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Opioid-free Pain Management after Cleft Lip Repair

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Background: Side effects of opioid pain management after surgical repair of cleft lips are numerous and affect postoperative course. We compared opioid versus opioid-free pain management regimens for infants who underwent cleft lip repair to evaluate the impact on postoperative recovery.

Methods: Cleft lip repairs at our institution from December 2016 to February 2021 were retrospectively reviewed, comparing patients who received opioids to patients receiving a nonopioid pain control regimen. Data collected include length of stay, oral morphine equivalents (OME) received on day of surgery (DOS)/postoperative day (POD) 1, time to and volume of first oral feed, and Face/Legs/Activity/Cry/Consolability (FLACC) scores.

Results: Seventy-three infants were included (47 opioid and 26 nonopioid). The opioid group received average 1.75 mg OME on DOS and 1.04 mg OME on POD1. Average DOS FLACC scores were similar between groups [1.57 ± 1.18 nonopioid versus 1.76 ± 0.94 (SD) opioid; $P = 0.46$]. Average POD1 FLACC scores were significantly lower for the nonopioid group (0.73 ± 1.05 versus 1.35 ± 1.06; $P = 0.022$). Median time to first PO (min) was similar [178 (interquartile range [IQR] 66–411) opioid versus 147 (IQR 93–351) nonopioid; $P = 0.65$]. Median volume of first feed (mL) was twice as high for the nonopioid group [90 (IQR 58–120) versus 45 (IQR 30–60); $P = 0.003$].

Conclusions: Nonopioid postoperative pain management was more effective than opioids for pain management in infants after cleft lip repair, as evidenced by FLACC scores and increased volume of the first oral feed. *(Plast Reconstr Surg Glob Open 2023; 11:e5259; doi: 10.1097/GOX.0000000000005259; Published online 8 September 2023.)*

INTRODUCTION

The incidence of cleft lip with or without cleft palate is about one in every 500–700 live births in the United States.[1,2] Cleft lip and palate require multiple staged operations throughout a patient's life. The initial stage of repair addresses the cleft lip and involves mainly soft tissue of the upper lip, without bone manipulation.[1] This first stage generally takes place between 3 and 6 months of age. Although some reports describe discharge immediately following surgery, most infants are admitted overnight for postoperative observation and pain management.[3–6]

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Postoperative pain control is crucial for optimal postoperative recovery after cleft lip repair. The standard of care has been to rely on opioids. However, opioid use is associated with risks that can affect postoperative recovery, including nausea, poor oral intake, constipation, and more seriously, sedation or respiratory depression.[5] Even restricting opioid use to the acute postoperative period has potential for long-term neurocognitive effects in these infants, which can affect areas of development such as vocabulary and behavior.[7] Yet, untreated pain in neonates and children can negatively impact neurocognitive development and future responses to pain.[8,9]

Although several studies have documented nonopioid pain control after cleft palate repair, including intraoperative nerve blocks or intraoperatively administered acetaminophen,[6,10–12] the literature on nonopioid pain management or multimodal medication strategies after cleft lip repair is inconclusive. A Cochrane systematic review about the effectiveness of infraorbital nerve blocks compared with placebo block or opioids or peri-incisional infiltration concluded there was low to very low evidence that infraorbital nerve blocks may reduce postoperative pain more than placebo and IV opioids.[13] We therefore sought to compare the effectiveness of managing

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postoperative pain with opioids versus nonopioids in infants who underwent cleft lip repair.

Takeaways

Question: Is nonopioid postoperative pain management as effective as opioids in infants after cleft lip repair?

Findings: This retrospective review comparing patients who received opioids to patients who received a nonopioid pain control regimen after cleft lip repair found that patients who received only nonopioid pain medication had lower pain scores and had increased oral intake during their hospital course.

Meaning: Nonopioid postoperative pain management was more effective than opioids for pain management in infants after cleft lip repair and improved overall recovery.

METHODS

Study Design

After obtaining approval for this study from the institutional review board at the University of California, San Francisco (UCSF), we retrospectively reviewed all cleft lip repairs that took place from December 16, 2016, to February 25, 2021, at UCSF Mission Bay Children's Hospital. Patients were separated into nonopioid and opioid groups. A nonopioid pain regimen was instituted in March 2019 for management of postoperative pain after cleft lip repair, and patients in this group are included in the time frame for this study. The nonopioid group received scheduled acetaminophen and ibuprofen during their postoperative hospital stay. The opioid group received intravenous (IV) hydromorphone, IV morphine, or oral (PO) oxycodone during their postoperative hospital stay. All analgesic medications were dosed based on weight. The intraoperative protocol for pain management included a dose of IV acetaminophen (15 mg/kg). Short- or long-acting opioids such as fentanyl, morphine, or hydromorphone were also given at the discretion of the anesthesiologist. None of the patients received an infraorbital block. This pain management regimen remained unchanged with the start of the study both for intraoperative and post-anesthesia care unit (PACU). Once patients in the nonopioid group were admitted to the ward from PACU, both acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg) were administered every 6 hours, alternating the two analgesics so that every 3 hours, the patient was receiving either acetaminophen or ibuprofen. After our March 2019 protocol was implemented, eight patients received opioids during the postoperative period. Due to the nature of this retrospective study, it is unclear the indication for these patients' receiving opioids after the protocol was implemented, and these patients were therefore included in the opioid group for statistical analysis.

The use of ibuprofen in patients under 6 months of age is considered off-label use. At our institution, the use of ibuprofen for patients under 6 months of age is generally accepted. In addition to close monitoring by our teams, our pharmacists review each patient's renal function/gastrointestinal contraindication as part of their normal workflow for order verification.

The outcomes investigated were time to first feed, volume of first feed, oral morphine equivalents (OMEs) in patients who received opioids, and evaluation of pain. Intake and output for each patient are documented in the electronic health record by nursing staff both in the PACU and once the patient has been admitted to the floor. Time to first feed is determined by minutes passed from the end of the procedure until the start of first feed. Patients are encouraged to feed while still in PACU. If a patient does feed while in PACU, the time of the feed is documented and reported directly to floor nursing staff upon handoff. Nurses on the floor also document time of each feed to a 15-minute window. Volume of first feed is recorded in milliliters (mL) and documented in the intake/output section of the electronic health record during hospital stay. Both PO and IV opioid narcotics given were evaluated and reported as OME/kg, documented in the medication administration report from the patient's hospital stay and recorded in milligrams (mg). Any administration of medication used for analgesia is documented in the medication administration report. Pain levels are assessed every 4 hours and recorded based on the FLACC (Face/Legs/Activity/Cry/Consolability) scale, which was developed to help assess pain in infants who cannot verbally express level or degree of pain. Each category of the FLACC scale is rated on a scale of 0–2 (2 being severe) and combined to give a total score ranging between 0 and 10, with 10 being severe.

Statistical Methods

Descriptive statistics used to summarize data included mean and SD, or median and interquartile range (IQR). Group differences were analyzed using *t* tests and Wilcoxon rank-sum tests. *P* values less than or equal to 0.05 were considered significant. Linear regression models were used to analyze amount of opioid administered and outcome on pain scores and volume of feeds. Because length of stay (LOS) had a strongly skewed distribution, LOS was modeled as generalized linear regression models with a gamma log link. Univariate logistic regression models were used to analyze variables associated with narcotic use.

RESULTS

Demographics

Among 73 infants who underwent cleft lip repair between December 2016 and February 2021, 47 received opioids during the postoperative period for pain management and 26 received scheduled acetaminophen and ibuprofen (Table 1). All patients received their cleft lip repair by 6 months of age, except for three in the opioid group who presented late. Average LOS was 1.62 days in the opioid group and 1.33 days in the nonopioid group (P = 0.01). Three patients (6%) in the opioid group were admitted to pediatric intensive care unit postoperatively for respiratory stridor and had longer LOS. Three

Table 1. Demographics of Infants Who Underwent Surgery for Cleft Lip

	Opioid, n = 47	Nonopioid, n = 26
Mean age (mo)	4.21 (range 2–21)	3.58 (range 26)
Male	31 (66%)	18 (69%)
Female	16 (34%)	8 (31%)
Mean LOS (d)	1.62 (range 0.96–7.21)	1.33 (range 1–5.29)
Readmission	3 (5%)	0
Mean OME administered (mg/kg)		
DOS	0.24 (range 0.09–0.31)	0
POD1	0.122 (range 0–0.23)	0

patients in the opioid group (6%) visited an emergency department (ED) within 7 days of discharge. Reasons for two of the ED visits were inguinal hernia and constipation, both of which self-resolved while in the ED. A third patient was readmitted for bleeding. No patients in the nonopioid group visited the ED or were readmitted within 7 days of discharge. There were no readmissions for postoperative pain or failure to thrive in either the opioid or nonopioid group.

Pain

As summarized in Table 2, the mean FLACC score for day of surgery (DOS) did not differ significantly between the nonopioid and opioid groups [1.57 ± 1.18 versus 1.76 ± 0.94 (SD); $P = 0.46$]. However, the postoperative day (POD) 1 FLACC score was significantly lower in the nonopioid group (0.73 ± 1.05 versus 1.35 ± 1.06; $P = 0.022$).

Time to First Feed and Volume of First Feed

As shown in Table 3, median time to first PO did not differ significantly between nonopioid and opioid groups [178 min (IQR 66–411) versus 147 min (IQR 93–351); $P = 0.653$]. Median volume of first feed was twice as high for the nonopioid group and for the opioid group [90 mL (IQR 58–120) versus 45 mL (IQR 30–60); $P = 0.003$].

Dose-related Impact on Outcomes

As summarized in Table 4, for every point increase in FLACC score on DOS, the amount of opioid administered increased by 0.56 OME/kg [95% confidence interval (CI) 0.12–1.01, $P = 0.015$]. For every point increase in FLACC score on POD1, the amount of opioid administered increased by 0.11 OME/kg (95% CI –0.07 to 0.29, $P = 0.242$]. The amount of opioid administered was not a factor in volume of feeds on either DOS or POD1. For every unit increase in OME/kg given on POD1, LOS was increased by 17% (Est: 1.17, 95% CI 1.08–1.26, $P < 0.001$).

Variables Associated with Opioid Administered

Table 5 demonstrates that for each kg increase in weight, the odds of being on opioid medication increased by 52% (OR: 1.52, 95% CI 1.07–2.15, $P = 0.020$). For every 1 mL increase in PO, the odds of being on opioid medication decreased by 2% (odds ratio: 0.98, 95% CI 0.97–0.995, $P = 0.007$). For each point increase in the FLACC score on POD1, the odds of being on opioid pain medication increased by 84% (odds ratio: 1.84, 95% CI 1.07–3.18, $P = 0.028$). Unilateral versus bilateral cleft lip, complete versus incomplete cleft lip, and gender were also evaluated and were not found to have statistically significant associations with opioid medication use.

DISCUSSION

Combining opioids with local anesthetics and non-steroidal anti-inflammatory drugs (NSAIDs), with or without acetaminophen, has become an important postoperative pain management strategy in pediatric surgery.[14–17] Opioid-sparing, especially with NSAIDs, decreases the severity of opioid-related side effects.[18,19] Some trials have shown that an NSAID in combination with acetaminophen performs better than acetaminophen alone.[20,21] The addition of ibuprofen to acetaminophen reduced the need for early analgesia by 50% in children undergoing tonsillectomy.[22] Nonetheless, there has been a lack of consensus and evidence concerning the best postoperative analgesic strategy for cleft lip repair in infants. Cleft palate repair is thought to be more painful than cleft lip repair. Accordingly, pain management for cleft lip repair should involve less use of opioids than what is required to manage pain after cleft palate repair. A survey about opioid-prescribing patterns after cleft lip or palate repair, sent to members of the American Cleft Palate-Craniofacial Association in 2019/2020, found that opioid prescribing decreased over time with more operative experience, and although only half of the surgeons surveyed are prescribing opioids in the inpatient setting, all surgeons are prescribing opioids upon discharge, ranging from 1 to 3 or 4 to 7 days.[6] This study, however, was limited by a low response rate and incomplete survey responses. A study of 100 consecutive cases of primary cleft lip repair found that despite oral acetaminophen administration alone, 44% of the infants continued to have excess pain postoperatively

Table 2. Opioid and Nonopioid Pain Management for Infants Who Underwent Cleft Lip Repair

Variable		Opioid	Nonopioid	Overall	P*
DOS FLACC score	n, missing	45, 2	25, 1	70, 3	0.46
	Mean (SD)	1.76 (0.94)	1.57 (1.18)	1.70 (1.03)	
	min, max	0.0, 5.4	0.0, 4.2	0.0, 5.4	
	95% CI	1.8 (1.2, 2.2)	1.3 (0.7, 2.1)	1.7 (0.9, 2.2)	
POD1 FLACC score	n, missing	1.48, 2.05	1.08, 2.06	1.45, 1.94	
	Mean (SD)	44, 3	25, 1	69, 4	0.022
	min, max	1.35 (1.06)	0.73 (1.05)	1.13 (1.09)	
	95% CI	0.0, 4.0	0.0, 3.5	0.0, 4.0	

*t test.

Table 3. Oral Intake among Infants After Cleft Lip Repair

Variable	Opioid	Nonopioid	Overall	*P**
Time to first PO (min)				
n, missing	47, 0	26, 0	73, 0	
Median (IQR)	178.0 (66.0–411.0)	147.0 (93.0–351.0)	148.0 (68.0–391.0)	0.6532
95% CI	195.3–386.8	143.1–322.8	202.0–338.8	
First PO amount (mL)				
n, missing	43, 4	23, 3	66, 7	
Median (IQR)	45.0 (30.0–60.0)	90.0 (58.0–120.0)	60.0 (30.0–120.0)	0.0031
95% CI	41.31–66.74	68.16–108.5	54.69–77.28	

*Nonparametric Wilcoxon rank-sum tests.

Table 4. Regression Analysis for Variables Affected by Volume of Opioid Administration

Variables	Estimate	95% CI	*P**
FLACC			
DOS	0.56	0.12–1.01	0.015
POD1	0.11	−0.07 to 0.29	0.242
Volume of feed			
DOS	5.06	−3.73 to 13.85	0.252
POD1	−1.65	−8.80 to 5.50	0.644
LOS			
DOS	0.99	0.91–1.08	0.807
POD1	1.17	1.08–1.26	<0.0001

*Linear regression models; LOS analyzed using generalized linear regression with a gamma log link.

Table 5. Regression Analysis for Variables Associated with Opioid Administration

Variables	Odds Ratio	95% CI	*P**
Unilateral versus bilateral cleft lip	1.49	0.42–5.31	0.542
Complete versus incomplete cleft lip	0.39	0.14–1.05	0.062
Weight (kg)	1.52	1.07–2.15	0.020
Gender (M versus F)	0.86	0.31–2.41	0.776
Mean FLACC score			
DOS	1.21	0.74–1.99	0.453
POD1	1.84	1.07–3.18	0.028
Volume of first feed (mL)	0.98	0.97–0.995	0.007

*Univariate logistic regression models.

that required morphine administration.[4] Finally, in a study that compared infants who received either bupivacaine (without epinephrine) or saline bilateral extraoral infraorbital nerve blocks at the end of the operation, infants who received bupivacaine nerve blocks had lower FLACC scores in recovery and required less paracetamol administration postoperatively.[23] These previous studies continue to reinforce that no singular medication is able to effectively manage patients after cleft lip repair and rather, the focus should be on multimodal pain control. Furthering this idea, our study shows that nonopioid postoperative pain management using both scheduled acetaminophen and ibuprofen was more effective than opioids for pain management in infants after cleft lip repair, as evidenced by FLACC score on POD1.

Besides pain, another major criterion for discharge after cleft lip repair is sufficient oral intake postoperatively.[3,4] Studies have demonstrated that immediate feeding is safe following cleft lip and palate surgery,[24,25] but opioid use can influence an infant's ability to feed and therefore affect overall recovery. In a study of factors that affected length of hospital stay after primary cleft lip repair, decreased LOS correlated with higher acetaminophen dosage on the floor and the volume of postoperative intake.[4] In that study, although most infants could take oral fluids within a few hours after the procedure, their intake was not sufficient to discontinue IV fluids.[4] Another study demonstrated that adequate feeding is vital to postoperative recovery as some degree of weight loss is expected after cleft lip repair in infants, finding that it takes a median of 14.08 days (IQR 7.6) to recover their preoperative weight.[26] Not only is adequate oral intake important to regain weight lost during the postoperative period but also poor oral feeding can result in dehydration, poor wound healing, and inadequate nutrition necessary for patient recovery after surgery. Infants in our study who did not receive opioids postoperatively on average doubled the volume of oral intake during the first feed as compared to infants in our study who received opioids. All infants were allowed to feed immediately after surgery. Although time to first feed did not differ significantly between our two groups, the increased amount of PO taken in by our nonopioid group further demonstrated improved postoperative course with nonopioid use. We attribute the increased intake to the decreased side effect of sedation, as normally seen with opioids.

Another important aspect of decreasing opioid use in infants who undergo cleft lip procedures is the potential for long-term neurocognitive effects in a patient population that is otherwise not able to communicate pain. Studies that have evaluated cumulative opioid use and neurocognitive development are limited and inconsistent. For example, a retrospective evaluation of the relationship between opioid exposure and neurodevelopment outcome in extremely low birth weight infants at 20 months found a potential association between cumulative opioid dose and decreasing cognitive scores.[27] However, in infants who underwent cardiac surgery at younger than 6 weeks of age and received sedatives and opioids pre-, intra-, and postoperatively, sedation and analgesia were not associated with mental, motor, or vocabulary delays at 18–24 months of age.[28] A UK study that assessed children who as preterm infants (<34 weeks gestation) had received either morphine or nonmorphine treatment for assistance with mechanical ventilation found no significant difference in IQ, behavior, and

motor development between children when reassessed at 5–6 years of age, although children who received morphine as infants had slightly better performance in intelligence, motor development, and behavior tests.[29] By eliminating the use of opioids after cleft lip repair in infants, our study is decreasing the potential for long-term neurocognitive effects while improving pain control and increasing the volume of initial feed after surgery. With the literature being inconsistent, the possibility of potential adverse effects of cumulative opioid use is important to keep in mind and aim to negate whenever possible.

This study has some important limitations. First, its retrospective design makes our results and conclusions less reliable than if it were a prospective study. Second, we were unable to control for oral intake in breastfed infants. Although parents felt their breastfed infants were taking in adequate breastmilk at discharge, our inability to quantify that intake led us to omit these patients from our statistical analysis. Last, we had a smaller number of patients in the nonopioid group, which is a disparity from our opioid group. This is attributed to the fact that we started our opioid-free regimen in March 2019. The smaller number of patients in the nonopioid group could limit the power of the study. However, all 73 infants included in the study were consecutive, which is a strength to the study.

This study has highlighted the impact of opioid-free pain management in treating postoperative acute pain in cleft lip infants by looking at metrics of recovery. The culture of nonopioid postoperative pain management in this patient population has changed dramatically from the results of this study at our institution. At our institution, we provide educational lectures to our PACU nursing staff and have a pain resource nurse on our general floors who helps educate nursing staff on appropriate pain medication usage. This multidisciplinary team approach is critical to minimize overtreating pain in this patient population.

CONCLUSIONS

Our study aimed specifically to compare opioid and nonopioid pain management after cleft lip repair and the impact on pain and feeding. Scheduled use of acetaminophen and ibuprofen not only improved pain control in infants after cleft lip repair but also eliminated the need to give opioids, including on discharge. Nonopioid pain management also improved overall recovery with increased volume of initial feed after surgery. Eliminating the use of opioids after cleft lip repair helps decrease the potential for long-term neurocognitive effects.

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DISCLOSURE

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

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