicians. Table 5 gives their background characteristics. The mean pain score, across all respondents and all procedures, on the 10-point scale was 5.2 ± 1.3. The mean pain score per procedure varied from 1.7 ± 1.6 for diaper change to 8.9 ± 1.4 for intubation. Pain ratings given by the nurses and physicians are shown in Figure 2.

Because procedures were scored on a 10-point scale, results of this questionnaire can be considered as moderately painful. Procedures that received lower scores included the control variables, diaper change and cranial ultrasound, as well as insertion of nasal cannulae, X-rays, and the removal of nasogastric tubes.

| Table 4. Random Regression Model for Predicting the Frequency of Procedures |
|--------------------------------|--------|---------|---------|---------|
| Variable*†‡ | \(\beta\) | SE of \(\beta\) | \(t\) | \(P\) Value |
| Nasal oxygen† | .18 | .02 | 8.57 | < .001 |
| Continuous positive airway pressure† | .40 | .02 | 19.40 | < .001 |
| Ventilation† | .42 | .02 | 22.38 | < .001 |
| Gestational age | −.001 | .002 | −.65 | .51 |
| Postnatal age | −.0003 | .0008 | −.35 | .72 |
| Day of admission | .001 | .002 | 0.67 | .50 |
| Day 1 vs days 2-14‡ | −.21 | .03 | −6.16 | < .001 |
| Length of stay | .02 | .001 | 13.81 | < .001 |

*The outcome variable was the frequency of procedures. Boldface indicates significant predictor variables \((P < .05)\).
†Dummy coding was used, with no respiratory support as the reference group.
‡Day of admission was dichotomized as 0 (day 1) vs 1 (days 2-14).

| Table 5. Background Characteristics of 148 Questionnaire Respondents |
|-----------------------------|---------|---------|---------|
| Characteristic | Nurses \((n = 119)\) | Physicians \((n = 29)\) |
| Participants | | |
| NICU Rotterdam, the Netherlands | 49 | 9 |
| PSICU Rotterdam | 31 | 6 |
| NICU Zwolle, the Netherlands | 39 | 14 |
| Age, mean ± SD, y | 37 ± 7 | 34 ± 7 |
| Male/female | 7/112 | 12/17 |
| Parent/not parent | 64/55 | 12/17 |
| NICU experience, mean ± SD, y | 7.9 ± 6.2 | 4.2 ± 6.6 |

Abbreviations: NICU, neonatal intensive care unit; PSICU, pediatric surgical intensive care unit.
physicians scored various procedures as more painful than nurses. Although some nurses used pacifiers as a nonpharmacological analgesic treatment, it was not very high, the results of our questionnaire might have been unmotivated and not interesting in pain management in the NICU. However, a formal analysis of their motives was not undertaken. This lack of interest is probably related to their belief that these daily procedures are not that painful. As the response rate was not very high, the results of our questionnaire might show some overestimation of clinicians’ overall opinion about the pain level of these procedures.

In our NICU, nurses tried to cluster procedures during routine nursing care, after which they comforted patients by touch, pacifiers, or positioning (eg, swaddling), whereas other behavioral and environmental approaches were used irregularly. Similar to our results, the frequency of procedures per day was not related to gestational age, perhaps because term neonates admitted to the NICU may have a severity of illness comparable to that of preterm neonates.

In sharp contrast to the accumulating evidence that repetitive pain is harmful in newborns, and despite major clinical advances over the past 10 years, neonates experience up to 14 painful procedures per day, and, remarkably, more than 65% of the patients in this study did not receive appropriate analgesic therapy.

We report a higher number of painful procedures in this study compared with previous studies, perhaps because we used a more extensive list of procedures and accounted for failed procedures (Table 1). For instance, Benis and Suresh reported a mean of 6 procedures per day during the entire NICU stay of 15 neonates. Barker and Rutter reported an increased number of procedures in infants younger than 31 weeks’ gestation compared with older infants, but did not mention the length of NICU stay, which may explain the exposure to a greater number of invasive procedures. In the present study, however, the frequency of procedures per day was not related to gestational age, perhaps because term neonates admitted to the NICU may have a severity of illness comparable to that of preterm neonates.

To our knowledge, we are the first to report prospective data on a substantial number of failed procedures in the NICU. Although attempts by even the most experienced clinicians may be unsuccessful, the relative inexperience of trainees may partly explain the high proportion of failed procedures in this study. These findings may, therefore, be applicable to NICUs located in other academic centers.

Efforts should be aimed at minimizing the number of invasive procedures, as stated in recent consensus guidelines. Our study showed that the number of procedures is significantly higher in neonates requiring nasal oxygen, continuous positive airway pressure, or ventilation and that procedures occur mostly on the first day of admission, because of initial stabilization, monitoring, and diagnostic evaluation. Furthermore, the number of heelsticks and venipunctures is subsequently decreased in patients having arterial lines. Our nursing protocols require tracheal suctioning every 4 hours and as needed for ventilated neonates, whereas a recent study showed comparable ventilatory outcomes when the frequency of routine suctioning was decreased to every 8 hours.

Nurses and physicians agreed that most neonatal procedures cause moderate or severe pain, with pain scores above 4 estimated for 26 of the 31 procedures. Physicians ascribed lower pain scores; because they are mostly responsible for prescribing analgesics, this may contribute to the limited use of analgesic therapy in neonates. Others have reported comparable significant differences in pain scores of invasive procedures between nurses and physicians. The clinicians not returning the questionnaire might have been unmotivated and not interested in pain management in the NICU. However, a formal analysis of their motives was not undertaken. This lack of interest is probably related to their belief that these daily procedures are not that painful. As the response rate was not very high, the results of our questionnaire might show some overestimation of clinicians’ overall opinion about the pain level of these procedures.

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In our NICU, nurses tried to cluster procedures during routine nursing care, after which they comforted patients by touch, pacifiers, or positioning (eg, swaddling), whereas other behavioral and environmental approaches were used irregularly. Similar to our results,
a multicenter study in France also showed minimal use of analgesics and a lack of standardization in the pharmacological regimens used in the NICU. Kahn et al reported a 28.6-fold variation in the use of opioids among 6 NICUs. Variations in attitude toward pain may limit the generalizability of our study findings to other centers around the world.

Restrained use of opioids by neonatologists can be explained by the fact that there is wide disagreement as to whether the evidence base is sufficient to justify prolonged exposure to opioids in this vulnerable population. There is some evidence, from studies in rats, that neonatal morphine exposure causes specific long-term behavioral effects and might cause retarded growth and motor development. Underlying pathologic mechanisms have been demonstrated by morphine-induced apoptosis in human fetal cell cultures and by μ-opiate receptor down-regulation following morphine treatment in neonatal rat brain. Prolonged use of high doses of opioids in animal and in vitro models complicates extrapolation of these findings to daily NICU practice. The only study investigating long-term effects of human neonatal morphine treatment showed no effects in 5- to 6-year-olds. Anand and colleagues reported decreased mortality with the use of postoperative analgesia in premature infants. However, a similar benefit of routine use of morphine has not been reported in this population without a surgical operation. Grunau et al found that altered pain responses in preterm neonates were predicted by the number of previous painful procedures and were normalized by the early use of morphine analgesia. Although accumulating data suggest that analgesic therapy with morphine might be useful to prevent some of the long-term effects of repetitive neonatal pain, further evidence about the safety of prolonged use of opioids is needed.

**CONCLUSIONS**

We recommend that a continuous intravenous infusion of opioids should be considered for infants requiring respiratory support during the first 24 hours of admission, in combination with well validated pain scores as part of routine nursing care. Use of an algorithm would enable caregivers to respond immediately and in a structured way when they observe pain in these infants. Although this recommendation is supported by preliminary studies, results from larger randomized controlled trials are needed to decide if ventilated neonates should be routinely treated with continuous opioids. As treatment regimens evolve, consistent practices in the NICU should be developed to minimize invasive procedures that continue to hurt our newborns.

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