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Perioperative pain management for cleft palate surgery: a systematic review and procedure-specific postoperative pain management (PROSPECT) recommendations

Nergis Nina Suleiman,¹ Markus M Luedi,^{2,3} Girish Joshi,⁴ Geertrui Dewinter,⁵ Christopher L Wu ,⁶ Axel R Sauter ,⁷ on behalf of the PROSPECT Working Group

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For numbered affiliations see end of article.

Correspondence to

Dr Axel R Sauter, Department of Anaesthesia and Intensive Care Medicine, Oslo University Hospital, Oslo, Norway; axsa@online.no

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ABSTRACT

Background/importance Cleft palate surgery is associated with significant postoperative pain. Effective pain control can decrease stress and agitation in children undergoing cleft palate surgery and improve surgical outcomes. However, limited evidence often results in inadequate pain control after cleft palate surgery.

Objectives The aim of this review was to evaluate the available evidence and to develop recommendations for optimal pain management after cleft palate surgery using procedure-specific postoperative pain management (PROSPECT) methodology.

Evidence review MEDLINE, Embase, and Cochrane Databases were searched for randomized controlled trials and systematic reviews assessing pain in children undergoing cleft palate repair published in English language from July 2002, through August 2023.

Findings Of 1048 identified studies, 19 randomized controlled trials and 4 systematic reviews met the inclusion criteria. Interventions that improved postoperative pain, and are recommended, include suprazygomatic maxillary nerve block or palatal nerve block (if maxillary nerve block cannot be performed). Addition of dexmedetomidine to local anesthetic for suprazygomatic maxillary nerve block or, alternatively, as intravenous administration perioperatively is recommended. These interventions should be combined with a basic analgesic regimen including acetaminophen and nonsteroidal anti-inflammatory drugs. Of note, pre-precisional local anesthetic infiltration and dexamethasone were administered as a routine in several studies, however, because of limited procedure-specific evidence their contribution to pain relief after cleft palate surgery remains unknown.

Conclusion The present review identified an evidence-based analgesic regimen for cleft palate surgery in pediatric patients.

PROSPERO registration number CRD42022364788.

INTRODUCTION

With reported incidences of 1 to 25 in 10 000 live births, cleft palate is among the most frequent congenital birth defects.^{1,2} The focus of cleft palate surgery is to improve functional impairments such as speech, hearing, and dentition.³ Furthermore, a significant improvement in the psychosocial development of the treated children can be achieved.⁴

Adequate pain relief is key for successful surgical correction of cleft palate. Agitated and crying children are more likely to experience wound dehiscence and develop fistulas. Hence, adequate postoperative pain relief should improve surgical outcomes including a decrease in postoperative opioid consumption, time to first postoperative feeding, and length of hospital stay.⁵ However, postoperative pain is often inadequately treated because it is difficult to assess in the pediatric cohort. Also, the evidence pertaining to appropriate postoperative analgesia is sparse, and specific recommendations are lacking. We hypothesized that multimodal perioperative analgesia impacts postoperative pain in cleft palate surgery patients.

To develop evidence-based procedure-specific pain management recommendations, a collaboration of anesthetists and surgeons has established a Working Group–PROcedure-SPECific postoperative pain management (PROSPECT).^{6,7} The recommendations are made based on randomized controlled trials (RCTs), systematic reviews, and meta-analyses. The methodology includes a Delphi process that takes clinical practice, efficacy, and adverse effects of each potential analgesic technique into consideration.⁶

This systematic review aims to assess the available literature on the effects of analgesics and anesthetics on pain after surgical correction of congenital cleft palate. Secondary outcomes, including rescue analgesics, the time to recovery, and adverse effects, were addressed when reported, and the limitations of the data were reviewed. The intent was to develop evidence-based recommendations for management of pain accompanying surgical correction of congenital cleft palates.

METHODS

The search and review strategy were followed as defined by the PROSPECT methods.⁶ The study was prospectively registered in PROSPERO (CRD42022364788). In line with the standards of the PROSPECT group, five electronic databases (PubMed, Embase, Ovid MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials) were searched using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)⁸ search protocols to identify RCTs published in the English



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RECOMMENDATIONS

- ⇒ Basic analgesic regimen should include acetaminophen and nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-specific inhibitors administered preoperatively or intraoperatively and continued postoperatively administered as scheduled (round-the-clock) dosing.
- ⇒ Pre-incisional suprazygomatic maxillary nerve block is recommended, and if that cannot be performed, pre-incisional palatal nerve block should be administered.
- ⇒ Dexmedetomidine is recommended as an additive to local anesthetic for suprazygomatic maxillary nerve block. Alternatively, intravenous dexmedetomidine may be administered if not used as an additive for the block.
- ⇒ Opioids should be reserved as rescue analgesia in the postoperative period.

WHY WAS THIS GUIDELINE DEVELOPED?

- ⇒ Cleft palate surgery is associated with significant postoperative pain. Effective pain control can decrease stress and agitation in children undergoing cleft palate surgery and improve surgical outcomes. We aim to provide clinicians with evidence-based recommendations for optimal pain management for cleft palate surgery.

ARE THERE GUIDELINES AVAILABLE ON THIS TOPIC?

- ⇒ Systematic reviews and meta-analyses assessing analgesic interventions for cleft palate surgery have been published. However, there are no comprehensive guidelines published specifically for cleft palate surgery. Next, the published systematic reviews/meta-analyses on postoperative analgesia for cleft palate surgery do not critically evaluate available evidence similar to the PROSPECT approach.

HOW DOES THIS GUIDELINE DIFFER FROM OTHER GUIDELINES?

- ⇒ These systematic review-based recommendations were conducted according to the PROSPECT methodology. Thereby, the included studies are critically assessed and interpreted in consideration of clinical relevance, effectiveness, the use of basic analgesia, adverse effects, and the invasiveness of each analgesic technique in an interdisciplinary fashion by surgeons and anesthesiologists.

language from July 2002 through August 2023. We used a search string with a sequence of Medical Subject Heading (MeSH) terms, text words, and word variants related to perioperative analgesia in cleft palate surgery (online supplemental table 1).

As defined by the PROSPECT methodology,⁶ two authors (NNS and MML) working independently conducted the literature search, screening, and exclusion of irrelevant articles. The reference lists of retrieved reviews, systematic reviews, and meta-analyses were hand searched for additional relevant studies. After a comparison of the initial screening results, disagreements were resolved by consensus between the reviewing authors. In the case of discrepancies, a third reviewer (AS) made the final decision, a standard process used for systematic reviews.⁹

Only studies of pediatric populations (population under 18 years) were included. Articles reporting combined data from patients undergoing mixed surgical procedures were only included if data specific for cleft palate surgery were available for extraction. In addition, only studies stating pain intensities

were considered. Observational and behavioral assessment tools that are typically used in a pediatric population, as well as Visual Analog Scales (VAS) or Numerical Rating Scales (NRS) were considered. The criteria are summarized in online supplemental table 2 according to the Patient Intervention Comparison Outcome system as defined by PROSPECT.¹⁰

The primary outcome analyzed was postoperative pain intensity. A difference of more than 10% (ie, 10 mm on a 100 mm VAS) was considered clinically relevant.¹¹ Secondary objectives included postoperative analgesic consumption, available basic analgesia, time to first analgesic consumption, the effect on the incidence of postoperative nausea and vomiting, the impact on the time to return to normal activities, length of hospital stay, the duration of operation, the duration of anesthesia, and postoperative complications. We defined adequate basic analgesia as any routinely given nonopioid analgesics (eg, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs), or cyclooxygenase (COX)-2-specific inhibitors).

A meta-analysis was not performed because of significant heterogeneity of the evidence. The literature search results were presented and discussed initially within the subgroup and the draft recommendations were developed according to the PROSPECT methodology.⁶ Briefly, the validity of each intervention investigated in the included studies was assessed based on the quality of the studies (risk of bias analyses), and the presence of basic analgesic treatment as well as the risks and benefits of each analgesic technique were considered while developing the final recommendations. The proposal of all recommendations and the underlying literature/summary of results from each study was subsequently submitted to the entire PROSPECT Working Group, followed by face-to-face round-table discussions and an exchange of expert opinions using the Delphi technique.¹² Once a consensus was reached, the lead authors drafted the manuscript, which then required a decision on final approval from the entire Working Group.

RESULTS

A total of 1148 records were identified. After removal of duplicates and publications not fulfilling the inclusion criteria, 23 studies were selected for quality analysis (figure 1). Nineteen studies were RCTs involving 1238 patients; four studies were systematic reviews and meta-analyses. The characteristics of the included RCTs are shown in online supplemental table 3 and online supplemental table 4; and the risk of bias analysis is summarized in online supplemental table 5.

Suprazygomatic maxillary nerve block

Two studies assessed the analgesic effects of suprazygomatic maxillary nerve blocks.^{13 14} Abu Elyazed and Mostafa¹³ compared ultrasound-guided maxillary nerve blocks with palatal blocks against a control group without nerve blocks. Maxillary nerve blocks showed a clinically significant decrease in postoperative pain during the first 12 hours and reduced cumulative meperidine consumption for 24 hours. Pain scores of palatal block patients were not significantly different from maxillary nerve block patients; however, opioid consumption was higher. Placebo-controlled landmark-guided suprazygomatic maxillary nerve blocks were compared with saline injections by Chiono *et al.*¹⁴ Morphine consumption over a 48-hour period was clinically and statistically reduced in the active treatment group. No significant reduction was found for postoperative pain scores. Mild adverse events including temporary bleeding at the puncture sites or spontaneously resolving hematoma were reported in

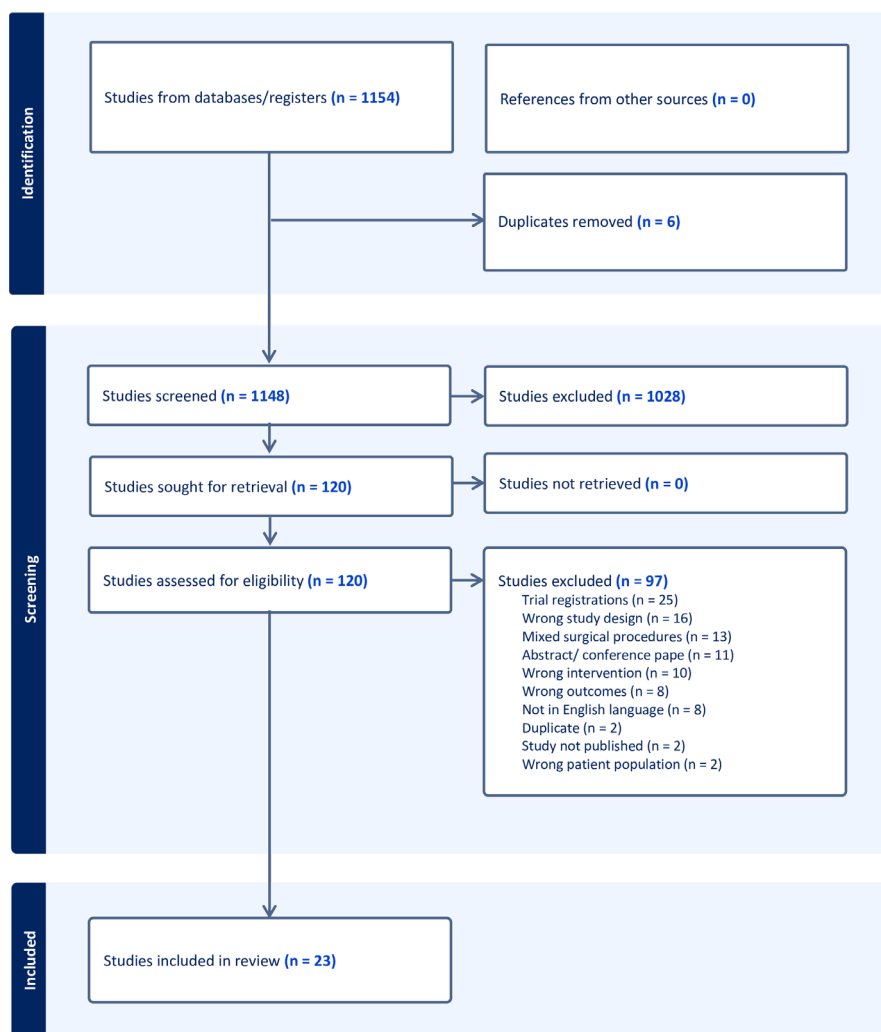


Figure 1 Flow diagram of studies identified, screened, and included in this systematic review.

the two maxillary block studies.^{13 14} Intravenous acetaminophen was administered in both studies, however, NSAIDs or COX-2-specific inhibitors were not administered.

Palatal nerve blocks

Palatal nerve blocks were studied in three RCTs.^{13 15 16} As described above, Abu Elyazed and Mostafa¹³ found palatal blocks provided clinically relevant reduction of pain scores compared with a control group but was inferior to suprazygomatic maxillary block. One of the 30 patients treated with palatal blocks experienced a spontaneously resolving hematoma after palatal nerve block. Jonnavithula *et al*¹⁵ allocated patients into three groups in which no block, a palatal block with saline, or a palatal block with 0.5 mL bupivacaine 0.25% was applied. Patients receiving a palatal block with bupivacaine had clinically significant lower pain scores and reduced ibuprofen consumption compared with patients in the two control groups. Greater palatal nerve blocks were compared with an intraoperative intravenous injection of 1 mg/kg meperidine by Kamath and colleagues.¹⁶ For greater palatal nerve block, 1 mL bupivacaine 0.25% was applied on each side. Compared with intravenous meperidine, patients receiving palatal block had significantly lower pain scores and needed significantly less rescue analgesics during a 10-hour postoperative period. Among the three studies on palatal nerve blocks, only Abu Elyazed and Mostafa reported

the use of acetaminophen, IV. However, none of the studies administered NSAIDs or COX-2-specific inhibitors.

Sphenopalatine ganglion block

Parameswaran and colleagues¹⁷ assessed sphenopalatine ganglion blocks with a transoral approach using 1 mL ropivacaine 0.75% as a standard dose. Patients receiving sphenopalatine ganglion blocks had a longer postsurgical pain-free period, but no significant differences were found for pain scores compared with the patients in the control group that did not receive sphenopalatine ganglion blocks. Postoperative rescue analgesic consumption was not reported, and the use of basic analgesia was not mentioned.

Systematic reviews of regional anesthetic techniques

Four systematic reviews addressed the use of regional anesthetic techniques for patients undergoing palatal repair surgery. An updated systematic review from 2018 on regional anesthesia in pediatric surgery was conducted by Kendall and colleagues.¹⁸ For cleft palate repair, only the study of Chiono *et al*¹⁴ on suprazygomatic maxillary blocks was included. The authors concluded that additional confirmation was needed to reinforce the use of regional anesthesia techniques for cleft palate repair.¹⁸ In their systematic review, which included 17 randomized and 10 non-randomized controlled studies on cleft palate surgery, Morzycki

and colleagues¹⁹ found that palatine block provided the greatest latency to first analgesia compared with other block techniques and other analgesic interventions after cleft palate surgery. Pain scores were not assessed. Pfaff *et al*²⁰ included 12 studies in their systematic review on perioperative pain management for palate cleft repair. The authors recommend the use of nerve blocks as part of nonopioid-based multimodal therapy but did not indicate a preference for a specific technique. Studies using maxillary nerve, sphenopalatine ganglion, and greater or lesser palatine nerve blocks had been reviewed by the authors. One study on palatal blocks and one study on sphenopalatine ganglion blocks were included in a meta-analysis showing an increased time to analgesic after palate repair when blocks were used.^{15–17} Oberhofer and colleagues²¹ included 10 prospective and retrospective trials in their systematic review. Based on the reduction of postoperative pain scores and opioid consumption, the authors recommend the use of intraoperative nerve blocks for cleft palate repair and consider suprazygomatic maxillary nerve blocks with combined bupivacaine and dexmedetomidine to be the preferred modality.

Dexmedetomidine as adjuvant for peripheral nerve blocks

The effect of dexmedetomidine as an adjuvant to bupivacaine for suprazygomatic maxillary nerve blocks was compared with blocks with bupivacaine alone in three RCTs.^{22–24} Mansour and Abdelghany²² investigated the effect of 0.5 mcg/kg dexmedetomidine as an adjuvant to bupivacaine 0.25% for maxillary nerve blocks. While postoperative pain was comparable to the control group during the first 6 postoperative hours, a clinically significant reduction in pain scores was found between 8 and 24 hours postoperatively in the dexmedetomidine group compared with bupivacaine alone. Total opioid consumption was also significantly reduced in blocks with dexmedetomidine. Intravenous acetaminophen was administered in both studies, however, NSAIDs or COX-2-specific inhibitors were not administered. In the study by Mostafa *et al*,²³ a clinically significant reduction of pain scores was found 8 to 24 hours after surgery when 0.5 mcg/kg dexmedetomidine was used as an adjuvant to bupivacaine 0.125%. In another study, conducted by Ramasamy and colleagues,²⁴ a clinically and statistically significant reduction of pain scores was already evident after 2 hours when 0.5 mcg/kg dexmedetomidine was added to bupivacaine 0.25%. Fentanyl and acetaminophen were used less frequently as a rescue analgesic when dexmedetomidine was used as an adjuvant.

In the three studies mentioned above,^{22–24} basic analgesia was only mentioned by Mansour and Abdelghany.²² The use of ultrasound guidance was described in two of the studies.^{22–24} The use of dexmedetomidine as an adjuvant to maxillary nerve blocks was supported by Oberhofer *et al*²¹ in their systematic review on intraoperative nerve blocks for palatoplasty.

Obayah *et al*²⁵ investigated the analgesic effect of 1 mcg/kg dexmedetomidine used as an adjuvant with bupivacaine 0.25% for greater palatine nerve blocks. Pain scores were lower in the dexmedetomidine group between 8 and 24 hours postoperatively. Time to first analgesia was reduced and fewer patients required rescue analgesics in the dexmedetomidine group. The use of basic analgesic techniques was not reported by the authors.

In the four studies in which dexmedetomidine was used as an adjuvant for nerve blocks, no significant increase in side effects was observed.^{22–25} The study by Mansour and Abdelghany,²² however, showed an increased incidence of hypotension (5% vs 0%) and bradycardia (20% vs 7.5%) in the dexmedetomidine

group compared with a control group, although this difference was not statistically significant.

As mentioned earlier, a combination of bupivacaine and dexmedetomidine for maxillary nerve blocks has been advocated by Oberhofer *et al*²¹ in a systematic review on intraoperative nerve blocks for primary palatoplasty.²¹

Clonidine as adjuvant for peripheral nerve blocks

The effect of 3 mcg/kg clonidine as an adjuvant to lidocaine 1% with epinephrine 1:200 000 was investigated in a study on suprazygomatic maxillary nerve blocks for cleft lip and cleft palate surgery.²⁶ Subgroup analysis for cleft palate repair did not show significant differences in pain scores and postoperative analgesic consumption. Acetaminophen and ibuprofen were used as basic analgesia in the study.

Levobupivacaine for peripheral nerve blocks

Mostafa *et al*²⁷ compared levobupivacaine 0.25% with bupivacaine 0.25% for suprazygomatic maxillary nerve blocks. Both isomers were used with an injection volume of 0.15 mL/kg. Pain scores and supplemental analgesic requirements were similar in both treatment groups. No basic analgesia was given in this study. Jindal and colleagues²⁸ chose infraorbital nerve blocks to treat postoperative pain after palate cleft surgery. Patients either received levobupivacaine 0.375% or ropivacaine 0.375% in a volume of 2–3 mL for the blockades. The authors report lower pain scores in the levobupivacaine group.

Local infiltration

A submucous infiltration at the incision site with 0.1 mL/kg ropivacaine 0.2% was compared with no infiltration in a study by Coban and colleagues.²⁹ Patients in the ropivacaine group had clinically significant lower pain scores at most time points during the first 12 hours after surgery. The authors did not report regular use of basic analgesia in the postoperative period. Jha *et al*³⁰ compared a surgical site infiltration with 2 mg/kg bupivacaine or 0.5 mg/kg ketamine. No significant differences were found in postoperative pain or rescue medication.

Systemic dexmedetomidine

The postoperative analgesic effect of systemic dexmedetomidine was investigated in four studies.^{31–34} In each of these studies, the occurrence of delirium was a primary endpoint, and in each the observation time was short—a maximum of 2 hours. All four studies used sevoflurane-based anesthesia techniques. Luo *et al*³³ administered 0.5 µg/kg dexmedetomidine intravenously before anesthesia induction and compared outcomes with saline infusion. Patients receiving dexmedetomidine received 0.2 µg/kg sufentanil during induction and at end of surgery, whereas patients in the control group were treated with 2 µg/kg fentanyl at the same time points. Patients treated with dexmedetomidine exhibited a clinically significant reduction of maximum pain scores during the 60 min follow-up. No basic analgesia was used in the study. Huang *et al*³² compared intraoperative infusions of 0.5 µg/kg/h dexmedetomidine with infusions of 2 µg/kg/h propofol and with saline infusion in a control group. Pain scores were lower in the dexmedetomidine group compared with the saline and the propofol groups. While no basic analgesics were used, the patients received a continuous intravenous sufentanil infusion in the postoperative period. Surana and colleagues³⁴ compared a dexmedetomidine treatment group with a control group. Patients in the dexmedetomidine group received a loading dose of 1 µg/kg dexmedetomidine intravenously followed by a 0.5 µg/kg/h infusion. Patients in the control group received a loading dose of 0.05 mg/

kg midazolam intravenously followed by a saline infusion. A clinically significant reduction of pain scores was observed at multiple time points during a 2-hour observation period. Depending on the age of the patients, either rectal acetaminophen or ibuprofen was used as basic analgesia. Boku *et al*³¹ compared a saline infusion with an infusion of 6 µg/kg/h dexmedetomidine administered for a 10 min period before the end of the surgery followed by a 0.4 µg/kg/h dexmedetomidine infusion extending until 5 min after extubation. Pain scores were significantly lower during all time points within a 2-hour follow-up period. Adverse events were not observed. Rectal acetaminophen was used as basic analgesia. Adverse events related to dexmedetomidine were only reported by Surana *et al*.³⁴ Two of the 30 patients in the dexmedetomidine group experienced hypotension and bradycardia and were successfully treated with atropine and fluid infusion.

Various systemic drugs

Kheirabadi *et al*³⁵ compared an intravenous injection of 0.2 mg/kg dexamethasone with an injection of 1 mg/kg lidocaine or saline given prior to anesthesia induction. A statistically significant decrease was seen in the dexamethasone and lidocaine groups compared with the control group. However, the differences did not reach clinical significance. An intraoperative propofol infusion was compared with dexmedetomidine and saline infusions in the study by Huang *et al*³² mentioned above.³² Postoperative pain scores of patients who received 2 mg/kg/h propofol were comparable to pain scores after saline infusion and were significantly higher than pain scores of patients that were treated 0.5 µg/kg/h dexmedetomidine. No basic analgesia technique was used in the two studies.

DISCUSSION

Cleft palate surgery is associated with moderate-to-severe pain in the immediate postoperative period and if inadequately treated can negatively impact postoperative outcome. Based on the PROSPECT methodology, recommendations for pain management in patients undergoing cleft palate repair are displayed in box 1. A number of interventions are not recommended due to insufficient evidence (table 1). Some of these techniques may potentially be effective, however, there is not yet enough data available to consider a recommendation.

Box 1 Recommendations for procedure-specific pain management in patients undergoing cleft palate repair

Overall preoperative and intraoperative recommendations

- ⇒ Basic analgesic regimen should include acetaminophen and nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-specific inhibitors administered preoperatively or intraoperatively.
- ⇒ Pre-incisional suprazygomatic maxillary nerve block, and if that cannot be performed, administer pre-incisional palatal nerve block.
- ⇒ Dexmedetomidine as an additive to local anesthetic for suprazygomatic maxillary nerve block. Alternatively, intravenous dexmedetomidine if not used as an additive for the block.

Overall postoperative recommendations

- ⇒ Basic analgesic regimen should include acetaminophen and nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-specific inhibitors administered as scheduled (round-the-clock) dosing.
- ⇒ Opioids reserved for rescue medication.

Table 1 Nonrecommended interventions for procedure-specific pain management in patients undergoing cleft palate repair

| Intervention | Reason for not recommending |
|---|--|
| Sphenopalatine ganglion block | Lack of procedure-specific evidence |
| Clonidine as adjuvant to suprazygomatic maxillary nerve block | Lack of procedure-specific evidence |
| Dexmedetomidine as adjuvant for palatine nerve block | Limited procedure-specific evidence to recommended one local esthetic over another |
| Specific local anesthetics (for nerve block) | Limited procedure-specific evidence to recommended one local esthetic over another |
| Local anesthetic infiltration | Limited procedure-specific evidence |
| Specific local anesthetics (for infiltration) | Limited procedure-specific evidence to recommended one local esthetic over another |
| Dexamethasone | Limited procedure-specific evidence |
| Ketamine local infiltration | Limited procedure-specific evidence |
| IV Lidocaine | Lack of procedure-specific evidence |
| IV Propofol | Limited procedure-specific evidence |

In addition to basic analgesics, a pre-incisional bilateral suprazygomatic maxillary nerve block is recommended. Since the block can be performed as landmark-guided technique, it is also suitable for low-resource settings.¹⁴ Ultrasound guidance has been used with the aim of improving the technique.^{13 36 37} However, visualization of the pterygopalatine fossa which contains the maxillary nerve is not described in most reports. Instead, a visualization of the more superficially situated infratemporal fossa and local anesthetic spread within this region are described. At present, there are no studies comparing landmark-based with ultrasound-guided suprazygomatic maxillary nerve blocks. Therefore, no specific recommendation on needle guidance can be given.

Although palatal blocks give a similar reduction in pain intensity, a higher postoperative opioid consumption was found compared with maxillary nerve blocks in one study.¹³ Therefore, we recommend palatal nerve blocks when suprazygomatic nerve blocks cannot be performed. Reasons for not performing the suprazygomatic blocks include craniofacial deformations, skin infections at the needle insertion site, or lack of experience with the method. Our recommendation corresponds to the conclusions of a systematic review by Oberhofer and colleagues²¹ who identify suprazygomatic maxillary nerve blocks as the preferred method for reducing pain in cleft palate surgery. In contrast, Morzycki *et al*¹⁹ conclude that palatal nerve blocks demonstrate the greatest effectiveness in palatal repair, based on an their systematic review, but it included both randomized- and non-randomized controlled studies.

Dexmedetomidine might be used either as an adjuvant for maxillary nerve block or as perioperative intravenous systemic application. Studies investigating the use of dexmedetomidine as an adjuvant to bupivacaine demonstrate improved postoperative pain relief lasting from 8 to 24 hours postoperatively.^{23 24 38} However, the effect only becomes clear several hours after surgery. This can be seen as an indication that dexmedetomidine as an adjuvant mainly prolongs the duration of a nerve block rather than producing a systemic analgesic effect.³⁹ Prolonged duration of analgesia with dexmedetomidine as perineural adjuvant for various nerve blocks has been previously demonstrated.^{40 41} Dexmedetomidine as an adjuvant for palatal nerve blocks was investigated in only one study.²⁵ Currently, procedure-specific evidence for dexmedetomidine as adjuvant in cleft palate repair only relates to suprazygomatic maxillary nerve blocks,^{23 24 38} however, it is possible that the same observations may be true with palatal nerve blocks.

The studies investigating the analgesic effects of intravenous dexmedetomidine after cleft palate surgery focused on emerging agitation as a primary endpoint. Therefore, the follow-up periods

were short, with a maximum of 2 hours postoperatively,^{31–34} and studies investigating the effect during a longer postoperative period are necessary. High dexmedetomidine plasma concentrations can cause pronounced side effects including dizziness, bradycardia, or hypotension.⁴² The same concern applies for the simultaneous use of dexmedetomidine or other alpha-2 agonists for premedication.

Although there was limited procedure-specific evidence, two interventions were administered in most included studies and may have contributed to pain control. A local anesthetic combined with a vasoconstrictive drug is routinely infiltrated before surgery to reduce perioperative bleeding.⁴³ Also, local wound infiltration is a key component of multimodal analgesia in numerous surgical procedures.⁴⁴ However, the analgesic effects of local anesthetic infiltration for cleft palate repair are only supported by one study.²⁹ Similarly, dexamethasone that was used intraoperatively in some of the studies, most likely for antiemetic prophylaxis, could have provided some analgesia. Anti-inflammatory, antiemetic, and analgesic properties have been extensively shown for this drug.⁴⁵ For orofacial surgery, corticosteroids are frequently used to reduce edema of the upper airway during and after surgery.⁴⁶ Caution is advised, when combining local anesthetic infiltration and peripheral nerve blocks to avoid systemic local anesthetic toxicity. For both palatal and suprazygomatic maxillary nerve blocks, a relatively low injection volume of 0.15 mL or less on each side is used.^{13–16} When choosing appropriate concentrations of the local anesthetic agent, the maximum injection volumes will not be exceeded.

Young children cannot communicate pain, challenging both clinical work and trial designs. While the VAS and NRS are well established and validated in adult maxillofacial surgery,⁴⁷ neither VRS nor NRS is suitable for objective pain assessment in young children.⁴⁷ Instead, observational and behavioral assessment tools, such as Face, Legs, Activity, Cry, Consolability (FLACC) scale or Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), are frequently used to assess postoperative pain intensity.⁴⁸ However, these measures are not specific to pain and may also be triggered by fear.⁴⁹ Postoperative analgesic consumption has also been suggested for objective pain assessment in pediatric trials.⁵⁰

Our work has several limitations: first, available RCTs are sparse, and a significant share of evidence defined by retrospective studies could not be included. Therefore, and given that surgical techniques have not changed significantly in this time, we assessed a period of 20 years rather than 10–12 years as usually recommended by PROSPECT. Second, most studies come from a single country, India, with a moderate incidence of 1.7 cases/10000/year.^{1 51} Yet, given the estimated population size of 1.4 billion and more than 25 million births per year, India's health system deals with some 30000 cleft palate patients undergoing surgery per year.⁵¹ This vast experience allows other institutions and countries with less case load to benefit. However, country-specific medical practices might make certain strategies for postoperative analgesia difficult to transpose to other regions in the world. Third, in recent years there are increasing concerns that the country of study origin and the publications in predatory journals might influence the strength of evidence.⁵² However, the included studies had minimal risk of bias and overall quality is deemed good by the PROSPECT group.

Only studies published in English language were included in this systematic review. As a result, 8 of the 97 studies assessed for eligibility were excluded from the review. Even though the number of excluded studies is low, language restriction is a limitation of our review that could have led to language bias.⁵³

Finally, in several studies basic analgesic techniques were not included or only acetaminophen was administered to the patients. Ideally, basic analgesia should have included a combination of acetaminophen with NSAIDs or COX-2-specific inhibitors.⁴⁴ In

patients receiving a comprehensive basic analgesia treatment, the effects of analgesic interventions, for example, nerve block and additives, might be smaller or even insignificant. According to the PROSPECT methodology, recommended interventions must add a clinically relevant analgesic effect when added to a basic analgesic regimen.⁶

In summary, as cleft palate surgery has to occur in early childhood, appropriate analgesia is key to avoid wound dehiscence following agitation. Evidence-based analgesic efficacy and risks of each analgesic technique were considered to determine the PROSPECT recommendations (box 1). Basic perioperative analgesia should include acetaminophen, NSAIDs, or COX-2-specific inhibitors, unless contraindicated. We also recommend pre-incisional bilateral suprazygomatic maxillary nerve blocks or, when this is not possible, palatal nerve block. Dexmedetomidine should be used either as a perineural adjuvant for maxillary nerve block or as a perioperative intravenous administration. Of note, preincisional local anesthetic infiltration and dexamethasone were administered in most studies, but their contribution to postoperative pain relief remains unknown. Future well-designed studies are necessary to examine the role of surgical site infiltration and dexamethasone as components of multimodal analgesia recommended in this study.

Author affiliations

¹Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway

²Department of Anaesthesiology and Pain Medicine, University Hospital Bern Inselspital, University of Bern, Bern, Switzerland

³Department of Anaesthesiology, Cantonal Hospital of St Gallen, St Gallen, Switzerland

⁴Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas, USA

⁵Department of Cardiovascular Sciences, Section Anesthesiology, KU Leuven and University Hospital Leuven, Leuven, Belgium

⁶Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, New York, USA

⁷Department of Anaesthesia and Intensive Care Medicine, Oslo University Hospital, Oslo, Norway

Collaborators PROSPECT Working Group: M Van de Velde, E Albrecht, H Beloeil, M P Bonnet, G Dewinter, S M Freys, G Joshi, H Kehlet, P Lavand'homme, D N Lobo, E M Pogatzki-Zahn, J Raeder, N Rawal, A R Sauter, T Volk, C L Wu.

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ORCID iDs

Christopher L Wu <http://orcid.org/0000-0002-4484-0787>Axel R Sauter <http://orcid.org/0000-0003-1415-8143>

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SUPPLEMENTARY TABLE 1: THE SEARCH STRING**Ovid MEDLINE(R) ALL**

- #1: Cleft Palate/su
- #2: (((cleft adj3 palat*) and (surg* or repair*)) or palatoplast*).ti,ab,kf.
- #3: #1 or #2
- #4: exp Pain/ or Pain Management/ or exp Analgesia/ or exp Anesthesia/ or Pain Measurement/ or Visual Analog Scale/
- #5: (pain* or ((peripheral or nerve) adj block*) or analges* or anesthet* or anaesthet* or "visual analog scale*" or "visual analogue scale*" or VAS or "visual rating scale*" or VRS or "face legs activity cry consolability" or flacc).ti,ab,kf.
- #6: #4 or #5
- #7: #3 and #6
- Time frame: May 4, 2022 - August 29, 2023

Embase Classic+Embase

- #1: Cleft Palate/su
- #2: (((cleft adj3 palat*) and (surg* or repair*)) or palatoplast*).ti,ab,kf.
- #3: #1 or #2
- #4: exp pain/ or exp analgesia/ or exp anesthesia/ or exp pain assessment/
- #5: (pain* or ((peripheral or nerve) adj block*) or analges* or anesthet* or anaesthet* or "visual analog scale*" or "visual analogue scale*" or VAS or "visual rating scale*" or VRS or "face legs activity cry consolability" or flacc).ti,ab,kf.
- #6: #4 or #5
- #7: #3 and #6
- Time frame: May 4, 2022 - August 29, 2023

Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials

- #1 [mh ^"Cleft Palate"/su]
- #2 (((cleft NEAR/3 palat*) AND (surg* OR repair*))OR palatoplast*):ti,ab,kw
- #3 #1 OR #2
- #4 [mh "Pain"] OR [mh ^"Pain Management"] OR [mh "Analgesia"] OR [mh "Anesthesia"] OR [mh ^"Pain Measurement"] OR [mh ^"Visual Analog Scale"]
- #5 (pain* OR ((peripheral OR nerve) NEXT block*) OR analges* OR anesthet* OR anaesthet* OR (visual NEXT analog* NEXT scale*) OR VAS OR (visual NEXT rating NEXT scale*) OR VRS OR "face legs

activity cry consolability" OR flacc):ti,ab,kw

#6 #4 OR #5

#7 #3 AND #6 in Cochrane Reviews, Cochrane Protocols

#8 #3 AND #6

Time frame: May 4, 2022 - August 29, 2023

SUPPLEMENTARY TABLE 2: PATIENT INTERVENTION COMPARISON OUTCOME (PICO) FOR INCLUSION AND EXCLUSION OF STUDIES EVALUATING PAIN MANAGEMENT AFTER CLEFT PALATE SURGERY

| | Inclusion criteria | Exclusion criteria |
|---------------------|--|---|
| Population | Pediatric patients undergoing cleft palate surgery | Non-operative procedure |
| Intervention | Any intervention addressing perioperative pain management | No pain management intervention assessed |
| Comparison | No limitations | |
| Outcome | Linear pain intensity scale (VRS or NRS, etc.) or observational and behavioural assessment tools (FLAGG or CHEOPS, etc.) | Studies not including any form of a pain intensity measure |
| Study design | Randomized controlled trials, systematic reviews, meta-analyses | Retrospective or observational studies |
| Publication | Full text articles, English language | Letters, study protocols, Studies without full text, non-English articles |

SUPPLEMENTARY TABLE 3: SUMMARY OF KEY RESULTS FROM STUDIES EVALUATING SYSTEMIC ANALGESICS, SYSTEMIC ANALGESIC ADJUNCTS AND REGIONAL ANALGESIA USED TO SUPPORT THE RECOMMENDED INTERVENTIONS IN PATIENTS UNDERGOING CLEFT PALATE SURGERY

| Study | Study design | Pain scores | Total opioid consumption | Basic analgesia and baseline analgesia |
|---|--|---|--|---|
| Suprazygomatic maxillary nerve block | | | | |
| Abu Elyazed, 2018 [12] | SMNB (n=30) vs Palatine block (n=30) vs control (n=30) | Favours SMNB vs control group; no significant difference between SMNB and palatine block group | Favours SMNB vs palatine block and control group | Basic analgesia: IV acetaminophen; no additional baseline analgesia |
| Chiono et al. 2014 [13] | SMNB with ropivacaine (n=28) vs SMNB with saline (n=29) | No significant difference between groups | Favours SMNB with ropivacaine vs SMNB with saline group | Basic analgesia: IV acetaminophen; baseline analgesia: IV methyl-prednisolone |
| Palatal nerve block | | | | |
| Abu Elyazed, 2018 [12] | SMNB (n=30) vs palatine block (n=30) vs control (n=30) | Favours palatine block vs control group; no significant difference between palatine and SMNB block group | Favours SMNB vs palatine block group and control group | Basic analgesia: IV acetaminophen; no additional baseline analgesia |
| Jonnavithula et al. 2010 [14] | Palatine block with bupivacaine (n=14) vs saline (n=15) vs no block (n=15) | Favours palatine block with bupivacaine group and saline group vs no block group; no significant difference between palatine block with bupivacaine vs saline group | Ibuprofen and acetaminophen as rescue (favours palatine block with bupivacaine group and saline group vs no block group) | Basic analgesia: only one dose of rectal acetaminophen after intubation; no additional baseline analgesia |

| | | | | |
|---|---|---|---|---|
| Kamath et al. 2009 [15] | Greater palatine nerve block (n=25) vs IV pethidine (n=25) | No significant difference between groups | Favours palatine nerve block vs IV pethidine group | No basic or baseline analgesia |
| Dexmedetomidine as adjuvant for suprazygomatic maxillary nerve block (SMNB) | | | | |
| Mansour et al. 2021 [21] | Bupivacaine + dexmedetomidine (n=40) vs bupivacaine (n=40) | Favours bupivacaine + dexmedetomidine vs bupivacaine group | Favours bupivacaine + dexmedetomidine vs bupivacaine group | Basic analgesia: IV acetaminophen; baseline analgesia: one dose of IV dexamethasone at end of surgery |
| Mostafa et al. 2020 [22] | Bupivacaine + dexmedetomidine (n=40) vs bupivacaine (n=40) | Favours bupivacaine + dexmedetomidine vs bupivacaine group | IV acetaminophen as rescue (favours bupivacaine + dexmedetomidine vs bupivacaine group) | No basic or baseline analgesia |
| Ramasamy et al. 2022 [23] | Bupivacaine + dexmedetomidine (n=23) vs bupivacaine (n=23) | Favours bupivacaine + dexmedetomidine vs bupivacaine group | Favours bupivacaine + dexmedetomidine vs bupivacaine group | No basic or baseline analgesia |
| Dexmedetomidine intravenous | | | | |
| Boku et al. 2016 [30] | IV infusion with dexmedetomidine (n=35) vs saline (n=35) | Favours dexmedetomidine vs saline group | N/A | Basic analgesia: rectal acetaminophen; baseline analgesia: local anaesthesia infiltration |
| Huang et al. 2022 [31] | IV infusion with dexmedetomidine (n=29) vs propofol (n=29) vs saline (n=28) | Favours dexmedetomidine vs propofol and saline group | N/A | No basic analgesia; baseline analgesia: IV infusion with sufentanil |
| Luo et al. 2017 [32] | IV dexmedetomidine and sufentanil (n=47) vs saline + fentanyl (n=50) | Favours dexmedetomidine + sufentanil vs saline + fentanyl group | Favours dexmedetomidine and sufentanil vs saline + fentanyl group | No basic or baseline analgesia |
| Surana et al. 2017 [33] | IV infusion with dexmedetomidine (n=30) vs | Favours dexmedetomidine vs midazolam group | Favours dexmedetomidine vs midazolam group | Basic analgesia: rectal acetaminophen or |

| | | | | |
|--|------------------|--|--|--|
| | midazolam (n=30) | | | ibuprofen (depending on age); baseline analgesia: local anaesthesia infiltration |
|--|------------------|--|--|--|

Abbreviations: IV (intravenous); N/A (not applicable); NRS (numeric rating score); PO (per os); post op (postoperatively); SMNB (suprazygomatic maxillary nerve block); VAS (visual analogue scale)

SUPPLEMENTARY TABLE 4. SUMMARY OF KEY RESULTS FROM STUDIES EVALUATING SYSTEMIC ANALGESICS, SYSTEMIC ANALGESIC ADJUNCTS AND REGIONAL ANALGESIA THAT ARE NOT RECOMMENDED INTERVENTIONS IN PATIENTS UNDERGOING CLEFT PALATE SURGERY

| Study | Study design | Pain scores | Total opioid consumption | Basic analgesia and baseline analgesia |
|---|--|--|--|--|
| Sphenopalatine ganglion block | | | | |
| Parameswaran et al. 2018 [16] | Sphenopalatine ganglion block (n=51) vs control (n=46) | No significant difference between groups | N/A | No basic analgesia; baseline analgesia: local anaesthesia infiltration |
| Clonidine as adjuvant to suprazygomatic maxillary nerve block | | | | |
| Barbero et al. 2021 [25] | Clonidine + bupivacaine + epinephrine (n=29) vs bupivacaine + epinephrine (n=25) | No significant difference between groups | Favours clonidine + bupivacaine vs bupivacaine group | Basic analgesia: PO acetaminophen and ibuprofen; no other baseline analgesia |
| Dexmedetomidine as adjuvant for palatine nerve block | | | | |
| Obayah et al. 2010 [24] | Dexmedetomidine + bupivacaine (n=15) vs bupivacaine (n=15) | Favours dexmedetomidine + bupivacaine vs bupivacaine group | Favours dexmedetomidine + bupivacaine vs bupivacaine group | No basic analgesia; baseline analgesia: dexamethasone peroperatively |
| Specific local anaesthetics (for nerve block) | | | | |
| Jindal et al. 2022 [27] | Infraorbital block with levo-bupivacaine 0.375% (n=40) vs ropivacaine 0.375% (n=40) | Favours levobupivacaine vs ropivacaine group | Favours levobupivacaine vs ropivacaine group | Basic analgesia: only one dose of IV diclofenac at end of surgery; no other baseline analgesia |
| Mostafa et al. 2018 [26] | Suprazygomatic maxillary nerve block with levobupivacaine (n=30) vs bupivacaine (n=30) | No significant difference between groups | No significant difference between groups | No basic or baseline analgesia |
| Specific local anaesthetics (for infiltration) | | | | |

| | | | | |
|---|---|---|--|---|
| Jha et al. 2013 [29] | Bupivacaine (n=25) vs ketamine (n=25) | Favours ketamine vs bupivacaine group at a single time point (24h) | No significant difference between groups | No basic or baseline analgesia |
| Ketamine local infiltration | | | | |
| Jha et al. 2013 [29] | Bupivacaine (n=25) vs ketamine (n=25) | Favours ketamine vs bupivacaine group at a single time point (24h) | No significant difference between groups | No basic or baseline analgesia |
| Pre-incisional infiltration with local anaesthetics | | | | |
| Coban et al. 2008 [28] | Ropivacaine infiltration (10) vs control (10) | Favours ropivacaine vs control group | N/A | No basic or baseline analgesia |
| IV Lidocaine | | | | |
| Kheirabadi et al. 2020 [34] | IV lidocaine (n=28) vs dexamethasone (n=30) vs distilled water (n=29) | Favours lidocaine vs distilled water group; no significant difference between dexamethasone and lidocaine group | N/A | No basic or baseline analgesia |
| IV Propofol | | | | |
| Huang et al. 2022 [31] | IV infusion with propofol (n=29) vs dexmedetomidine (n=29) vs saline (n=28) | Favours propofol vs control group; favours dexmedetomidine vs propofol group | N/A | No basic analgesia; baseline analgesia: IV infusion with sufentanil |
| Intravenous dexamethasone | | | | |
| Kheirabadi et al. 2020 [34] | IV dexamethasone (n=30) vs lidocaine (n=28) vs distilled water (n=29) | Favours dexamethasone vs distilled water group; no significant difference between dexamethasone and lidocaine group | N/A | No basic or baseline analgesia |

Abbreviations: IV (intravenous); N/A (not applicable); NRS (numeric rating score); PO (per os); post op (postoperatively); VAS (visual analogue scale)

SUPPLEMENTARY TABLE 5: RISK OF BIAS ANALYSIS

| | Randomisation process | Deviations from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|--------------------------|-----------------------|--|----------------------|----------------------------|----------------------------------|---------|
| Abu Elyazed et al. 2018 | + | + | + | ! | + | ! |
| Barbero et al. 2021 | + | + | + | + | + | + |
| Boku et al. 2016 | + | + | + | + | ! | ! |
| Chiono et al. 214 | + | + | + | + | + | + |
| Coban et al. 2008 | + | + | + | ! | ! | ! |
| Huang et al. 2022 | + | + | + | + | ! | ! |
| Jha et al. 2013 | + | + | + | + | ! | ! |
| Jindal et al. 2022 | + | + | + | + | + | + |
| Jonnavithula et al. 2010 | + | + | + | + | + | + |
| Kamath et al. 2020 | + | + | + | + | + | + |
| Kheirabadi et al. 2020 | + | + | + | + | + | + |
| Luo et al. 2017 | ! | + | + | + | ! | ! |
| Mansour et al. 2021 | + | + | + | + | + | + |
| Mostafa et al. 2020 | + | + | + | + | + | + |
| Mostafa et al. 2018 | + | + | + | + | + | + |
| Obayah et al. 2010 | + | + | + | + | ! | ! |
| Parameswaran et al. 2018 | ! | + | + | + | ! | ! |
| Ramasamy et al. 2022 | + | + | + | + | ! | ! |
| Surana et al. 2017 | + | + | + | + | ! | ! |

 Low risk
 Some concerns
 High risk