Reduced narcotic and sedative utilization in a NICU after implementation of pain management guidelines

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OBJECTIVE: To assess the opioid and benzodiazepine usage in a level IV NICU after implementation of pain guidelines.

STUDY DESIGN: Guidelines were developed for infants undergoing surgical procedures and infants on mechanical ventilation. Data collected for period 1 (July to December 2013) and period 2 (March to August 2014).

RESULTS: Gestational age, birth weight and infants with hypoxic respiratory failure or requiring major procedures were comparable in two periods. Number of patients exposed to opioids decreased from 62.9% (129/205) in period 1 to 32.8% (82/250) in period 2, \( P = < 0.001 \). Cumulative dose exposure decreased, opioids in morphine equivalent dose, mg kg \(^{-1} \) (1.64 (0.38 to 6.94) vs 0.51 (0.04 to 2.33), \( P = 0.002 \)), sedatives in midazolam equivalent, mg kg \(^{-1} \) (0.16 (0.03 to 7.39) vs 0.10 (0.00 to 4.00), \( P = 0.03 \)). Ten patients required treatment for iatrogenic opioid withdrawal versus only three in post guideline, \( P = 0.02 \).

CONCLUSIONS: Evidence-based guidelines led to significant reduction in opioids and sedatives exposure, and in the number of infants requiring methadone for iatrogenic narcotic dependence.

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INTRODUCTION

Significant progress has been made since the 1990s in the understanding of neonatal pain, especially the pathophysiology, short- and long-term consequences of chronic untreated pain.1–3 Studies in preterm infants have shown increased levels of stress hormones in response to surgery with increased morbidity and mortality in infants without adequate analgesia during induction of surgery.4–6 Current medical practice places much emphasis and, rightfully so, on the treatment of procedural pain in neonates, even though most minor and routine noxious procedures are still largely untreated in neonatal intensive care unit (NICU) patient population.7–9 The American Academy of Pediatrics also reiterated its position regarding neonatal procedural pain treatment and recommends center-specific guidelines and use of both non-pharmacological and pharmacological measures.10 Pharmacologic treatment with opioids is most common, although the use of benzodiazepines is also widespread and these medications are often used in conjunction.11 Long-term use of both opioids and benzodiazepines in neonates can lead to prolonged mechanical ventilation, delay in passage of meconium and carries inherent risk for tolerance and withdrawal, necessitating prolonged dose taper regimens.12–14 In addition, there is recent evidence of increase in severe neurological morbidity with these medications.15–17 Even though used extensively in NICU patients, including preterm infants, there is a paucity of pharmacokinetics18 or clinical studies assessing their safety and efficacy among this patient population.19 Use of pain and sedation guidelines has been shown to improve pain assessment and clinical outcomes.20–23 After review of current literature we devised guidelines for pain management for neonates undergoing surgical procedures and hypoxic respiratory failure. Our aim was to standardize procedural pain assessment and management with gestational age-specific dose recommendations.

METHODS

Setting

Le Bonheur Children’s Hospital is a level IV 60-bed NICU with an average daily census of 45 infants. This NICU serves as neonatal specialized surgical and medical care center. The project received approval from the institutional review board.

Implementation plan

A multidisciplinary team including a neonatologist, neonatal fellow, resident physician, nurse practitioner and pediatric clinical pharmacist reviewed all currently available literature, as well as published expert opinions and recommended guidelines on neonatal pain and sedation. The guidelines were also agreed upon with the pediatric surgeons. Procedural pain guidelines were formulated for patients undergoing major surgical procedures, for example, exploratory laparotomy, abdominal wall defect repairs and so on, and minor procedures such as central line placements, chest tube insertions and so on. Non-pharmacological methods such as swaddling, use of pacifier or oral 24% sucrose solution were recommended as first-line treatment for minor or noxious procedures. The current pediatric dose recommendations were used24 and gestational age-specific dosing was determined from published studies.25,26 Medication dosing guidelines were formulated for 72 h post procedure and for 7 days for infants with acute hypoxic respiratory failure requiring mechanical ventilation (Supplementary Appendix a–c). After finalizing the guidelines, extensive teaching was done for all physicians and nursing staff in January 2014. The guidelines were implemented in February 2014. Before implementation of our guidelines, the initiation and length of treatment with narcotics and sedatives was decided by the attending neonatologist for each individual patient. In addition, there were no changes in our feeding or ventilation practices during the study period.

Definitions

We defined hypoxic respiratory failure as need for mechanical ventilation with use of inhaled nitric oxide. Days on mechanical ventilation were calculated as total number of days on mechanical ventilation with endotracheal intubation. Days on parental nutrition were calculated as a
surrogate to inability to reach full enteral feeds and were calculated as the number of days an infant received intravenous nutrition. Length of hospital stay was calculated from the day of admission to NICU through to the day of discharge home, including days spent in other clinical areas of the hospital outside of the NICU. Use of enteral methadone was taken as a surrogate for iatrogenic opioid withdrawal.

Medication dose calculation
Data were extracted on acetaminophen, morphine, fentanyl, methadone, midazolam and lorazepam, as mg kg\(^{-1}\). Analgesics and sedatives given intraoperatively were also included for total cumulative dose calculations. All opioids were converted to morphine equivalents (IV fentanyl 0.1 mg = IV morphine 10 mg, enteral methadone 1 mg = IV morphine sulfate 1 mg).\(^{27}\) All benzodiazepines were converted to midazolam equivalents (IV lorazepam 0.025 mg = IV midazolam 0.1 mg).\(^{28}\)

Intervention analysis and assessment
A retrospective chart review was done and designated as pre-guideline period: July through December 2013 (period 1) and prospective data collection was done from March through August 2014 (period 2) designated as post-guideline period. All infants admitted to the NICU were screened and data were collected on infants who received any analgesic or sedative, or had any major or minor procedure performed during NICU stay. We also included infants on mechanical ventilation requiring opioids or sedatives. We excluded patients who received benzodiazepines for treatment of their seizure disorder. Infant and maternal demographics, days on mechanical ventilation and days on parenteral nutrition or intravenous fluids were recorded. Neonatal Infant Pain Score (NIPS) for 72 h post procedure was recorded. The highest NIPS score attained for the 0 to 24, 24 to 48 and 48 to 72 h period was included. Pain Score (NIPS) for 72 h post procedure was recorded. The highest NIPS score of >3 was recommended for pharmacological treatment. Hospital-based patient satisfaction survey scores were recorded to follow parental satisfaction with procedures, time on mechanical ventilation, length of hospital stay and mortality.

Statistical analysis
Comparisons between groups were performed with the \(t\)-test or Mann–Whitney \(U\)-test or Wilcoxon signed-rank test as applicable and with \(\chi^2\)-test for categorical variables. Multivariable logistic regression model was used to determine predictors of opioid or sedative exposure correcting for gestational age, major surgical procedure and hypoxic respiratory failure for pre- or post-guideline period. The odds ratio was reported with 95% confidence interval. The level of significance was set at \(P < 0.05\).

RESULTS
During the pre-guideline period there were 205 NICU admissions and 62.9\%(129/205) received some opioid or benzodiazepine, whereas during the post-guideline period there were 250 admissions and 32.8\%(82/250) \((P < 0.001) were exposed to an opioid or benzodiazepine. After implementation of our guidelines in the NICU, adherence to guideline recommendations was measured at 95% and the most common reason for non-initiation of pharmacological treatment was for minor procedures. Although the compliance for recommended medication dose regimen was at 89%, the most common reasons for non-adherence were the use of a higher dose at initiation of continuous infusion or use of multiple repeat bolus doses without a documentation of need.

Demographics including gestational age, birthweight, gender, number of patients requiring a major surgical procedure and patient with hypoxic respiratory failure were similar in the two time periods (Table 1). There was a significant decrease in the number of patients exposed to various opioids and benzodiazepines during these two time periods (Figure 1). In addition, 4.9\%(10/205) of patients required methadone taper for iatrogenic withdrawal during the pre-guideline period compared with only 1.2\%(3/250) \((P = 0.02)\) in the post-guideline period. Cumulative dose exposure for both opioids expressed in morphine equivalent was shown in Figure 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-guideline (July–December 2014), n = 129</th>
<th>Post-guideline (March–August 2015), n = 82</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, weeks</td>
<td>33.9 ± 5.3</td>
<td>34.5 ± 5.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>2.2 ± 1.2</td>
<td>2.4 ± 1.1</td>
<td>0.16</td>
</tr>
<tr>
<td>PMA at admission, weeks</td>
<td>36.1 ± 4.7</td>
<td>36.4 ± 4.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>75 (58.1)</td>
<td>47 (57.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mechanical ventilation, days</td>
<td>3.0 (1.0–7.0)</td>
<td>2.0 (0.8–7.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>33.4 (13.6–61.8)</td>
<td>23.0 (11.0–46.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>PMA at discharge, weeks</td>
<td>42.5 ± 6.8</td>
<td>41.3 ± 4.9</td>
<td>0.18</td>
</tr>
<tr>
<td>TPN, days</td>
<td>10.0 (3.0–27.5)</td>
<td>6.0 (3.0–12.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>BPD, n (%)</td>
<td>25 (19.4)</td>
<td>18 (22.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>HRF, n (%)</td>
<td>14 (10.9)</td>
<td>9 (11.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Iatrogenic NAS, N (%)</td>
<td>10 (7.8)</td>
<td>3 (3.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>NAS(^{2}), n (%)</td>
<td>2 (1.6)</td>
<td>0 (0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Major surgery, n (%)</td>
<td>58 (45.0)</td>
<td>29 (35.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Minor surgery, n (%)</td>
<td>104 (80.6)</td>
<td>66 (80.5)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 1. General clinical characteristics

Abbreviations: BPD, bronchopulmonary dysplasia; HRF, hypoxic respiratory failure; LOS, length of hospital stay; NAS, neonatal abstinence syndrome; PCA, postmenstrual age; TPN, total parenteral nutrition. Values are expressed as mean ± s.d. or median (interquartile range) or N (%). P-value derived with Wilcoxon–Mann–Whitney test or \(\chi^2\)-test. *NAS secondary to maternal use of opioids.
dose (mg kg\(^{-1}\)) and benzodiazepines expressed in midazolam equivalent dose (mg kg\(^{-1}\)) markedly decreased in the post-guideline period (Table 2). Use of acetaminophen with cumulative dose (mg kg\(^{-1}\)) remained the same in both periods (\(P = 0.06\)).

Using logistic regression model correcting for gestational age, need for major procedure and hypoxic respiratory failure, implementation of guidelines demonstrated a significant decrease in risk of exposure to any opioid (odds ratio 0.06 confidence interval (0.14 to 0.56)) in the post-guideline period. Total mechanical ventilation days did not differ but there was a significant decrease following guideline implementation for days on parenteral nutrition (Table 1). Mortality among this cohort remained same at 8.5% (11/129) versus 8.5% (7/82) in both time periods. Overall, mortality for the NICU did not change for 2014, suggesting that decreased use of pain medications did not increase mortality.

Pain assessment
Post-procedural pain abstracted with NIPS score in the post-guideline implementation period. We can postulate that this decrease in opioid or sedative use, although we cannot confirm this with our present study, as it was not accurately documented and thus not assessed.

Routine use of opioids for analgesia can lead to an increase in days on mechanical ventilation and hospital stay and potential risk of tolerance and withdrawal.\(^{13-15,19,26,32}\) Fentanyl is a highly potent synthetic opioid analgesic with added benefit of less hemodynamic side effects.\(^{33,34}\) This makes it more attractive for use in acutely ill infants at risk for hypotension or shock.\(^{20,35,36}\) However, a cumulative dose of fentanyl \(\geq 415\) mcg kg\(^{-1}\) or \(\geq 7\) days of infusion has been shown to be highly predictive of opioid withdrawal.\(^{37,38}\) In our cohort, cumulative fentanyl drug exposure decreased to a median dose of 2.55 mcg kg\(^{-1}\), from 7.00 mcg kg\(^{-1}\) before the implementation of guidelines with a significant decrease in the number of patients requiring treatment for opioid withdrawal. Unlike opioids, there is limited data supporting the use of benzodiazepines such as midazolam or lorazepam for procedural pain. These medications are used extensively in critically ill patients and also carry risk for iatrogenic withdrawal with total cumulative dose, length of therapy and dosing weight being contributory risk factors.\(^{39}\) The safety and efficacy evidence of this class of medication is lacking with concerns of adverse neurological events in premature infants and longer duration of NICU stay.\(^{29,34,40,41}\) We were able to show a significant decrease in both the proportion of infants exposed to benzodiazepines and the cumulative dose exposure after implementation of guidelines. Acetaminophen use for mild to moderate pain has been recommended in infants and has potential opioid sparing effect.\(^{42,43}\) However, lack of efficacy with minor procedures and adverse effects on hepatic and hematological systems remain concerns with acetaminophen use.\(^{44}\) As our use of acetaminophen remained unchanged, it is unlikely to be the etiology for the decreased exposure of sedatives and opioids in the post-guideline implementation period.

We saw a decrease in TPN days after implementation of guidelines. Opioids are known to decrease gut motility with possible effects on neuromuscular activity and colonic peristalsis on mature gut but the effects on a premature gut remains uncertain, but there is recent evidence suggesting a delay in passage of meconium and increase in time to full enteral feeds in preterm infants.\(^{34,36,45}\)

### DISCUSSION

Implementation of evidence-based consensus guidelines resulted in overall decreased opioid and benzodiazepine use in our NICU, while maintaining adequate procedural pain management. Our aim was to provide a standardized approach to procedural pain assessment and management. Extensive staff education done prior to initiation of guidelines resulted in good compliance.

### Table 2. Comparison of cumulative dosing

<table>
<thead>
<tr>
<th>Cumulative Dose</th>
<th>Pre-guideline (July–December 2014), n = 129</th>
<th>Post-guideline (March–August 2015), n = 82</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids, Morphine equivalents (mg kg(^{-1}))</td>
<td>1.64 (0.38–6.94)</td>
<td>0.51 (0.04–2.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Benzodiazepines, Midazolam equivalents (mg kg(^{-1}))</td>
<td>0.16 (0.03–7.39)</td>
<td>0.10 (0.00–4.00)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fentanyl (mcg kg(^{-1}))</td>
<td>7.00 (0.00–23.93)</td>
<td>2.55 (0.00–8.74)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range). P-value determined by Wilcoxon–Mann–Whitney test.

### Table 3. Neonatal infant pain assessment scores

<table>
<thead>
<tr>
<th>Post-procedural time</th>
<th>Pre-guideline (July–December 2014), n = 129</th>
<th>Post-guideline (March–August 2015), n = 82</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 h</td>
<td>1 (0–4)</td>
<td>3 (0–5)</td>
<td>0.01</td>
</tr>
<tr>
<td>24–48 h</td>
<td>2 (0–5)</td>
<td>0 (0–4)</td>
<td>0.55</td>
</tr>
<tr>
<td>48–72 h</td>
<td>0 (0–4)</td>
<td>0 (0–3)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range). P-value determined by Wilcoxon–Mann–Whitney test.
The NIPS is a validated tool which uses behavioral cues and two physiologic variables. Even though our first 24 h were statistically significantly higher in post-guideline period, they still remained low enough scores to be treated with non-pharmacological interventions.46

Our study has several limitations. Our guidelines were implemented and evaluated in a single level 4 NICU. The data in this report are only for short-term compliance and ongoing sustenance of this improvement need to be monitored. The guidelines also need to be validated in a different setting with assessment of non-procedural pain management measures.

Overall, our project has several strengths. A multidisciplinary approach, high compliance rate and improved outcomes across different procedures, highlighting the fact that center-specific pain and sedation guidelines can be successfully implemented in NICU.

In conclusion, consensus pain and sedation guidelines improved patient care with a decrease in cumulative drug exposure and iatrogenic opioid withdrawal. Research on long-term consequences of these medications is lacking and judicious use is imperative. Consensus guidelines are helpful for optimal utilization of pain medications and adequate pain control. We demonstrate in our report that narcotic analgesic and sedative use can be successfully reduced, while optimizing pain control in a level 4 NICU.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Journal of Perinatology website (http://www.nature.com/jp)