Individual QI projects from single institutions

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Reducing Opioid Exposure in a Level IV Neonatal Intensive Care Unit

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Abstract

Introduction: Infants in neonatal intensive care units require painful and noxious stimuli as part of their care. Judicious use of analgesic medications, including opioids, is necessary. However, these medications have long- and short-term side effects, including potential neurotoxicity. This quality improvement project's primary aim was to decrease opioid exposure by 33% in the first 14 days of life for infants less than 1,250 g at birth within 12 months. **Methods:** A multidisciplinary care team used *Define, Measure, Analyze, Improve, Control* methodology to identify root causes of the quality gap including: (1) inconsistent reporting of objective pain scales; (2) variable provider prescribing patterns; and (3) variable provider bedside assessment of pain. These root causes were addressed by two interventions: (1) standardized reporting of the premature infant pain profile scores and (2) implementation of an analgesia management pathway. **Results:** Mean opioid exposure, measured in morphine equivalents, in infants less than 1,250 g at birth during their first 14 days of life decreased from 0.64 mg/kg/d (95% confidence interval 0.41–0.87) at baseline to 0.08 mg/kg/d (95% confidence interval 0.03–0.13) during the postintervention period ($P < 0.001$). There was no statistical difference in rates of days to full feedings, unintentional extubations, or central line removals between epochs. **Conclusions:** Following the implementation of consistent pain score reporting and an analgesia management pathway, opioid exposure in the first 14 days of life for infants less than 1,250 g was significantly reduced by 88%, exceeding the project aim. *(Pediatr Qual Saf 2020;4:e312; doi: 10.1097/pq9.0000000000000312; Published online 26 June, 2020.)*

INTRODUCTION

Infants cared for in neonatal intensive care units (NICU) are routinely exposed to painful and noxious interventions and procedures as part of their care. An American Academy of Pediatrics statement recognizes that neonates experience pain and that pharmacologic and nonpharmacological interventions are necessary to relieve pain and associated stress.[1] Along with pain management, it is essential to minimize painful exposures.[2,3]

Although analgesic medications remain a central component in the management of pain and stress in premature infants, a growing body of evidence raises concern for the potential neurotoxicity of these medications. The neonatal period is a time of rapid brain growth and development, leaving these infants particularly vulnerable to neurotoxic medication exposure.[4] McPherson et al.[5] found that premature infants with greater fentanyl exposure had a higher incidence of cerebellar hemorrhage and cerebellar hypoplasia. Rat models have demonstrated decreased hippocampus size in rats exposed to morphine as neonates.[6]

In addition to potential neurotoxic impacts, analgesic medication use exposes premature infants to several other possible side effects. Opioid use is associated with longer courses of mechanical ventilation, hypotension, pharmacologic withdrawal, urinary retention, and decreased intestinal motility.[7–9]

We identified a quality gap in our NICU related to the potential overuse of opioid medications in premature infants. There is limited literature on the optimal opioid exposure for hospitalized premature and very low birth weight infants to provide adequate analgesia and minimize side effects.[10] Prior trials in intubated infants less

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than 32 weeks gestation at birth have used morphine infusions of 10 µg/kg/h.[11,12] This equates to 0.24 mg/kg/d of morphine. A baseline review of opioid exposure in our NICU demonstrated that infants under 1,250 g at birth received, on average, 0.64 mg/kg/d of morphine equivalents during their first 2 weeks of life. This dose corresponds to a cumulative morphine equivalent exposure of 8.96 mg/kg in the first 2 weeks of life and is substantially higher than the cumulative morphine exposure of 0.17–0.37 mg/kg observed in a study of very low gestational age infants cared for in an NICU in Finland.[13]

Through a multidisciplinary quality improvement (QI) effort, we focused our project on the smallest infants within our NICU during the first 2 weeks of life. We recognized that these infants were at a greater risk of exposure to opioid medications than other infants in the NICU. We targeted the first 2 weeks of life for 2 reasons. First, this period incorporates the most immature period of postnatal brain development. Second, procedures are commonly indicated for preterm infants in this phase of the hospitalization.[14,15] Carbajal et al.[16] found that infants hospitalized in an NICU undergo a median of 10 painful procedures per day during the first 2 weeks of life. We suspected that opioid prescribing patterns during the first 2 weeks of life impact the cumulative opioid exposure throughout an infant's NICU course. Opioid tolerance can develop after as few as 7–10 days of exposure, requiring dose escalation during pain treatment followed by gradual dose tapering to avoid physiologic withdrawal.[14,17]

The specific aim of our QI effort was to reduce the mean daily opioid exposure, measured in morphine equivalents, in infants with a birth weight less than 1,250 g during the first 14 days of life from 0.64 to 0.42 mg/kg/d within 12 months. A 33% reduction was chosen as we felt this would be achievable and aligned with published opioid use in hospitalized premature infants.[11,12]

METHODS

Context

Our QI team conducted this project at the 35-bed level IV NICU in Rochester, Minn. Over 350 infants are cared for in this NICU annually, with approximately 60 admissions per year with birth weight less than 1,250 g. We did not utilize any intramural or external funding for this project.

QI Team and Improvement Model

A neonatologist (J.E.B.) led this project. The multidisciplinary team also included a second neonatologist with QI expertise (J.L.F.), a neonatal-perinatal medicine fellow (R.C.S), a pediatric resident (A.R.S.), three neonatal nurse practitioners (N.L.S., M.A.M., and L.J.F.), a pediatric pharmacist (B.N.S.), nurses (including V.S.S.), and a respiratory therapist. We utilized the Six Sigma tool of *Define, Measure, Analyze, Improve, Control* throughout this QI project. The project was deemed not human subjects research by the Mayo Clinic Institutional Review Board, and therefore, exempt from its review.

Planning the Interventions

We employed several QI tools to understand better the root causes of the quality gap of potential excessive opioid exposure in the first 2 weeks of life for infants born weighing less than 1,250 g. We began by conducting multidisciplinary stakeholder meetings focused on the use of analgesic medications in the NICU. Stakeholders included neonatologists, neonatal-perinatal medicine fellows, neonatal nurse practitioners, neonatal bedside nurses, pediatric residents, pediatric respiratory therapists, and pediatric pharmacists. These discussions identified perceived barriers to minimizing the use of analgesic medications.

From August 2017 through March 2018, stakeholders participated in educational sessions related to potential side effects of analgesic medications, such as potential neurotoxicity and risk of withdrawal. These sessions included didactic small group lectures related to opioid, benzodiazepine, barbiturate, and alpha-2 agonist use in premature infants.

We also sent electronic surveys (REDCap version 7.4.23 2018 Vanderbilt University) to NICU providers, nurses, and respiratory therapists. Each survey had 20 questions related to potential contributors to analgesic medication overuse identified during stakeholder meetings. Respondents were also able to provide comments about analgesia use within the NICU. We constructed a Fishbone diagram (Fig. 1) and the 5-Whys diagram (Fig. 2) based on the common themes identified during stakeholder sessions and analysis of survey responses.

From the stakeholder meetings, surveys, and analysis tools, we identified the following major root causes of overuse of analgesic medications within the NICU:

1. Variable staff knowledge of the neurodevelopmental and withdrawal risks associated with these medications;
2. Lack of staff familiarity with the premature infant pain profile (PIPP) scores;
3. Provider variability in prescribing habits;
4. Variability in provider performance of bedside assessment at the time of nursing concern of inadequate pain control.

Interventions

The Improve phase of the project spanned for 6 months, from April 2018 through September 2018. We implemented 3 plan-do-study-act (PDSA) cycles, as summarized in Table 1. Each of the PDSA cycles focused on a root cause of the potential overuse of analgesic medications identified during the Analysis phase.

1. In April 2018, the first PDSA cycle targeted a lack of familiarity with PIPP scores and inconsistent review of PIPP scores during rounds. Despite PIPP

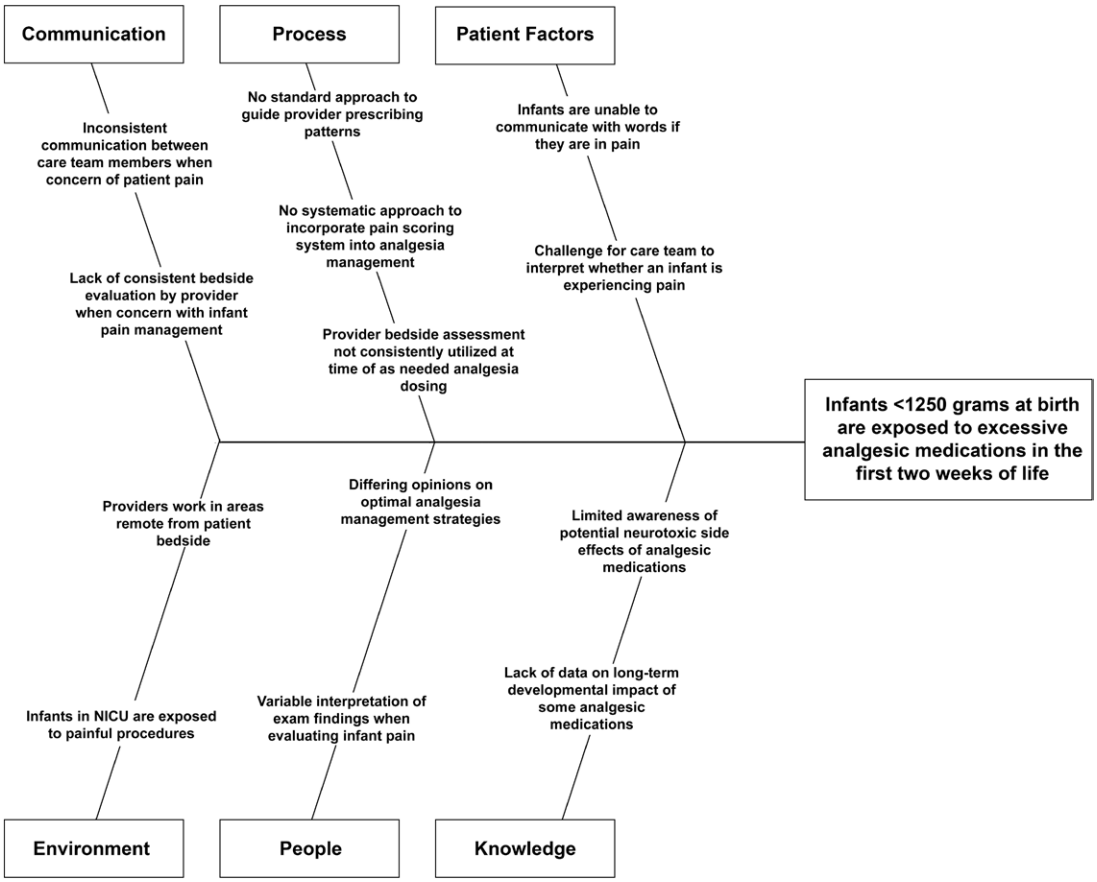

Fig. 1. The fishbone diagram analysis of baseline factors contributing to opioid exposure.

scores being charted on each patient cared for in our NICU, during the Analysis phase, we found that prescribing providers often relied heavily on qualitative descriptions of pain or irritability, without incorporating PIPP scores, into their clinical assessment. PIPP scoring is a validated objective tool used by bedside nursing to quantify signs of pain in premature infants.[18] In this PDSA cycle, prescribing providers received education on PIPP components, location of PIPP scores in the electronic medical record, and incorporation of PIPP scores into oral presentations on daily rounds for all infants receiving analgesic medication.

2. We implemented the second PDSA cycle in July 2018. A pathway for the management of pain for the opioid-naïve infant was created and adopted by the Division of Neonatal Medicine (**online supplement, Supplemental Digital Content 1**, ***http://links.lww.com/PQ9/A190***). The pathway outlined PIPP score interpretation, guidance on nonpharmacological interventions for pain, indications for provider bedside evaluations, postoperative pain management recommendations for common procedures, initial analgesic medication dosing, escalation guidance, and weaning guidelines for infants on analgesic medications based on dose and duration of drug exposure.
3. In September 2018, a third PDSA cycle was implemented to align oral analgesic medication dosing intervals in the analgesia management pathway with the weight and gestational age-based feeding intervals used in the NICUs feeding protocol. This enabled coordination between analgesic medication administration and infant feeds. In addition to this revision of the analgesia management pathway, NICU stakeholders received email communication on these changes and reinforcement of interventions implemented in the first 2 PDSA cycles.

Study of Interventions

During the baseline period, we calculated the baseline mean daily opioid exposure for infants admitted within 24 hours of birth with birth weight less than 1,250 g during their first 14 days of life. We abstracted data for the baseline period for infants born from January 1, 2016, to August 15, 2017. We recorded opioid exposure in average daily morphine equivalents (mg/kg/d) for infants. For example, fentanyl dosing was converted to morphine equivalents using an opioid conversion calculator with a 0% reduction for cross-tolerance.[19,20] The same conversion was used to calculate average daily morphine equivalents (mg/kg/d) during the Improve and Control phases,

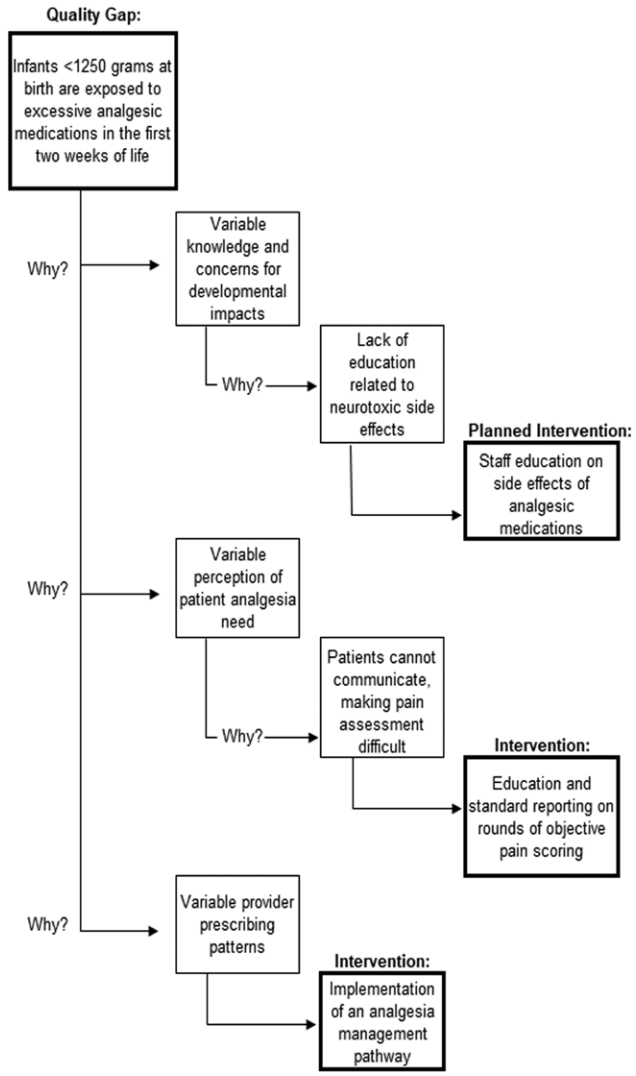

Fig. 2. Five-Whys analysis of causes of opioid exposure.

which spanned from April 1, 2018, through December 31, 2019.

Measures

The QI project started on August 16, 2017, with a stakeholder meeting and concluded on December 31, 2019, following completion of the Control phase. We collected baseline preintervention data from January 1, 2016, through August 15, 2017. A project planning period comprising the Define, Measure, and Analyze phases ranged from August 16, 2017, to March 31, 2018. The Improve phase ran from April 1, 2018, through September 30, 2018. The Control phase spanned from October 1, 2018, to December 31, 2019. Data analysis included all infants with birth weight less than 1,250 g admitted to the NICU within 24 hours of birth during these periods. Study subjects included 72 infants in the baseline period, 39 infants in the project planning period, and 111 infants in the Improve and Control phases.

The primary outcome measure for the QI project was mean daily opioid exposure in morphine equivalents (mg/kg/d) for infants with birth weight less than 1,250 g for the first 14 days of their NICU hospitalization. We censored infants who died during the first 2 weeks of life at the time of death. For example, if an infant died on the second day of life, we included their mean opioid exposure for 2 days, rather than 14. A single team member (V.S.S.) extracted the census of infants with birth weight less than 1,250 g. One pediatric resident (A.R.S.), 1 neonatal medicine fellow (R.C.S.), and 2 bedside nurses with QI training compiled the data by chart abstraction from the electronic health record. Data were tracked in Microsoft Excel (version 14.0.7208.5000, 2010 Microsoft Corporation).

We evaluated rates of unintentional extubations, unintentional central line removals, urinary catheterization use, and time to full enteral feeding volumes as balancing measures. We chose to follow unintentional extubations and central line removals because of a concern that decreased opioid use could have led to infants being more active and at higher risk for these adverse events. Urinary catheter use and days to full feeds were chosen out of concern that these outcomes could worsen if the QI project inadvertently increased opioid exposure, as increased opioid exposure has been reported following the implementation of analgesia prescribing pathways.[21] Also, there was a shift from fentanyl to morphine as a first-line agent, which increased incidences of urinary retention.[22] For balancing measures, the calendar years 2016 and 2017 were used as a baseline, and the calendar years 2018 and 2019 were used for the Improve and Control phases. These date cutoffs were selected rather than the actual start date of the Improvement phase as our NICU had prior systems in place to track these outcomes by calendar year.

Analysis

Intervention effectiveness was assessed using an annotated XBar & R control chart (Fig. 3). Monthly mean daily opioid exposure in morphine equivalents (mg/kg/d) was plotted with a notation of the project phase and PDSA cycles. Statistical analysis was performed to compare baseline to postintervention data for the primary outcome as well

Table 1. PDSA Cycles

PDSA Cycle Number*	Date	Intervention
1	April 2018	PIPP score education and integration of PIPP score reporting into daily rounds
2	July 2018	Implementation of an analgesia management pathway for prescribing and weaning analgesics
3	September 2018	Modification of analgesia management pathway to align dosing intervals with infant feeding protocol

*PDSA cycle annotation used in Fig. 3.

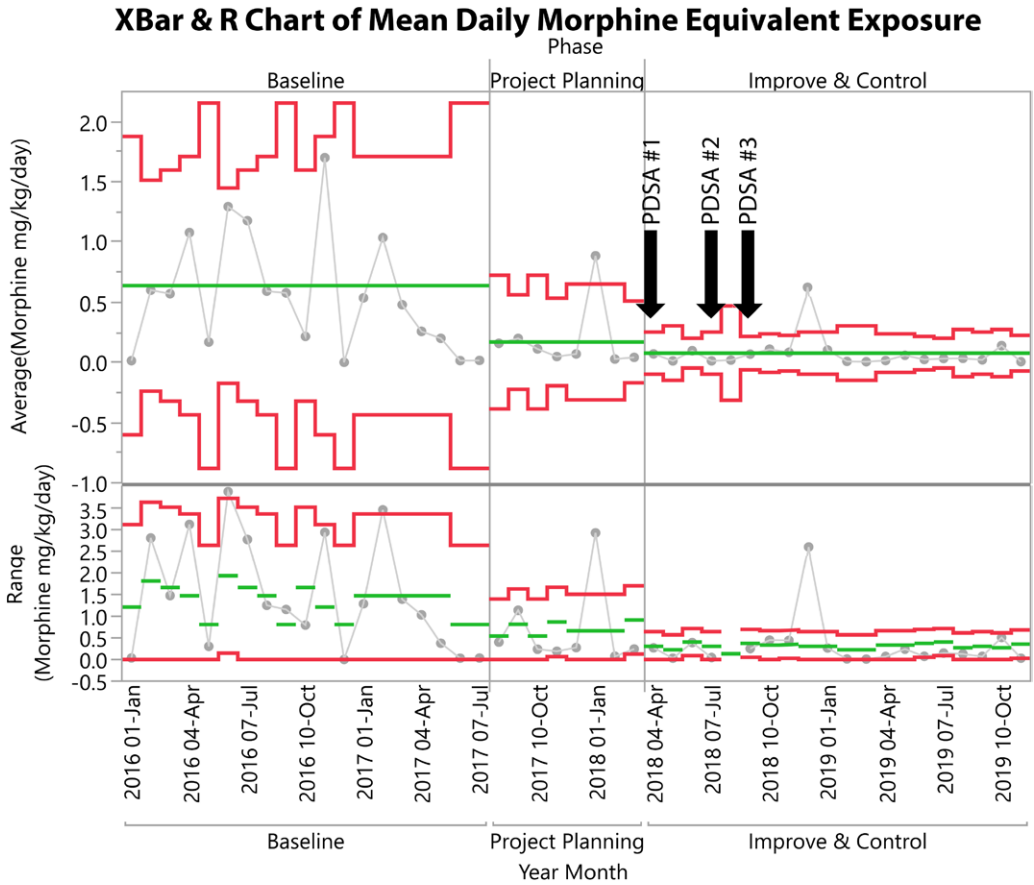

Fig. 3. XBar & R chart of opioid exposure during the first 14 days of life for infants born less than 1,250 g measured in daily mean equivalents of morphine per kilogram.

as the countermeasure rates. We utilized Microsoft Excel and JMP Software (version 14.1.0, SAS Institute Inc., Cary, N.C., 2019) for statistical analysis and creation of the control chart. A neonatal medicine fellow with graduate-level training in statistical methodology (R.C.S.) completed all statistical analyses. We used 2-tailed t-tests for continuous variables and 2-tailed Fisher's exact tests for categorical variables. A P value of <0.05 was considered statistically significant.

RESULTS

During the preintervention baseline period from January 1, 2016, to August 15, 2017, 72 infants with a birth weight of less than 1,250 g were admitted to the NICU within 24 hours of birth. The mean morphine equivalent exposure for these infants was 0.64 mg/kg/d [95% confidence interval (CI) 0.41–0.87]. The Improve and Control phases (April 1, 2018, through December 31, 2019) included 111 infants. Infants in the baseline period, Improve and Control phases were similar in birth weight, gestational age at birth, length of stay, sex, inborn status, and survival to discharge as summarized in Table 2. Opioid use decreased to a mean morphine equivalent exposure of 0.08 mg/kg/d (95% CI 0.03–0.13, P < 0.001). There was no difference in the proportion of infants who received any morphine during the first 14 days of life, 75% at baseline, and 72.1% in the Improve and Control phases (P = 0.66). An XBar & R control chart was used to plot temporal patterns of mean daily morphine equivalent exposure by quarter (Fig. 3). One month of the Improve and Control phases, December 2018, was outside of the upper control limit for both the XBar and R charts. This month included a critically ill infant born at 22 weeks gestation who received a mean of 2.6 mg/kg/d of morphine equivalents. The following 11 months were within the control limits of the XBar & R control chart, and below the baseline mean opioid exposure, demonstrating special cause variation.

There was no statistically significant difference in rates of the balancing measures of unintentional extubations, central line removals, or time to full feeds comparing calendar years 2016–2017 and 2018–2019 (Table 3). Rates of urinary catheter use, for any indication, decreased during the same periods (60.1 per 100 admissions vs 37.7 per 100 admissions, P < 0.001).

Contextual elements related to our NICU and unrelated to the project's interventions may have influenced these results. Initiation of the Improve phase was delayed by 8 months due to the implementation of a new electronic

Table 2. Patient Characteristics in Baseline and Improve and Control Phases

	Baseline (n = 72)	Improve and Control (n = 111)	*P*
GA at birth, mean weeks	26.6 (CI 26.0–27.3)	26.7 (CI 26.3–27.3)	0.72
Birthweight, mean grams	914 (CI 860–967)	878 (CI 834–921)	0.31
Length of stay, mean days	63 (CI 50–75)	70 (CI 59–81)	0.39
Inborn, n	56 (80%)	94 (85%)	0.43
Female, n	38 (54%)	62 (56%)	0.88
Survival to discharge, n	60 (83%)	103 (93%)	0.06

GA, gestational age.

Table 3. Balancing Measure Rates

Balancing Measure	2016–2017	2018–2019	*P*
Unintentional extubations	3.0 per 1,000 ventilator days	1.5 per 1,000 ventilator days	0.33
Unintentional central line removal	1.0 per 1,000 central line days	0.5 per 1,000 central line days	0.62
Urinary catheter use	60.1 per 100 admissions	37.7 per 100 admissions	<0.001
Time to full enteral feeds (120 cc/kg/d)	16.1 days	15.9 days	0.89

health record in our practice and associated restrictions on staff education that were unrelated to the new electronic health record. This limited staff available to receive formal training related to our project. Draft versions of the analgesia management pathway were under review by multidisciplinary team members in the first 6 months of 2018. This fact may have influenced provider prescribing patterns leading to some of the opioid use reduction seen during that period.

DISCUSSION

Our multidisciplinary QI project was able to significantly decrease opioid exposure for infants less than 1,250 g at birth during their first 14 days of life in the NICU. We exceeded our goal of a 33% reduction and reduced mean daily equivalents of morphine exposure by 88% from baseline.

Our practice's QI interventions are in line with those reported by others in studies of analgesia exposure in various NICU populations. A QI effort in an Ohio NICU successfully reduced the duration of opioid exposure for NICU infants following tracheostomy placement with the implementation of practice prescribing standardization, improved communication strategies, and timely addition of dexmedetomidine.[23] In another 60-bed level IV NICU, providers improved neonates' pain management through increased use of an objective pain assessment scale.[24] A collaboration of 7 NICUs in Japan improved neonatal pain management through staff education, the use of objective pain scales within the electronic health record, and the implementation of best practice prescribing guidance.[25] Clinicians need to assess analgesia use after practice changes as increased opioid prescribing has also been observed following the implementation of neonatal pain and sedation protocols.[21]

We found no statistically significant increase in the balancing measures of unintentional extubations, unintentional central line removals, or time to full enteral feeds. We did see a reduction in urinary catheter use; however, it is difficult to determine if this was due to reduced opioid exposure. Our data include all urinary catheter usage and not only urinary catheter use related to opioid-induced urinary retention.

Our project did have several limitations. This project was concurrent with the implementation of a new electronic health record system within the practice. This impacted staff education and the implementation of new electronic order sets due to institutional restrictions during the transition period. Our NICU also had a higher than usual census in 2018, which led to the cancelation of the planned formal education for all nursing staff related to the project. This canceled intervention would have addressed a root cause of opioid overuse identified during the Analysis phase. Formation of our QI group in August 2017 and the circulation of draft versions of the analgesia management pathway in early 2018 may have contributed to the decrease in opioid use observed before the formal implementation of the first PDSA cycle.

Additionally, the project focused only on infants less than 1,250 g at birth during their first 2 weeks of life. NICU infants outside of these parameters commonly receive opioid medications. We attempted to mitigate this limitation by extrapolating lessons learned from our target population to best practices for the care of other infants within our NICU. Finally, in our project, we followed only opioid equivalent exposure without assessing the use of other analgesic medications as balancing measures.

Management of pain in neonates cared for in the NICU setting requires a careful and thoughtful approach. These infants encounter frequent painful and stressful stimuli related to their care requiring analgesia; however, excessive opioid use exposes these infants to detrimental side effects. Within our NICU, we found that consistent reporting of objective neonatal pain scales and the implementation of an analgesia management pathway for prescribing reduced opioid exposure significantly in our target population. Similar strategies may be useful for other NICUs working to reduce opioid exposure for their patients.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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