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Is the Use of Opioids Safe after Primary Cleft Palate Repair? A Systematic Review

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Background: Pharmacologic treatment of postoperative pain after cleft palate repair includes opioids and nonopioid analgesics, nerve blocks, and local anesthetic infiltration. Use of opioids in infants has concerns regarding sedation, risk of aspiration, respiratory depression, and respiratory distress. The main objective of this review was to analyze information available on the safety of the use of opioids during perioperative management of pain related to primary cleft palate repair in published studies.

Methods: A systematic review of the literature for studies published until March 2020 was performed to evaluate the safety of opioid drugs during primary cleft palate repair pain management. The authors chose the following MesH terms for this systematic review: cleft lip and palate AND opioids AND pain management. The investigators performed a systematic literature search using the Pubmed/MEDLINE, Embase, Web of Science, and Cochrane Library databases.

Results: After a literature search resulting in 70 identified studies, 9 were qualified for the final analysis, which included 772 patients. There was a high level of evidence in the selected studies according to the Oxford CEBM Level of Evidence classification and GRADE scale. The most common adverse event reported was postoperative nausea and vomiting (from 5% to 25%). Episodes of oxygen desaturation have been reported from 2.5% to 7.4% of the studied patients.

Conclusions: Definitive conclusions about the safety of opioid drugs during primary cleft palate repair pain management cannot be drawn. Vomiting and oxygen desaturation have been associated with the use of opioids in the studied population.
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INTRODUCTION

Cleft lip and palate is a common birth defect that occurs in approximately 1 in every 700 live births, and requires surgical repair at an early age.[1] Repair of a primary cleft lip and palate defect can improve breathing, hearing, facial appearance, and speech development. Although these surgeries can be beneficial to patients, they can also be painful. Furthermore, inadequate treatment of postoperative pain poses an immediate burden to patients and may result in the onset of postoperative complications (eg, bleeding).

Based on the Declaration of Montreal, around 80% of the global population is affected by inadequate pain management.[2] Postoperative pain management in children is a critical issue that is frequently underestimated. Recent studies show that pediatric postoperative pain management is not well addressed, and children may experience severe pain as a result.[3] The objective of postoperative pain management is to reduce or eliminate pain and discomfort with minimal adverse events. Pharmacologic treatment is often used to address postoperative pain after cleft lip and palate repair. Commonly used pharmacologic treatments include opioids, nonopioid analgesics, nerve blocks, and local anesthetic infiltration. However, opioid use in infants raises concerns regarding sedation, risk of aspiration, and respiratory depression and distress (Fig. 1).

Furthermore, approximately 12% of cleft lip and palate repairs are associated with postoperative respiratory complications.[4] This is largely attributed to the fact that children at an early age are susceptible to opioid-induced

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respiratory depression that occurs due to the immaturity of hepatic glucuronidation, in addition to the altered hepatic blood flow that occurs during periods of acute illness, which ultimately shunts blood away from the liver.[5,6] In a pediatric population, any adverse event could be translated into a major medical issue; therefore, opioids should be cautiously prescribed and administered. In this study, we performed a systematic review to evaluate the safety of opioid use to manage postoperative pain following a primary cleft palate repair.

MATERIAL AND METHODS

We conducted a systematic review of the literature based on a protocol developed following the guidelines outlined in the PRISMA-P statement and registered in PROSPERO (CRD42020177537). The research question of interest was: Is it safe to use opioids to manage postoperative pain following a primary cleft palate repair? Library databases, such as PubMed, Embase, Web of Science, and Cochrane, were electronically searched by 4 of the authors up to March 31, 2020 to identify eligible studies.

The medical subject headings (MeSH) used to search for eligible studies included the following combinations: Cleft lip and palate AND opioids AND pain management. The eligibility criteria were based on the PICOS framework: *P*articipants: Children born with nonsyndromic cleft lip and palate; *I*ntervention: Intra or postoperative use of opioids for cleft lip and palate surgery pain management; *C*omparison: Pain management using nonopioids drugs; *O*utcomes: Adverse effects related to opioid use; *S*tudy design: Any prospective and retrospective follow-up, cohort studies, case series, and randomized control studies related to the use of opioids during cleft lip and palate surgery pain management, animal studies, systematic (and nonsystematic) reviews, and meta-analyses were excluded.

During the search process, titles were screened first to exclude nonpertinent studies, then abstracts were evaluated to exclude studies based on the aforementioned eligibility criteria. After reviewing the full-text of eligible studies, 9 articles were selected. An assessment of study quality was performed independently by the same authors who performed the search. The assessment was done according to the Oxford CEBM Level of Evidence classification and GRADE scale. Any disagreements regarding the eligibility of a study were resolved by consensus or by an independent reviewer. The included studies were restricted to those in English. No ethical approval was required for this systematic review.

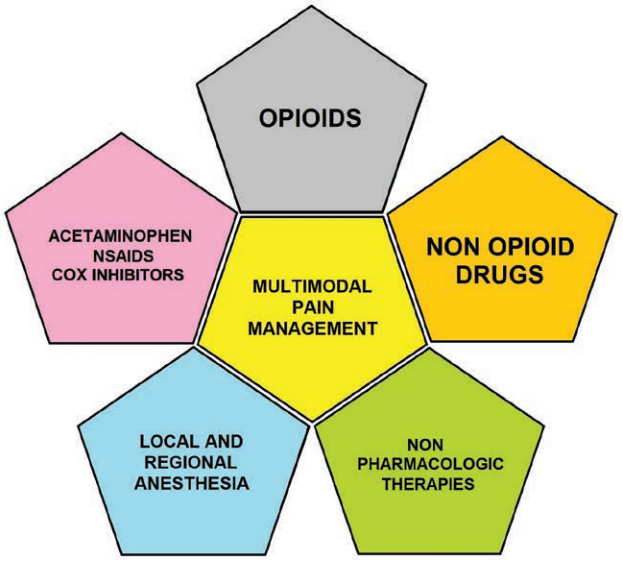

Fig. 1. Multimodal analgesia.

RESULTS

A flowchart representing the literature search and selection process is presented in Figure 2. Initially, a total of 70 eligible studies were identified; however, 63 were excluded according to the exclusion criteria (Figs. 2 and 3). Additionally, 2 more articles were included following a suggestion by 1 of the reviewers. Finally, 9 full-text studies, which included data derived from 772 patients, were included in the systematic review.[7–15] The qualification of these 9 papers were sorted by the issue they addressed and are presented in Tables 1 and 2.

A GRADE scale was applied to assess the qualification of these studies. In this study, the GRADE scale was A (High: several high-quality studies with consistent results). There was also a high level of evidence in the selected studies that was assessed according to the Oxford CEBM Level of Evidence classification and GRADE scale.

Six of the 9 articles were prospective randomized clinical trials that reported multimodal management of postoperative pain in cleft lip and palate patients, and used opioids to manage postoperative pain.[7,8,11–13,15] These clinical trials reported a high statistical power in their studies (>80%) and included a total number of 321 patients. These studies evaluated the effect of multimodal analgesia by reducing the use of opioids that have been demonstrated to be efficacious in pain management. However, in these studies, the safety of opioid use in patients who underwent a cleft lip and palate repair was not well addressed. Three of the 9 studies were observational studies (cross-sectional), and only evaluated the therapeutic effect and safety of drugs.

DISCUSSION

Cleft lip and palate is the most common congenital disease of the head and neck, and requires early surgical repair to reduce phonation, feeding difficulties, and complications (eg, respiratory tract infections). Specifically, patients with bleeding and airway obstruction, particularly after cleft palate repair, should be considered for postoperative pain management. Other respiratory complications associated with cleft palate surgery include airway, spasm, and epiglotic edema.

Repair of a cleft lip and palate is painful, and high doses of intravenous opioids are commonly used for pain management.[16,17] Cleft palate repair may lead to postoperative hypoxemia due to a reduction in airflow. Moreover, according to Takemura et al, there is also an increased

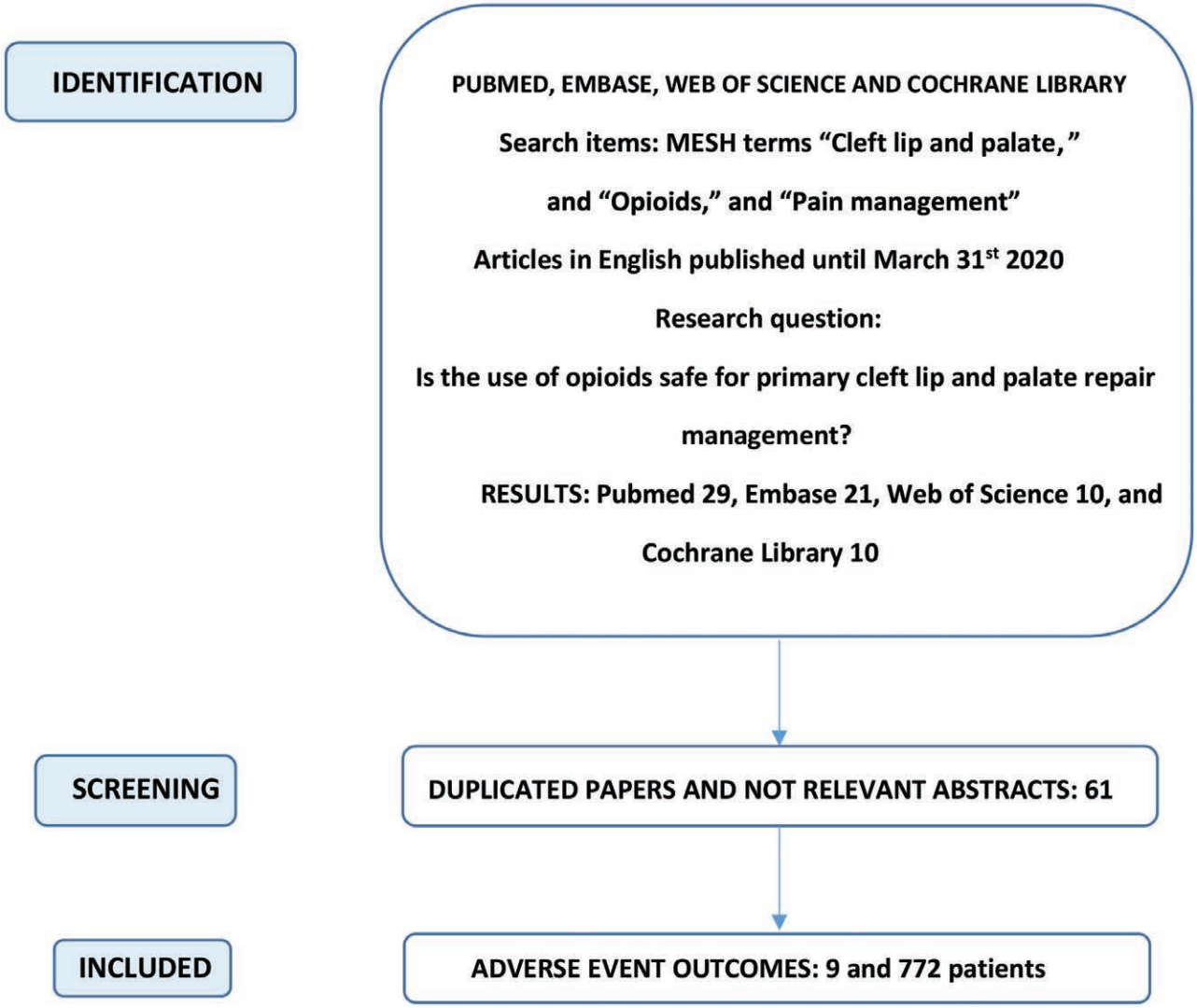

Fig. 2. Flow diagram of studies' selection according to PRISMA guidelines.

risk of obstruction in patients treated with opioids.[18] Multimodal pain management has successfully reduced postoperative pain and opioid-related adverse events, such as sedation, dizziness, nausea, vomiting, constipation, respiratory depression, immunosuppression, physical dependence, and death.[19–23]

However, pain management after cleft palate repair is further complicated by the association between a difficult airway and undesirable respiratory events. The risk of respiratory depression and airway obstruction may be increased following cleft lip and palate repair, which requires continuous postoperative monitoring during the initial 24 hour period. Notably, the use of opioids to manage pain may increase these risks.[19–23] Conversely, 16 clinical trials revised by Whittaker in 2013 involving a pediatric population indicated a low rate of opioid-associated respiratory depression and no deaths. However, these clinical trials did not include cleft palate patients.[24]

Furthermore, there are several reasons why the main objective of multimodal analgesia is to reduce the opioid dosage provided to patients. Nonsteroidal anti-inflammatory drugs are effective when used in combination with a nerve block and opioids, and their opioid-sparing effect is 30%–40%.[25] However, nonsteroidal anti-inflammatory drugs are not recommended for use in children younger than 6 months due to the heightened risk of pulmonary hypertension, renal dysfunction, and altered hemostasis.[26,27]

Acetaminophen has fewer adverse events compared with nonsteroidal anti-inflammatory drugs and is used in combination with nerve blocks to decrease opioid requirements. A randomized clinical trial published by Nour et al concluded that intravenous administration of acetaminophen decreased the opioid requirement after primary cleft palate repair.[12] As such, acetaminophen is an effective opioid-sparing analgesic that can be used in children who have undergone repair of a primary cleft palate.

Nerve blocks are a safe and effective alternative to opioids to manage postoperative pain following cleft lip and palate surgery and to reduce opioid requirements.

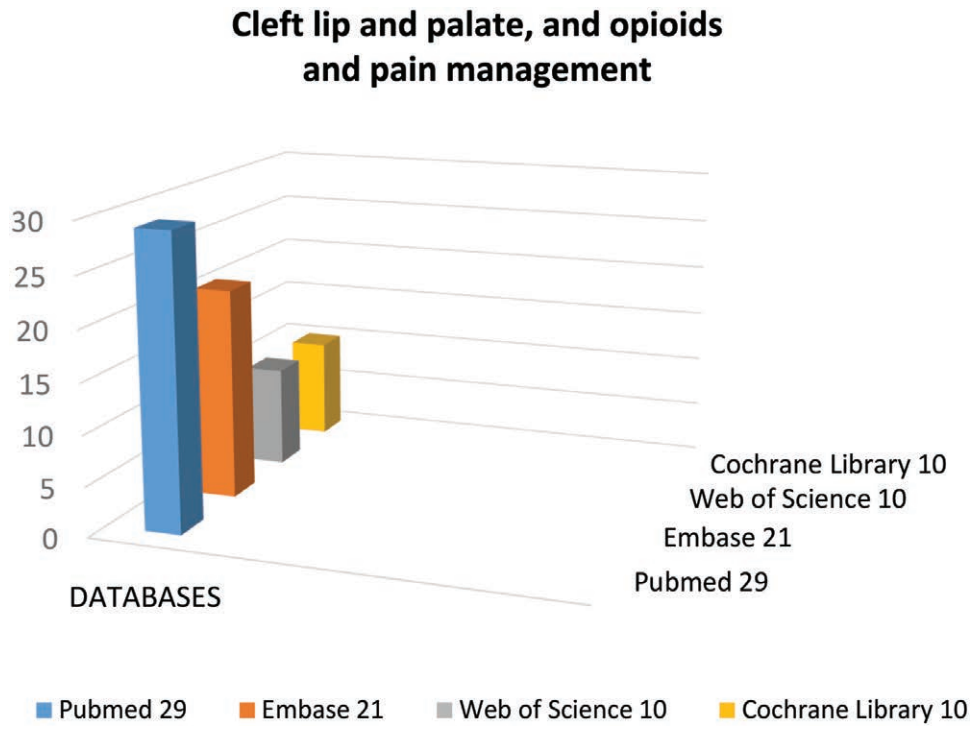

Fig. 3. Result of searches on "cleft lip and palate," "opioids," and "pain management."

Table 1. Selected Articles according to Inclusion Criteria Used for Data Extraction to Evaluate the Safety of Use of Opioids for Pain Management in Cleft Lip and Palate Repair (Articles 1–4)

Study	Sample Size/Treatment	Design	Evidence Level	Results
Echaniz et al[7]	34 CP patients randomized in 2 groups comparing 2 techniques of nerve block based on opioid dose reduction, and respiration-related complications. Fentanyl (50–100 μg/kg) and nalbuphine (50 μg/kg) were used as rescue analgesia.	RCT	1b	Bilateral suprazygomatic nerve block group required fewer doses of opioids in comparison with infraorbital nerve block. No differences were observed regarding adverse events between groups. One patient (5%) had postoperative nausea and vomiting. One patient (7.1%) had SpO_2 below 95%.
Mostafa et al[8]	Two groups of 30 CP patients were compared receiving 2 different local anesthetics in combination with general anesthesia. Outcomes were measured regarding the amount of opioid (nalbuphine) as rescue analgesia (18 and 17.1 mg totally used in each group).	RCT	1b	Lower incidence of complications were observed using levobupivacaine in comparison with bupivacaine. Required rescue analgesia using opiods was not different between groups. No prolonged sedation was observed and 2 cases of vomiting (6.6%) were observed in the studied group.
Day et al[9]	27 CP patients received liposomal bupivacaine for postoperative pain control. Hydroxicodone was used as rescue analgesia in these patients (0.46 mg/kg per dose, 8.5 mg).	Retrospective cross-sectional study	4	Liposomal bupivacaine can yield low postoperative opioid use (hydroxicodone). Opioid-related adverse events were emesis in 7.4% and pruritus in 3.7%.
Bunsangjaroen et al[10]	334 CP patients received general anesthesia in association with opioid drugs (fentanyl) (22.52 mcg/kg).	Retrospective cross-sectional study	4	9% of CP surgeries observed postoperative vomiting A statistical significant association between use of fentanyl and postoperative desaturation was observed (OR: 1.2). Seven patients (10.87 %) had postoperative nausea or vomiting. Three patients were reintubated (1.39 %) and 3 patients had postoperative bleeding (4.31 %).

CP: Cleft Palate.

Infraorbital, external nasal, and suprazygomatic nerve blocks have been used for pain management in these patients, and have resulted in good efficacy and low rates of adverse events.[7,8,11]

Different systematic reviews and meta-analyses have evaluated the analgesic impact of opioids versus opioid-free anesthesia in noncleft surgery; based on high-quality evidence, the pain scores were equivalent in both opioid

Table 2. Selected Articles, according to Inclusion Criteria Used for Data Extraction to Evaluate the Safety of Use of Opioids for Pain Management in Cleft Lip and Palate Repair (Articles 5–9)

Study	Sample Size/Treatment	Design	Evidence Level	Results
Chiono et al[11]	Two groups of 30 CP patients received 2 different protocols of pain management and compared based on morphine requirements for rescue analgesia (Max. 0.25 mg/kg).	RCT	1b	Supramaxillary nerve block in combination with general anesthesia reduces total consumption of morphine after cleft palate repair. Five patients had postoperative nausea and vomiting. (8.33%). Three patients (5%) presented an episode of oxygen desaturation requiring oxygen therapy.
Nour et al[12]	Three groups of CP 16 patients received acetaminophen or placebo and compared based on the need for opioid administration for rescue analgesia.	RCT	1b	Fewer morphine doses were required using oral or intravenous acetaminophen in comparison with the control group. No episodes of respiratory depression or other opioid-related adverse events were documented.
Milic et al[13]	Two groups of CLP patients (76 versus 64) were operated on using sevoflurane-fentanyl or midazolam-fentanyl and compared based on adverse events occurrence. Dose: (0.001 mg/kg).	RCT	1b	Different adverse events were evaluated, and midazolam-based anesthesia is safer than sevoflurane-based anesthesia regarding occurrence of emergence agitation. Five patients (3.6%) had postoperative nausea and vomiting.
Choi et al[14]	Thirty consecutive CP patients were operated on and received fentanyl as rescue therapy for postoperatory pain management using a continuous intravenous catheter (0.1/μg/kg/h). Pain was evaluated through the Wong-Baker scale and parent-controlled analgesia.	Prospective. Cross-sectional study	4	The observed effective dose (0.66 μg/kg/h) and most of bolus injections were administer only during the first postoperative day. Three patients (25%) who are managed with fentanyl had vomiting on the day of surgery. None of the patients was apneic or over sedated.
Steinmetz et al[15] .	Two groups of CLP patients (17 versus 22) were operated on using remifentanil-propofol or sevoflurane and compared based on hemodynamic differences and postop morphine doses (total amount: 4–4.5 mg).	RCT	1b	The remifentanil-propofol group was associated with higher blood pressure and lower heart rate in comparison with sevoflurane group. None of the children had signs of respiratory depression and nausea or vomiting were not reported.

CLP, Cleft Lip and Palate; CP, Cleft Palate.

and opioid-free groups.[28–30] In addition, the rates of postoperative nausea and vomiting were significantly reduced in the opioid-free group. This complication should be considered in patients with cleft lip and palate due to their increased rate of aspiration.

All the selected studies in this systematic review included patients with cleft palates. The main outcome of all the studies included in our review was to evaluate the effectiveness of 2 multimodal analgesia methods that aimed to reduce opioid use. In addition, these studies assessed opioid-related adverse events. The main limitation related to these publications is the sparse information regarding adverse events associated with the medications administered to patients for pain management. Studies in cleft lip and palate patients reported significant rates of postoperative nausea and vomiting and oxygen desaturation (Tables 1 and 2). The most commonly reported adverse event related to opioid use was postoperative nausea and vomiting (range 5%–25%). Episodes of oxygen desaturation were reported to affect 2.5%–7.4% of patients, and 2 studies did not observe any adverse events in their study population.[12,15] Vomiting is associated with complications resulting from a cleft palate surgery, such as bleeding and aspiration.[18] Only 1 study reported bleeding after palatoplasty (3 patients, 4.3%). In this same study, aspiration was not reported. Bleeding is the most commonly observed complication associated with cleft palate surgery (~6% in a study published by the author), and is also associated with aspiration.[31]

Six studies included in this systematic review were randomized clinical trials, but most of them involved a small population of patients, which may compromise their statistical power conclusions. Three of the included publications were observational cross-sectional studies that only evaluated associations between the analgesics used and the reported adverse events. Further studies, such as randomized controlled trials with a high statistical power, are warranted to answer our research question of interest and verify the conclusions of this review.

Currently, the available scientific evidence is not sufficient to demonstrate the safety of opioid use in this population because adverse events were not well addressed in the included studies. This study provides scientific evidence that highlights the need for quality improvement in managing postoperative pain in cleft lip and palate patients to reduce the onset of adverse events associated with opioid use.

CONCLUSIONS

Based on the available scientific evidence, vomiting and oxygen desaturation are associated with opioid use in

the studied population. Currently, definitive conclusions regarding the safety of opioid drugs to manage postoperative pain following primary cleft palate repair cannot be made. To evaluate the safety of opioids and their associated adverse events, randomized clinical trials are required to compare opioid-free versus opioid pain management following cleft palate repair.

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