Original Research

The Association Between Opioid Use and Outcomes in Infants Undergoing Pyloromyotomy

Cory McLaughlin, MD[1,2]; Anthony I. Squillaro, MD, MPH[1,2]; Shadassa Ourshaliman, MPH[1,2]; Ashley Song, MPH[3,4]; Ashwini Lakshmanan, MD, MPH[3,4,5]; Giovanni Cucchiaro, MD, MPP[6]; Matthew Hall, PhD[7]; Rita V. Burke, PhD, MPH[1,2]; and Lorraine I. Kelley-Quon, MD, MSHS[1,2,4]

[1]Division of Pediatric Surgery, Children's Hospital Los Angeles, Los Angeles, CA, USA; [2]Department of Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; [3]Fetal and Neonatal Institute, Division of Neonatology, Department of Pediatrics, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [4]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [5]Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, CA, USA; [6]Division of Anesthesia, Johns Hopkins All Children's Hospital, St. Petersburg, Florida, USA; and [7]Children's Hospital Association, Lenexa, KS, USA

ABSTRACT

Purpose: The purpose of this study was to describe the frequency and variation of opioid use across hospitals in infants undergoing pyloromyotomy and to determine the impact of opioid use on postoperative outcomes.

Methods: A retrospective cohort study (2005−2015) was conducted by using the Pediatric Health Information System (PHIS) database, including infants (aged <6 months) with pyloric stenosis who underwent pyloromyotomy. Infants with significant comorbidities were excluded. Opioid use was classified as a patient receiving at least 1 opioid medication during his or her hospital stay and categorized as preoperative, day of surgery, or postoperative (≥1 day after surgery). Outcomes included prolonged hospital length of stay (LOS; ≥3 days) and readmission within 30 days.

Findings: Overall, 25,724 infants who underwent pyloromyotomy were analyzed. Opioids were administered to 6865 (26.7%) infants, with 1385 (5.4%) receiving opioids postoperatively. In 2015, there was significant variation in frequency of opioid use by hospital, with 0%−81% of infants within an individual hospital receiving opioids ($P < 0.001$). Infants only receiving opioids on the day of surgery exhibited decreased odds of prolonged hospital LOS (odds ratio [OR], 0.85; 95% CI, 0.78−0.92). Infants who received an opioid on both the day of surgery and postoperatively exhibited increased odds of a prolonged hospital LOS (OR, 1.71; 95% CI, 1.33−2.20). Thirty-day readmission was not associated with opioid use (OR, 1.03; 95% CI, 0.93−1.14).

Implications: There is national variability in opioid use for infants undergoing pyloromyotomy, and postoperative opioid use is associated with prolonged hospital stay. Nonopioid analgesic protocols may warrant future investigation. (*Clin Ther.* 2019;41:1690−1700) © 2019 Published by Elsevier Inc.

Key Words: infant, opioid, pyloric stenosis, pyloromyotomy.

Accepted for publication July 2, 2019
https://doi.org/10.1016/j.clinthera.2019.07.002
0149-2918/$ - see front matter

INTRODUCTION

Opioid analgesics are among the most commonly used medications in the hospital setting and are included in the World Health Organization Model List of Essential Medications for Children.[1] General indications for opioids include acute pain control and general anesthesia. More than 40% of hospitalized children and 90% of those undergoing surgery are exposed to opioids during their inpatient stay.[2] Unfortunately, in addition to being highly addictive, opioids are associated with significant side effects, including decreased gastrointestinal motility and respiratory depression. Furthermore, recent reports highlight an increased likelihood of long-term opioid use for children who receive an opioid prescription after surgery.[3]

Given these well-known adverse effects of opioids in children and the availability of nonopioid analgesic alternatives, avoiding opioid use in hospital settings may result in better outcomes for pediatric surgical patients. Several studies have reported that the use of nonopioid-based medications and regional anesthesia techniques can offer effective pain control during and after various surgical procedures.[4–9] More specifically, the majority of infants with hypertrophic pyloric stenosis who undergo pyloromyotomy are otherwise healthy and recover quickly after surgery. Infants requiring pyloromyotomy are often several weeks to a few months old and are particularly sensitive to opioids. Avoidance of opioids is generally recommended to decrease the risk of postoperative apnea.[10,11] Although the laparoscopic approach is often preferred over open pyloromyotomy to minimize postoperative pain, neither technique should necessitate significant postoperative analgesia.[12–14] In fact, previous data suggest that adequate pain control can be achieved with non-opioid modalities in most patients undergoing pyloromyotomy.[15,16]

Currently, there are no national data on the use of opioids for infants requiring a pyloromyotomy. Infants undergoing pyloromyotomy are typically healthy, thus providing a relatively uniform clinical population in which to explore variations in perioperative opioid use and its impact on clinical outcomes. The primary objective of the current study was to assess the frequency and variation of perioperative opioid use across hospitals in healthy infants undergoing pyloromyotomy. In addition, we aimed to determine the association between opioid use and postoperative outcomes, including length of stay (LOS) and 30-day readmission.

MATERIALS AND METHODS

Study Design, Participants, and Data Collection Procedures

Institutional Review Board approval was obtained from the Children's Hospital of Los Angeles. A retrospective cohort study was performed by using the Pediatric Health Information System (PHIS). The PHIS database is maintained by the Children's Hospital Association (Lenexa, Kansas) and includes clinical and resource utilization data for both inpatient and outpatient encounters for children's hospitals throughout the United States. All data are de-identified before their release for analysis. Data quality is monitored by the PHIS data quality program with issuance of quarterly data quality reports, chart audits, and feedback to participating hospitals.

Infants <6 months of age with a diagnosis of pyloric stenosis (*International Classification of Diseases, Ninth Revision, Clinical Modification,* code 750.5) who underwent pyloromyotomy (*International Classification of Diseases, Ninth Revision, Clinical Modification,* code 43.3) from 2005 to 2015 were identified. Infants with a complex chronic condition,[17–19] those without pharmacy data, and those with missing insurance or sex data were excluded. Patient demographic data included age, sex, race, ethnicity, and insurance status. Hospital characteristics included United States census region and total number of staffed beds as a proxy for hospital size.

Definition of Opioid Exposure

The primary exposure in this study was the use of any opioid medication during the infant's hospital stay. Opioid medications were defined according to the review by Womer et al[2] of opioid use in hospitalized children. Opioid use was determined from PHIS pharmacy billing data by using generic pharmacy codes that are time-stamped for date of exposure. Opioid use was dichotomized into "exposed" versus "unexposed." Time of opioid exposure was then subcategorized by comparing

surgery date versus the opioid exposure date. Preoperative exposure was defined as opioids received one or more days before the day of surgery. Postoperative exposure was defined as opioids received one or more days after the day of surgery. Opioids received on the day of surgery were categorized as day of surgery exposure, which included opioids received in the operating room and the recovery room. Dosage strength and frequency of administration are not captured by PHIS and thus were not included in the analysis.

Definition of Outcomes

Our primary outcome was total hospital LOS, defined as the number of days between admission and discharge dates. A patient admitted and discharged the same day was defined as having an LOS equal to 1 day. Secondary outcomes included postoperative LOS (discharge date minus surgery date) and all-cause readmission within 30 days of surgery. Total hospital LOS was dichotomized into $\leq$2 days or $\geq$3 days based on previously published reports of healthy infants undergoing pyloromyotomy.[20] Postoperative LOS was stratified into clinically relevant categories: $\leq$1 day, 2 days, or $\geq$3 days.

Statistical Analyses

Continuous variables were described by using mean and SD. Frequencies were calculated to describe categorical variables. Patient demographic and hospital-level data were compared by using bivariate analyses. Categorical and continuous variables were analyzed by using χ^2 and Wilcoxon-Mann-Whitney tests, respectively. Normality for continuous variables was assessed by using histograms and Q-Q plots. Hospital variation in opioid use was assessed according to two-proportion z-tests.

Multivariable logistic regression analysis with mixed effects was used to determine odds ratios (ORs) for opioid use and outcomes of interest: total hospital LOS, postoperative LOS, and readmission within 30 days. Mixed effects modeling was used to control for unmeasured hospital characteristics that may confound any associations. Single multinomial logistic models with dummy coding for perioperative opioid exposure were conducted for total hospital and postoperative LOS. Covariate selection was based on clinical assessment, availability from the PHIS databases, and variables with a significant bivariate association ($P < 0.05$). Covariates included: sex, race, age, insurance status, hospital region, and staffed beds. Pearson χ^2 statistics and Hosmer–Lemeshow tests were used to assess goodness-of-fit for logistic regression models.

Race was included in adjusted models; however, ethnicity was collected on observation or volunteered by the patient and in some cases applied to the patients' race. As such, adjustment for ethnicity was not included in the final logistic regression models. A sensitivity analysis was conducted by including race with missing observations (n = 1305). Estimates and conclusions were not significantly different in the sensitivity analysis. All analyses were conducted with two-sided significance, $\alpha = 0.05$. Data were analyzed by using SAS software 9.4 (SAS Institute, Inc, Cary, North Carolina) and StataCorp (StataCorp LLC, College Station, Texas).

RESULTS

The final cohort included 25,724 infants who underwent pyloromyotomy at 47 different hospitals in the United States (2005–2015) (Figure 1). Overall, 6865 (26.7%) infants received opioids (Table I) during their hospitalization. The overall rate of opioid use for all years varied significantly across hospitals from 3.5% to 89.4% ($P < 0.001$). Infants receiving opioids were slightly older (mean, 39 vs 36 days; $P < 0.001$), less likely to have public insurance (39% vs 41%; $P = 0.001$), and more frequently treated at hospitals in the South (44% vs 37%; $P < 0.001$). Unadjusted overall mean LOS stay was 2.0 (1.0) days, with no significant difference between infants who received opioids during hospitalization versus those who did not ($P = 0.19$). Unadjusted mean postoperative LOS among infants receiving opioids was 1.4 (0.8) vs 1.3 (0.8) with no significant difference ($P = 0.07$). Unadjusted 30-day readmission was more common for infants who received opioids (10.4% vs 9.0%; $P < 0.001$).

Among the infants who received opioids, 82% (n = 5564) received an opioid on the day of surgery, 3% (n = 229) before surgery, and 20% (n = 1385) postoperatively, with 16% (n = 1065) receiving opioids only after surgery. The most commonly used opioid was fentanyl (62.5%), followed by morphine (25.9%) (Table II). The highest overall opioid use was in 2007 (median, 28%; interquartile range

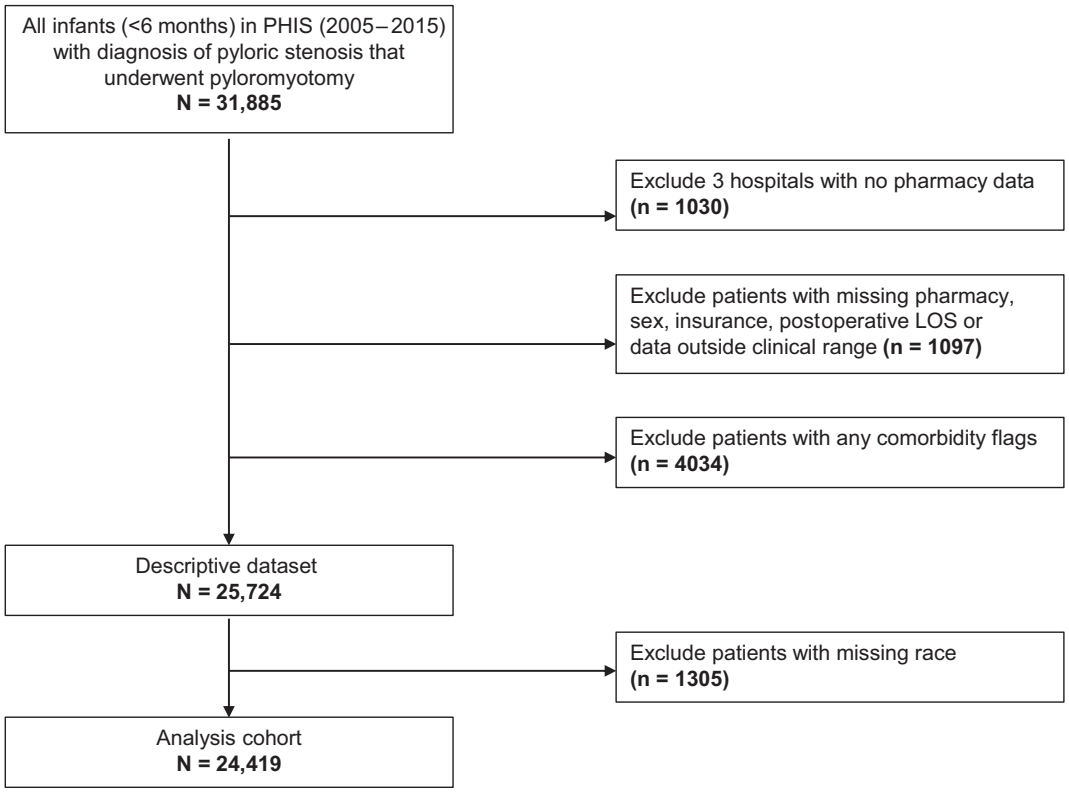

Figure 1. Flow diagram of cohort selection. LOS = length of stay; PHIS = Pediatric Health Information System.

[IQR], 15%–46%) and the lowest in 2008 (median, 18%; IQR, 12%–44%) (Figure 2A). The highest postoperative opioid use was in 2007 (median, 5.0%; IQR, 1.3%–10%) and the lowest in 2010 (median, 1.7%; IQR, 0%–3.9%) (Figure 2B). In the most recent year of data (2015), there was considerable variation in frequency of opioid use according to hospital (Figure 3), with 0%–81% of admitted infants within an individual hospital receiving opioids ($P < 0.001$). Similar variation according to hospital was seen in use of opioids after pyloromyotomy (0%–33%; $P < 0.001$).

In adjusted analyses, the administration of opioids at any time during hospitalization was not associated with total hospital LOS, 30-day readmission, or postoperative LOS (Table III). Preoperative opioid exposure was not significantly associated with hospital LOS, postoperative LOS, or 30-day readmission. Opioid use limited to the day of surgery was significantly associated with shorter hospital LOS (OR, 0.85; 95% CI, 0.78–0.92) and postoperative LOS ≤1 day (LOS 2 days OR, 0.67 [95% CI, 0.62–0.73]; LOS ≥3 days OR, 0.56 [95% CI, 0.48–0.66]). Opioid use on the day of surgery was not significantly associated with odds of 30-day readmission.

Opioid use limited to the postoperative period was not associated with increased total hospital LOS (OR, 1.12; 95% CI, 0.96–1.30) but was associated with longer postoperative LOS (LOS 2 days OR, 3.75 [95% CI, 3.25–4.34]; LOS ≥3 days OR, 4.73 [95% CI, 3.88–5.76]). There was no significant association between postoperative opioid use and odds of 30-day readmission. Patients who received an opioid both on the day of surgery and postoperatively exhibited increased odds of prolonged hospital LOS (OR, 1.71; 95% CI, 1.33–2.20) and longer postoperative LOS (LOS 2 days OR, 1.56 [95% CI, 1.20–2.02]; LOS ≥3 days OR, 1.96 [95% CI, 1.34–2.87]) but no significant difference in odds of 30-day readmission.

Table I. Hospital and patient demographic characteristics of infants who underwent pyloromyotomy. Values are given as no. (%) unless otherwise indicated.

Characteristic	Total	Opioid Use		*P*
		Yes	No	
	(N = 25,724)	(n = 6,865)	(n = 18,859)	
Patient age, d	36.7 (16.7)	38.9 (18.6)	35.8 (15.9)	<0.001
Sex				
Male	21,394 (83.2)	5761 (83.9)	15,633 (82.9)	0.06
Female	4329 (16.8)	1104 (16.1)	3226 (17.1)	
Ethnicity				
Hispanic or Latino	6151 (23.9)	1597 (23.3)	4555 (24.1)	0.09
Not Hispanic or Latino	11,026 (42.8)	3018 (43.9)	8008 (42.5)	
Unknown	8546 (33.3)	2250 (32.8)	6296 (33.4)	
Race				
Missing	1305 (5.1)	369 (5.4)	936 (5.0)	<0.001
White	19,000 (73.9)	5192 (75.6)	13,808 (73.2)	
Black	1871 (7.3)	418 (6.1)	1453 (7.7)	
Asian	175 (0.7)	57 (0.8)	118 (0.6)	
American Indian or Alaskan Native	177 (0.7)	52 (0.8)	125 (0.7)	
Native Hawaiian or Pacific Islander	18 (0.1)	<10 (0.1)	12 (0.1)	
Other	3178 (12.4)	771 (11.2)	2407 (12.8)	
Insurance				
Private	5952 (23.1)	1581 (23.0)	4371 (23.2)	0.001
Public	10,362 (40.3)	2656 (38.7)	7706 (40.9)	
Other	9410 (36.6)	2628 (38.3)	6782 (36.0)	
Hospital region				
Midwest	6960 (27.1)	1620 (23.6)	5340 (28.3)	<0.001
Northeast	3393 (13.2)	580 (8.4)	2813 (14.9)	
South	9971 (38.8)	3024 (44.0)	6947 (36.8)	
West	5400 (21.0)	1641 (23.9)	3759 (19.9)	
Hospital staffed beds	353.6 (133.1)	341.9 (124.1)	357.8 (136.0)	<0.001
LOS, mean (SD), d	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)	0.19
Postoperative LOS, mean (SD), d	1.4 (0.8)	1.3 (0.8)	1.4 (0.8)	0.07
30-Day readmission	2407 (9.4)	715 (10.4)	1692 (9.0)	<0.001

LOS = length of stay.
Note: The χ^2 and Wilcoxon-Mann-Whitney tests were used to compare categorical and continuous variables, respectively.

DISCUSSION

This large retrospective cohort study of opioid use in healthy infants who underwent pyloromyotomy revealed significant interhospital variation in opioid utilization. Furthermore, use of opioids after pyloromyotomy was associated with prolonged hospital LOS. Frequency of opioid use was highly variable among participating hospitals. Infants most often received opioids on the day of surgery, but 5.4% of infants received opioids postoperatively. The use of opioids in the postoperative period alone was significantly associated with longer postoperative LOS, and combined use of opioids on the day of surgery and postoperatively was associated with

Table II. Opioid medications used in infants who underwent pyloromyotomy. Values are given as no. (%).

Type of Opioid	Overall (N = 6865)
Fentanyl (base) (citrate)	4288 (62.5)
Morphine sulfate	1781 (25.9)
Meperidine HCl	583 (8.5)
Remifentanil HCl	341 (5.0)
Nalbuphine HCl	208 (3.0)
Narcotic analgesic combinations	167 (2.4)
Butorphanol tartrate	74 (1.1)
Hydromorphone HCl	13 (0.2)
Oxycodone HCl	13 (0.2)
Alfentanil HCl	<10 (<0.1)
Codeine (phosphate) (sulfate)	<10 (<0.1)
Methadone HCl	<10 (<0.1)
Tramadol	<10 (<0.1)

HCl = hydrochloride.

longer total hospital LOS and postoperative LOS. These results suggest that use of opioids after pyloromyotomy may prolong recovery and lead to increased health care utilization.

Infants with hypertrophic pyloric stenosis who undergo a pyloromyotomy are typically healthy, and postoperative pain can frequently be managed with nonnarcotic medications. Acetaminophen alone has been shown to achieve adequate analgesia in this population.[21] In addition, opioids are much less commonly used for infants with hypertrophic pyloric stenosis treated in centers outside of the United States. A case series from Australia found that only 3 of 72 patients received opioids after pyloromyotomy.[15] Similarly, a Canadian comparison of laparoscopic versus open pyloromyotomy in 38 infants reported very low rates of postoperative opioid use in either group (0% vs 5%, respectively).[16] These data suggest that opioids may not be needed for otherwise healthy infants undergoing pyloromyotomy. Our findings support this argument, as we found that most infants did not receive opioids postoperatively, with the most recent year of data (2015) showing 18 hospitals avoided postoperative opioids altogether.

Considerable interhospital variability in the frequency of postoperative opioid use was also found in the current study. Some hospitals avoided opioids altogether, whereas others used opioids in the majority of cases. A recent survey of anesthesiologists found that 24% administered opioids to children after pyloromyotomy.[22] Although surgeons were not included in this survey, it suggests a lack of uniformity in the analgesic management of infants undergoing pyloromyotomy, which may beget significant provider-level variability. Alignment of an analgesic plan among all providers (eg, anesthesia, surgery, nursing) may improve consistency. Improved outcomes in adult patients managed with enhanced recovery after surgery (ERAS) protocols[23–26] has fostered novel research in pediatric surgical patients. An enhanced recovery protocol for children undergoing colorectal surgery has been associated with decreased opioid use, time to regular diet, and overall LOS.[27] Similar improvements in patient outcomes have been associated with the use of ERAS in pediatric patients undergoing major urologic procedures.[28,29] Established guideline measures for infants with pyloric stenosis, similar to these other ERAS protocols, may warrant future investigation.

We found that opioid use after pyloromyotomy was associated with longer postoperative LOS. The mechanism by which opioids might have led to longer LOS is not clear, but discharge after pyloromyotomy typically requires that an infant is able to tolerate a large enough bolus of formula or breast milk to remain hydrated after several feedings. Opioids may exacerbate feeding intolerance by way of decreasing gut motility,[30] thereby prolonging LOS. Use of opioids may also increase the risk of postoperative apnea,[10,11,15] which may necessitate prolonged in-hospital monitoring. Limiting opioid use (or avoiding opioid use altogether) may decrease the likelihood of these adverse effects, thereby improving quality of care and outcomes after pyloromyotomy.

Timing of opioid use may play a pivotal role in post-pyloromyotomy outcomes. Although postoperative opioid use may prolong recovery, we found that opioid use limited to the day of surgery was associated with decreased LOS. This finding implies that judicious opioid use during general anesthesia may actually expedite recovery. This association is supported by previous randomized data comparing perioperative remifentanil versus halothane for

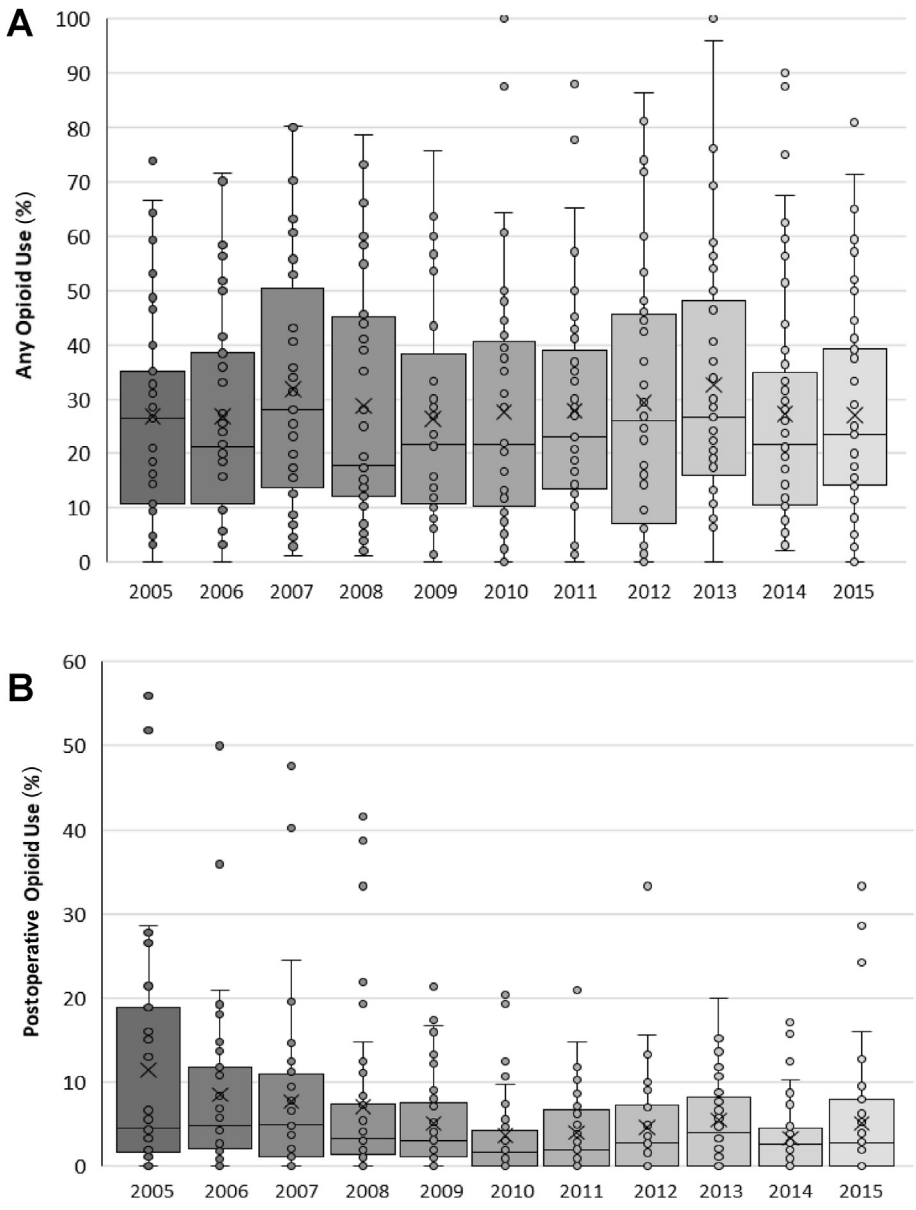

Figure 2. (A) Overall and (B) postoperative opioid use according to calendar year. Data are presented as median with interquartile range.

infants undergoing pyloromyotomy, which found a trend toward improved respiratory outcomes in the remifentanil group.[31] The theoretical risks of postoperative apnea and gastrointestinal dysfunction may be overestimated for infants who are only exposed to opioids intraoperatively. We would caution against this assumption, however, because there is still a paucity of data supporting intraoperative opioid use for infants undergoing pyloromyotomy. It is also possible that reverse causality may explain the association between decreased LOS and day of surgery opioid use (ie, children discharged within 1 day would not be eligible for postoperative opioid use).

The current study was limited by the retrospective nature of the PHIS database. Although we attempted

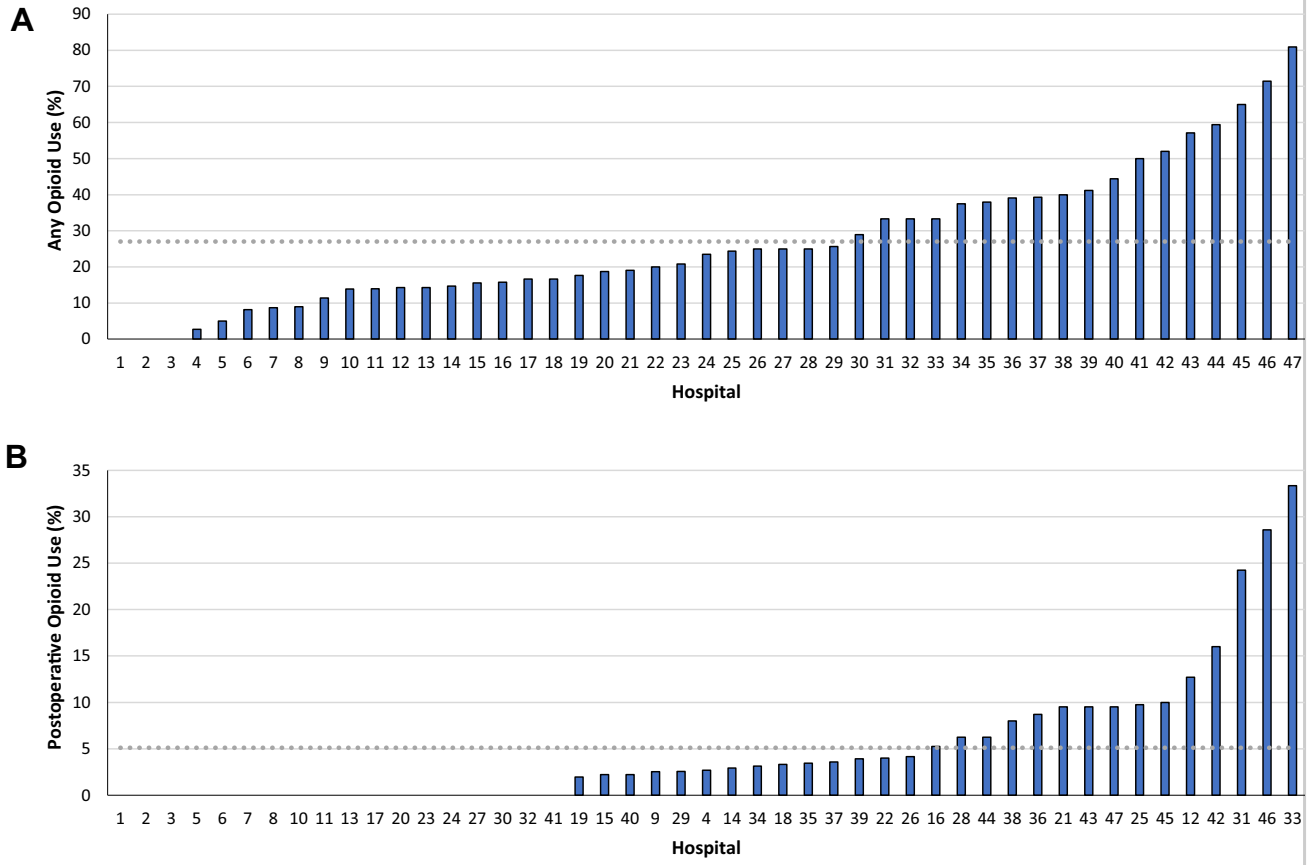

Figure 3. Variation of (A) overall and (B) postoperative opioid use according to hospital in infants undergoing pyloromyotomy in 2015. N = 1484 total patients who underwent pyloromyotomy in 2015. Significant variation ($P < 0.001$) for both overall and postoperative opioid use. Dashed line represents median percent opioid use.

to minimize treatment bias by excluding infants with comorbidities (who may be more likely to receive opioids), unmeasured confounding can still be present when analyzing retrospective data. Second, total daily dosing of medications was not available for analysis from this dataset, rendering opioid exposure a dichotomous variable. A dose-dependent association could exist between postoperative opioid use and LOS, but we were unable to test this hypothesis. Third, statistical confidence was low in ethnicity data due to missingness and potential for collinearity with race, which limited our ability to determine the effect of ethnicity on the likelihood of an infant to receive opioids. Previous studies have highlighted an association between race and amount of opioid use after surgery,[32] but racial disparities in outcomes after surgery may be lessened in the neonatal population.[33,34] In our sensitivity analyses, incorporation of ethnicity into the multivariate model showed no difference in outcomes. Finally, reverse causality may explain the association between time of opioid exposure and LOS. Infants who had a longer postoperative LOS, by definition, had longer potential time to be exposed to opioids. Similarly, those infants discharged within 1 day would not have been eligible for postoperative opioid exposure based on our definitions. However, the present analysis attempted to minimize reverse causality by stratifying

Table III. Comparison of postoperative outcomes according to opioid exposure in infants who underwent pyloromyotomy.

Variable	Unadjusted		Adjusted*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Any opioid use†				
Total LOS				
≤2 d	Ref	—	Ref	—
≥3 d	0.92 (0.85—0.99)	0.03	0.94 (0.87—1.01)	0.10
Postoperative LOS				
≤1 d	Ref	—	Ref	—
2 d	0.93 (0.87—1.00)	0.06	0.96 (0.89—1.03)	0.23
≥3 d	0.91 (0.81—1.03)	0.13	0.95 (0.85—1.08)	0.44
30-Day readmission	1.01 (0.91—1.12)	0.86	1.03 (0.93—1.14)	0.55
Day of surgery opioid use only‡				
Total LOS				
≤2 d	Ref	—	Ref	—
≥3 d	0.82 (0.76—0.90)	<0.001	0.85 (0.78—0.92)	<0.001
Postoperative LOS				
≤1 d	Ref	—	Ref	—
2 d	0.65 (0.60—0.71)	<0.001	0.67 (0.62—0.73)	<0.001
≥3 d	0.54 (0.46—0.63)	<0.001	0.56 (0.48—0.66)	<0.001
30-Day readmission	1.00 (0.89—1.12)	0.96	0.99 (0.89—1.11)	0.93
Postoperative opioid use only§				
Total LOS				
≤2 d	Ref	—	Ref	—
≥3 d	1.13 (0.97—1.31)	0.12	1.12 (0.96—1.30)	0.15
Postoperative LOS				
v ≤ 1 d	Ref	—	Ref	—
2 d	3.75 (3.26—4.33)	<0.001	3.75 (3.25—4.34)	<0.001
≥3 d	4.50 (3.67—5.41)	<0.001	4.73 (3.88—5.76)	<0.001
30-Day readmission	1.04 (0.84—1.30)	0.70	1.17 (0.94—1.46)	0.16
Day of surgery and postoperative opioid use‖				
Total LOS				
≤2 d	Ref	—	Ref	—
≥3 d	1.69 (1.32—2.18)	<0.001	1.71 (1.33—2.20)	<0.001
Postoperative LOS				
≤1 d	Ref	—	Ref	—
2 d	1.54 (1.19—1.98)	0.001	1.56 (1.20—2.02)	<0.001
≥3 d	1.85 (1.27—2.70)	0.001	1.96 (1.34—2.87)	<0.001
30-Day readmission	1.12 (0.76—1.65)	0.57	1.21 (0.82—1.79)	0.33

OR = odds ratio; LOS = length of stay.
* Models were controlled for sex, race, patient age (in days), insurance status, hospital size, hospital region, and year of surgery.
† n = 6496.
‡ n = 4987.
§ n = 1011.
‖ n = 278.

opioid use preoperatively, day of surgery, and postoperatively.

CONCLUSIONS

There is considerable interhospital variability in the frequency of opioid use after pyloromyotomy, suggesting that provider- and hospital-level factors may explain the variation of exposure. Infants receiving opioids in the days following pyloromyotomy exhibited a significantly prolonged hospital LOS. Post-pyloromyotomy pathways with nonopioid analgesic protocols may warrant future investigation to reduce unnecessary opioid use and improve outcomes.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

Dr. Kelley-Quon and Dr. Lakshmanan are supported by grant KL2TR001854 from the National Center for Advancing Translational Sciences (NCATS) of the U.S. National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. *21st WHO Expert Committee on the Selection and Use of Essential Medicines. WHO Model List of Essential Medicines for Children*. 6th ed.; March 2017. http://www.who.int/medicines/publications/essentialmedicines/4th_EMLc_FINAL_web_8Jul13.pdf. Accessed December 12, 2017.
2. Womer J, Zhong W, Kraemer FW, et al. Variation of opioid use in pediatric inpatients across hospitals in the U.S. *J Pain Symptom Manag*. 2014;48:903–914. https://doi.org/10.1016/j.jpainsymman.2013.12.241.
3. Harbaugh CM, Lee JS, Hu HM, et al. Persistent opioid use among pediatric patients after surgery. *Pediatrics*. 2018;141:e20172439. https://doi.org/10.1542/peds.2017-2439.
4. Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology*. 1999;91:442–447.
5. Alkhoury F, Knight C, Stylianos S, et al. Prospective comparison of nonnarcotic versus narcotic outpatient oral analgesic use after laparoscopic appendectomy and early discharge. *Minim Invasive Surg*. 2014;2014:509632. https://doi.org/10.1155/2014/509632.
6. Burnweit C, Diana-Zerpa JA, Nahmad MH, et al. Nitrous oxide analgesia for minor pediatric surgical procedures: an effective alternative to conscious sedation? *J Pediatr Surg*. 2004;39:495–499. discussion 495-499.
7. Pasarón R, Burnweit C, Zerpa J, et al. Nitrous oxide procedural sedation in non-fasting pediatric patients undergoing minor surgery: a 12-year experience with 1,058 patients. *Pediatr Surg Int*. 2015;31:173–180. https://doi.org/10.1007/s00383-014-3608-5.
8. Kelly LE, Sommer DD, Ramakrishna J, et al. Morphine or ibuprofen for post-tonsillectomy analgesia: a randomized trial. *Pediatrics*. January 2015. https://doi.org/10.1542/peds.2014-1906. peds.2014-1906.
9. Watcha MF, Jones MB, Lagueruela RG, Schweiger C, White PF. Comparison of ketorolac and morphine as adjuvants during pediatric surgery. *Anesthesiology*. 1992;76:368–372.
10. Kamata M, Cartabuke RS, Tobias JD. Perioperative care of infants with pyloric stenosis. *Paediatr Anaesth*. 2015;25:1193–1206. https://doi.org/10.1111/pan.12792.
11. Verghese ST, Hannallah RS. Acute pain management in children. *J Pain Res*. 2010;3:105–123.
12. Leclair MD, Plattner V, Mirallie E, et al. Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: a prospective, randomized controlled trial. *J Pediatr Surg*. 2007;42:692–698. https://doi.org/10.1016/j.jpedsurg.2006.12.016.
13. St Peter SD, Holcomb GW, Calkins CM, et al. Open versus laparoscopic pyloromyotomy for pyloric stenosis. *Ann Surg*. 2006;244(3):363–370. https://doi.org/10.1097/01.sla.0000234647.03466.27.
14. Hall NJ, Pacilli M, Eaton S, et al. Recovery after open versus laparoscopic pyloromyotomy for pyloric stenosis: a double-blind multicentre randomised controlled trial. *Lancet*. 2009;373:390–398. https://doi.org/10.1016/S0140-6736(09)60006-4.
15. Habre W, Schwab C, Gollow I, Johnson C. An audit of postoperative analgesia after pyloromyotomy. *Paediatr Anaesth*. 1999;9:253–256.
16. Lemoine C, Paris C, Morris M, Vali K, Beaunoyer M, Aspirot A. Open transumbilical pyloromyotomy: is it more painful than the laparoscopic approach? *J Pediatr Surg*. 2011;46:870–873. https://doi.org/10.1016/j.jpedsurg.2011.02.019.
17. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr*. 2014;14:199. https://doi.org/10.1186/1471-2431-14-199.
18. Feudtner C, Christakis DA, Connell FA. Pediatric deaths attributable to complex chronic conditions: a population-based study of Washington State, 1980-1997. *Pediatrics*. 2000;106(1 pt 2):205–209.

19. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. *Pediatrics*. 2001;107:E99.
20. Kelley-Quon LI, Tseng CH, Jen HC, Shew SB. Hospital type predicts surgical complications for infants with hypertrophic pyloric stenosis. *Am Surg*. 2012;78:1079–1082.
21. Yung A, Thung A, Tobias JD. Acetaminophen for analgesia following pyloromyotomy: does the route of administration make a difference? *J Pain Res*. 2016;9:123–127. https://doi.org/10.2147/JPR.S100607.
22. Cartabuke RS, Tobias JD, Rice J, Tumin D. Current perioperative care of infants with pyloric stenosis: comparison of survey results. *J Surg Res*. 2018;223:244–250. https://doi.org/10.1016/j.jss.2017.10.022. e3.
23. Teeuwen PHE, Bleichrodt RP, Strik C, et al. Enhanced recovery after surgery (ERAS) versus conventional postoperative care in colorectal surgery. *J Gastrointest Surg*. 2010;14:88–95. https://doi.org/10.1007/s11605-009-1037-x.
24. Lam J, Suzuki T, Bernstein D, et al. An ERAS protocol for bariatric surgery: is it safe to discharge on post-operative day 1? *Surg Endosc*. 2019;33:580–586. https://doi.org/10.1007/s00464-018-6368-9.
25. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg*. 2017;152:292–298. https://doi.org/10.1001/jamasurg.2016.4952.
26. Rawlinson A, Kang P, Evans J, Khanna A. A systematic review of enhanced recovery protocols in colorectal surgery. *Ann R Coll Surg Engl*. 2011;93:583–588. https://doi.org/10.1308/147870811X605219.
27. Short HL, Heiss KF, Burch K, et al. Implementation of an enhanced recovery protocol in pediatric colorectal surgery. *J Pediatr Surg*. 2018;53:688–692. https://doi.org/10.1016/j.jpedsurg.2017.05.004.
28. Haid B, Karl A, Koen M, Mottl W, Haid A, Oswald J. Enhanced recovery after surgery protocol for pediatric urological augmentation and diversion surgery using small bowel. *J Urol*. 2018;200:1100–1106. https://doi.org/10.1016/j.juro.2018.06.011.
29. Rove KO, Brockel MA, Saltzman AF, et al. Prospective study of enhanced recovery after surgery protocol in children undergoing reconstructive operations. *J Pediatr Urol*. 2018;14:252.e1–252.e9. https://doi.org/10.1016/j.jpurol.2018.01.001.
30. Leppert W. The impact of opioid analgesics on the gastrointestinal tract function and the current management possibilities. *Contemp Oncol*. 2012;16:125–131. https://doi.org/10.5114/wo.2012.28792.
31. Davis PJ, Galinkin J, McGowan FX, et al. A randomized multicenter study of remifentanil compared with halothane in neonates and infants undergoing pyloromyotomy. I. Emergence and recovery profiles. *Anesth Analg*. 2001;93:1380–1386 [table of contents].
32. Sadhasivam S, Chidambaran V, Ngamprasertwong P, et al. Race and unequal burden of perioperative pain and opioid related adverse effects in children. *Pediatrics*. 2012;129:832–838. https://doi.org/10.1542/peds.2011-2607.
33. Peterson JK, Chen Y, Nguyen DV, Setty SP. Current trends in racial, ethnic, and healthcare disparities associated with pediatric cardiac surgery outcomes. *Congenit Heart Dis*. 2017;12:520–532. https://doi.org/10.1111/chd.12475.
34. Allin BSR, Long AM, Gupta A, Lakhoo K, Knight M. One-year outcomes following surgery for necrotising enterocolitis: a UK-wide cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2018;103:F461–F466. https://doi.org/10.1136/archdischild-2017-313113.

Address correspondence to: Lorraine I. Kelley-Quon, MD, MSHS, FAAP, Department of Surgery, Division of Pediatric Surgery, Children's Hospital Los Angeles, 4650 Sunset Blvd, Mailstop #100, Los Angeles, CA 90027, USA. E-mail: lkquon@chla.usc.edu