The management of perioperative pain in craniosynostosis repair: a systematic literature review of the current practices and guidelines for the future

Hatan Mortada1,2*, Raghad AlKhashan3, Nawaf Alhindī4, Haifa B. AlWaily3, Ghada A. Alsadhan3, Saad Alrobaiea5 and Khalid Arab6

Abstract
Background: Craniosynostosis is a condition characterized by the premature fusion of one or more cranial sutures. The surgical repair of craniosynostosis causes significant pain for the child. A key focus of craniosynostosis repair is developing effective strategies to manage perioperative pain. This study aimed to review perioperative pain control strategies for craniosynostosis repair systematically.

Methods: Guidelines for reporting systematic reviews and meta-analyses were used in the design of this review. In May 2022, the following databases were used to conduct the literature search: MEDLINE, Cochrane, EMBASE, and Google Scholar. A search was performed using MeSH terms “craniosynostosis,” “pain management,” and “cranioplasty.”

Results: The literature review yielded 718 publications. After applying our inclusion criteria, 17 articles were included, accounting for a total of 893 patients. During the postoperative period, most studies used multimodal analgesia, primarily opioids, and acetaminophen. In the postoperative period, oral ibuprofen was the most commonly used NSAID, rectal codeine, and acetaminophen were the most commonly used weak opioids, and continuous remifentanil infusion was the most commonly used potent opioid.

Conclusion: The authors determined the best pain management options for pediatric patients undergoing cranioplasty by analyzing the most commonly used analgesics. A high-quality clinical trial comparing different types of analgesic combinations would be a valuable addition to the present literature.

Keywords: Pain control, Cranial vault reconstruction, Craniosynostosis, Pain management, Cranioplasty

Background

Craniosynostosis is a rare condition characterized by the premature fusion of one or more cranial sutures. The cranium is formed during development via intramembranous ossification, leaving the sutures not fully ossified to allow passage through the birth canal and expand brain growth [1]. Craniosynostosis must be managed early to avoid damaging adverse outcomes, including blindness, abnormalities in skull shape, and developmental impairments of the brain that may significantly affect the child’s quality of life. Craniosynostosis can be corrected through craniotomies and cranioplasties, which are invasive and painful procedures due to the extensive handling of the scalp and periosteum [2].

Currently, there is no standard protocol for managing perioperative pain associated with craniosynostosis repair [3]. Several studies have shown that steroids can
be used preoperatively to reduce postoperative pain as a secondary benefit, along with other benefits such as reducing facial edema, reducing postoperative ecchymosis, and improving nausea and vomiting [4–9].

Current recommendations mostly aim to achieve a balanced technique that provides cardiovascular stability by using opioids and volatile agents in addition to relaxants. Remifentanil infusion (0.25–0.5 mcg/kg/min) is also recommended [10–12]. In addition, in case of remifentanil usage for anesthesia maintenance, it is recommended to administer a bolus of morphine or piritramide before the end of the procedure to help manage postoperative pain [13]. However, there is still no clear evidence on a specific intraoperative opioid regimen that provides the maximal benefit to pain management. Kattail et al. found that among patients with non-syndromic craniosynostosis, within the first few days following surgery, a significant number of patients complained of moderate to severe pain, which suggests that pain was poorly treated despite the use of intraoperative opioids in all patients. Subsequently, the authors attributed this finding to the underutilization of non-opioid analgesics [14].

Despite the extensive body of literature exploring the operative treatment of craniosynostosis, there is still a lack of consensus on the optimal perioperative management protocols, including pain control regimens. This might be explained by the lack of verbalization in young children about their pain [3]. In the literature, opioids alone, opioids combined with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), and local nerve blocks have all been described as methods of treating postoperative pain [15]. It has been reported that many attending physicians in pediatric intensive care units (PICUs) use intravenous (IV) dexmedetomidine on a postoperative day one in conjunction with IV acetaminophen to replace morphine. Dexmedetomidine is rarely used postoperatively in pediatric plastic surgery, and current reports focus mostly on cases of pediatric cleft lip and cleft palate. These discrepancies in the available research regarding postoperative pain management in craniosynostosis make it a clinical challenge for plastic and reconstructive surgeons [15–18].

There is a lack of information specifically regarding the current techniques and efficacy of perioperative analgesia for such procedures among craniosynostosis patients [3]. Therefore, this systematic review aimed to compare the literature on perioperative pain management to provide the best evidence-based pain management options for all children undergoing craniosynostosis repair. In addition, clinical outcomes have been reviewed in the literature, recommendations, and administration methods for different perioperative pain management options.

Methods and materials

Review of the literature

We conducted this systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, in accordance with Cochrane review methods [19, 20]. The published literature was searched on MEDLINE, Cochrane, EMBASE, and Google Scholar from inception until May 2022 without specifying a timeframe. Bibliographies of reviewed articles identified additional articles. As part of the literature review, the following terms and keywords were used: (craniosynostosis or cranial vault reconstruction or cranial reconstruction or cranioplasty) and (pain management or analgesia or analgesics or pain control). This study aimed to review and compare literature on perioperative pain management to provide the best evidence-based options for all children undergoing craniosynostosis repair. The proposal was registered to the International Prospective Register of Systematic Reviews (PROSPERO) guidelines (ID number: CRD42022339835) [21].

Selection of the studies

The following criteria were used to determine inclusion:

1. published studies that are not time-limited,
2. published in English,
3. reported RCT,
4. prospective/retrospective cohort studies,
5. pediatric patients,
6. patients with craniosynostosis,
7. a clear description of pain management protocols, and
8. clinical outcomes of interest were reported.

Among the exclusion criteria were (1) studies published in non-English languages; (2) inappropriate methods (case reports, meta-analysis and systematic reviews, cadaver studies, narrative review, or editorial); (3) non-craniosynostosis patients; (4) animal studies; (5) not providing a complete description of the perioperative pain management protocol; and (6) reporting no findings.

Based on predefined inclusion and exclusion criteria, all abstracts of included studies were screened using the Rayyan search engine [22]. The studies were then included by title and abstract and were divided into two groups, each with two independent reviewers. All selected articles by both groups were reviewed by a fifth independent reviewer to resolve disagreements. Both groups reviewed the full texts of the studies to ensure compliance with inclusion and exclusion criteria.

Extraction of data

An Excel sheet was created to review the full texts, and the outcome measures were extracted. From the final included studies, data parameters included general parameters (title, author, year of publication, country, study design, total number of patients, number of
patients with craniosynostosis), demographics (age in months (SD), number of males and females, race, type of syndrome, type of craniosynostosis, comorbidities, and name of surgical intervention), methods of pain management (name of medications, doses, timing (preoperative, intraoperative, and/or postoperative), complete analgesic protocol, complications, length of hospital stay, and follow up), and name of pain score used to determine the efficacy of pain control, parental satisfaction, and a summary of the significant primary outcomes and clinical recommendations. A disagreement regarding the extraction and screening of data was resolved by two senior independent reviewers. The retrieved data were double-checked to avoid duplication. All articles included in the review were rated according to the level of evidence and grading recommendations of the American Society of Plastic Surgeons [23].

Assessment of bias
Two reviewers independently assessed the risk of bias using the Newcastle–Ottawa Scale for case–control and cohort studies [24]. With this scale, the risk of bias is assessed in the domains of selection, comparability, and outcomes and is rated up to a maximum of 9. Studies with scores of 0–3 had a high risk of bias, those with scores of 4–6 a moderate risk, and those with scores of 7–9 a low risk. Based on eight components, the methodological quality and synthesis of case series and case report assessment tools are divided into four domains: selection, ascertainment, causation, and reporting [25]. A Cochrane risk-of-bias tool for randomized trials was used for assessing randomized controlled trials for bias [26]. Every study category was rated based on randomization, allocation concealment, participant and employee blinding, observer blinding, incomplete data, and selective reporting.

Analysis of data
Although a basic descriptive statistical analysis was performed, meta-analysis was not possible due to the heterogeneity of the articles included.

Results
Findings from literature
In this systematic review, 919 published articles were found, including 338 articles from EMBASE, 369 articles from MEDLINE, 201 from Google Scholar, and 11 articles from the Cochrane Library. There remained 525 articles for review after removing duplicates. We included 34 articles based on their titles and abstracts in the initial screening. Based on the previously defined exclusion criteria, only 16 articles published between 2000 and 2022 were included (Fig. 1) [2, 10, 14, 27–39]. A total of 18 articles were excluded for the following reasons: improper methods (meta-analysis/systematic review, case reports) \( n = 4 \), reported no outcomes of interest \( n = 4 \), no full text was found \( n = 2 \), non-craniosynostosis patients \( n = 2 \), and incomplete description of perioperative pain management protocol \( n = 6 \). There were three prospective cohort studies, three randomized controlled trials, seven retrospective studies, two case–control studies, and one case series among the included studies. Most studies were conducted in the USA \( n = 7 \). Three studies were conducted in Italy, three in the Netherlands, two in France, and one in Canada. The included articles were all on pediatric patients with craniosynostosis who underwent cranioplasty, except for two papers that included other craniotomies. The study included only patients who had undergone cranioplasty. Detailed characteristics of all the included studies are demonstrated in Table 1.

An overview of the studies’ characteristics
From all the studies, 1038 patients were reviewed. There were a total of 848 patients with craniosynostosis. The age of the patients ranged from 3.1 to 55 months. The majority of included patients were males \( n = 527/848, 62.14\% \); however, gender was not mentioned in two articles [31, 38]. Race was only mentioned in three studies [14, 32, 35], which showed the majority of patients were White \( n = 124 \), Black \( n = 28 \), and Asian \( n = 2 \). There were only 11 patients with syndromic craniosynostosis, 4 with Apert syndrome, 2 with Muenke syndrome, and 5 with Crouzon’s syndrome. There were 184 cases of scaphocephaly, 121 trigonocephaly, 67 plagiocephaly, 11 brachycephaly, 4 pachycephaaly, and 69 multi-sutural craniosynostoses (Fig. 2). The type of craniosynostosis was not mentioned in 5 studies [14, 30, 33–35]. Among the included patients, the majority underwent cranial vault remodeling \( n = 111 \), followed by endoscopic strip craniectomy \( n = 129 \), and followed by fronto-orbital advancement \( n = 78 \). Figure 3 illustrates the different surgical interventions among the included patients. For greater clarity and comprehension, the authors separated analgesia delivery methods into two categories: intraoperative and postoperative.

Intraoperative analgesia
A total of 441 (52\%) patients were included in seven articles describing the complete intraoperative analgesic protocol [14, 32, 34, 36, 38, 39]. Reddy et al. reported eighty patients were placed into one of two groups, with 39 receiving intraoperative dexmedetomidine and 41 who did not. Postoperatively, neither group had a difference in opioid requirement or pain score. There was no significant difference between the two groups in terms
of the number of days spent in the PICU, overall hospital stay, or duration on a mechanical ventilator. However, in patients given higher doses of intraoperative dexmedetomidine, the use of rescue medications for nausea and vomiting was significantly lower ($p = 0.017$) [32].

A total of two studies used Scalp Nerve Block (SNB) [36, 39]. A study by Bracho et al. reported 32 children undergoing craniosynostosis surgery under general anesthesia with associated levobupivacaine (0.125% 2 mg/kg)/epinephrine (1.25 mg/mL) Scalp Nerve Block (SNB) followed by 15 mg/kg of IV acetaminophen 30–45 min prior to skin closure and then every 6 h. In the surgical ward, nalbuphine was prescribed at 0.2 mg/kg once a CHEOPS score of 8 or an Aono’s four-point scale score greater than 2 was reached. According to the study, the SNB technique offers many advantages, including the ability to limit injections to specific nerves, reduce the volume required of local anesthetic, provide better hemodynamic stability at skin incision and closure, and reduce opioid use and dosage. For intraoperative analgesia, five more studies were found. One study used IV morphine and acetaminophen, another IV opioid alone, and one followed enhanced recovery after surgery (ERAS), which involves hemoglobin optimization, cell-saver technology, tranexamic acid, and intraoperative interventions, such as gabapentin and local anesthetic, fluid titrations postoperatively, and transfusion protocols. Scheduled acetaminophen, ibuprofen, or ketorolac are the preferred analgesics, and dexmedetomidine is used with opioids only when breakthrough pain occurs. Analgesic protocols for each study are shown in Table 2.

**Postoperative analgesia**

In total, nine articles describing the complete postoperative analgesic protocol were identified [2, 10, 27–29, 31, 33, 35, 37], including 407 (47.9%) patients. In a
| Author       | Study design | Country     | Number of patients | Age in months, SD | M/F | Race | Comorbidities                                                                 | Type of syndrome                          | Type of craniosynostosis | Level of evidence |
|--------------|--------------|-------------|--------------------|-------------------|-----|------|--------------------------------------------------------------------------------|-------------------------------------------|-------------------------|-------------------|
| Chiaretti    | P            | Italy       | 20                 | 3.9               | 11/8| NA   | NA                                                                             | Crouzon's (5), Apert's (1)                | Scaphocephaly (8), anterior plagiocephaly (8) | II                |
| Marel        | RCT          | Netherland  | 40                 | 2.7               | 29/11| NA   | NA                                                                             | Trigonocephaly 7, scaphocephaly 20, plagiocephaly 9, brachycephaly 4 | I                  |
| Warren       | R            | Canada      | 71                 | 18                | NA  | NA   | NA                                                                             | Sagittal 16, coronal 12, metopic 7, other 5 | II                  |
| Jong         | RCT          | Netherland  | 60                 | 6.8               | 45/15| NA   | NA                                                                             | Trigonocephaly 5, scaphocephaly 8, plagiocephaly 5, other 2 | I                  |
| Bracho       | P            | France      | 32                 | 16                | 19/13| NA   | NA                                                                             | Trigonocephaly 12, scaphocephaly 7, plagiocephaly 6, brachycephaly 3, pachycephaly 4 | II                |
| Bronco       | P            | Italy       | 206                | 3.1               | 123/86| NA  | NA                                                                             | NA                                        | NA                      | II                |
| Fearon       | RCT          | USA         | 50                 | 52                | 38/12| NA  | NA                                                                             | Scaphocephaly 63, trigonocephaly 36, plagiocephaly 14, brachycephaly 1, syndromal (5), multisutural (2) | II                |
| Arts         | R            | Netherlands | 121                | 3.9               | 85/36| NA  | Atopy (4), viral infection (3), neutropenia (1), facial malformation (2), cardiac (2), pulmonary (2), Abert (3), Muenke (2) | NA                                        | NA                      | II                |
| Cercueil     | CC           | France      | 81                 | 11                | NA  | NA   | NA                                                                             | Trigonocephaly 35, scaphocephaly 31, other (15) | III               |
| Kattail      | R            | USA         | 54                 | 21.1              | 30/24| White (36), black (8), others (10) | NA                                             | Nonsyndromic NA | II                |
| Tuncer       | R            | USA         | 74                 | 30.6              | 44/30| NA  | None                                                                           | NA                                        | Sagittal (24), metopic (15), unilateral coronal (10), lambdoid (3), multisuture or complex (22) | II                |
| Reddy        | R            | USA         | 80                 | 30                | 47/33| Asian (2), black (20), white (50), other (8) | NA                                             | Single suture (37), double suture (10), triple suture (13), 4 or more (20) | II                |
| Xu           | CS           | USA         | 2                  | 20                | 2/0 | NA   | Short gut, premature, and enterocolitis, significant anemia and developmental delay | NA                                        | Sagittal and metopic craniosynostosis | IV                |
Table 1 (continued)

| Author            | Study design | Country     | Number of patients | Age in months, SD | M/F | Race | Comorbidities | Type of syndrome                                                                 |
|-------------------|--------------|-------------|--------------------|-------------------|-----|------|---------------|--------------------------------------------------------------------------------|
| Festa [39]        | CC           | Italy       | 26                 | 7.8               | 15/11 | NA   | NA            | Scalp block group: scaphocephaly (6), trigonocephaly (3), right anterior plagiocephaly (2), complex craniosynostosis (2) Control group: scaphocephaly (8), trigonocephaly (2), right anterior plagiocephaly (1), left anterior plagiocephaly (1), complex craniosynostosis (1) |
| Knackstedt [34]   | R            | USA         | 78                 | 33.6              | 34/34 | NA   | NA            | NA                                                                               |
| Zubovic [33]      | R            | USA         | 43                 | 48                | 5/38  | NA   | NA            | NA                                                                               |

CC Case control, CS Case series, R Retrospective cohort, P Prospective cohort, M Male, F Female, NA Not available, USA United States of America

* Gender distribution was based on the total number of patients with craniosynostosis
prospective randomized controlled trial of 40 craniosynostosis patients. Van der Marel et al. compared oral acetaminophen versus rectal acetaminophen. Each patient underwent preoperative SNB using bupivacaine and epinephrine. Those receiving rectal acetaminophen had significantly higher plasma levels of the drug. In addition, patients receiving oral acetaminophen scored significantly higher on the COMFORT and VAS scales (P<0.02 and P<0.04, respectively). However, plasma acetaminophen concentrations did not significantly correlate with pain scores [28]. Another study by Tuncer et al. showed that using 10 mg/kg ibuprofen; 0.25 mg/kg IV ketorolac postoperatively was associated with shorter hospital stay (P<0.05) and less morphine for pain control [37]. The use of narcotics in craniosynostosis repair surgery was described by Bronco et al. in a multicenter study of 90 patients. Postoperatively, oral ibuprofen was the most commonly used NSAID, rectal codeine in association with acetaminophen was the most commonly used weak opioid, and continuous infusion of remifentanil was the most widely used potent opioid [30]. In another study, Chiaretti et al. examined 20 patients using remifentanil prospectively [10]. The use of opioids in 54 pediatric patients undergoing primary open craniosynostosis repair was reported by Kattail et al. [14]. In the intravenous parent/patient-controlled analgesia (IV PCA) protocol, fentanyl (51%), morphine (41.2%), and hydromorphone (7.8%) were administered intravenously. De jong et al. compared the effects of the “M” technique massage with or without mandarin oil compared to standard postoperative care on infants [27]. A study by Xu et al. reported the use of dexmedetomidine as an adjunct to IV acetaminophen and as a substitute for morphine in craniosynostosis repair [2]. One study reported the use of continuous morphine infusion [31]. Another study reported the use of oxycodone suspension as the only opioid prescribed at discharge [33]. Lastly, one study described postoperative management as prescribing scheduled IV acetaminophen and Ketorolac or ibuprofen [35]. Table 3 provides a detailed description of the postoperative analgesic protocol.
The postoperative pain scales

Twelve of the 16 articles included mentioned the postoperative pain assessment scale. The 10-point Face, Legs, Activity, Cry, Consolability (FLACC) Behavioral Pain Scale was utilized in six articles. Kattail et al. used the Wong-Baker Face pain scale, the 0–10 numerical rating scale score, and the FLACC scale. One study used the objective pain scale (OPS). Children’s Hospital of Eastern Ontario Pain Score (CHEOPS) was used in two studies. In one study, the Children and Infants Postoperative Pain Scale (CHIPPS) score was used, and 3 studies used Comfort-B. In one included study, visual analog scales were used. Four studies did not mention the pain assessment score.

Complications related to the intervention

A total of seven studies reported postoperative complications. Nausea and vomiting were the main complications, reported in five studies [14, 30, 31, 35, 36]. Two studies observed a decline in hemoglobin levels, hematocrit levels, and blood loss [29, 37]. According to Tuncer et al., the ketorolac group had a lower postoperative hemoglobin than the control group [37]. There was one episode of urinary retention in the article by Chiaretti et al. [10]. Furthermore, Bronco et al.’s study was complicated by the emergence of delirium, sedation, respiratory depression, nausea, and vomiting [30]. There were three studies without complications [2, 38, 39].

Length of hospital stay and follow-up

The length of follow-up visits after surgery was not mentioned in any of the articles. Eight studies, however, reported the length of the hospital stay. In the study conducted by Reddy et al., the group that did not receive dexmedetomidine stayed for 4.2 ± 1.0 days, while the group that received dexmedetomidine stayed for 4.0 ± 0.8 days [32]. According to a study by Tuncer et al., the hospital stay for patients receiving Ketorolac postoperatively is 2.1 days for those receiving Ketorolac compared to 2.6 days for those receiving a control dose [37]. According to Festa et al., the length of PICU stay for the scalp block group was 21.1 days, and for the control group was 18.1 days [39]. Knackstedt et al. found that the group following the ERAS protocol had a shorter hospital stay than the group not following it (ERAS group: 2.3 days,
Table 2 An overview of characteristics and analgesic protocols for intraoperative pain management

| Author | Surgical intervention | Name of pain management drug | Dose of each drug | Complete analgesic protocol | Complications | LOS | Clinical recommendations | Significant outcomes |
|--------|------------------------|------------------------------|-------------------|-----------------------------|---------------|-----|-------------------------|---------------------|
| Bracho [36] | NA | Levobupivacaine, acetaminophen, morphine, and nalbuphine | Acetaminophen (1.5 mg/ kg IV*), morphine (0.02 mg/kg) | An acetaminophen dose 30–45 min before closing skin, then every 6 h (depending on postoperative pain score; addition analgesic administered (e.g., morphine)) | Sedation, N/V* | NA* | Patients undergoing craniosynostosis surgery can benefit from SNB* technique to complement analgesia | NA |
| Bronco [30] | NA | Acetaminophen, ibuprofen, codeine + acetaminophen, tramadol, remifentanil, morphine, fentanyl | Remifentanil (0.2 µg/kg), fentanyl (4 µg/kg) | Analgesic therapy given after extubation. Analgesics were not administered to 14 children (7%) during the first day after surgery, and another 41 (20%) during the second day. | Delirium, sedation, respiratory depression, N/V | NA | After a major craniotomy, children receiving multimodal analgesia experienced little or no pain. | NA |
| Cercueil [38] | NA | Morphine, acetaminophen, nalbuphine | Morphine (0.1–0.2 mg/kg), acetaminophen (1.5 mg/kg) | Both administered IV before the end of surgery; postoperative morphine in the recovery room until FLACC* is 3/10. Following recovery room discharge, administration of IV acetaminophen combined with oral morphine (or IV nalbuphine as rescue if necessary). | None | NA | Confirm data by prospective studies | Patients in the local anesthetic infiltration group had a modest reduction in morphine use, but no differences in pain scores compared to the SNB group |
Table 2 (continued)

| Author     | Surgical intervention          | Name of pain management drug             | Dose of each drug | Complete analgesic protocol                                                   | Complications | LOS  | Clinical recommendations | Significant outcomes                                                                 |
|------------|--------------------------------|------------------------------------------|-------------------|-----------------------------------------------------------------------------|---------------|------|----------------------------|--------------------------------------------------------------------------------------|
| Kattail    | Open craniosynostosis repair   | Acetaminophen, Intravenous ketorolac,    | Acetaminophen     | Intraoperative: All patients received IV opioids, in addition to: fentanyl, | Emesis        | 3.7  |                             | Pain control, emesis reduction, and LOS reduction can be achieved through the       |
|            |                                | Dexmedetomidine, Fentanyl, Morphine,     | 12.5 mg/kg every 4 h, | hydromorphone and fentanyl, hydromorphone, fentanyl and morphine,           |               | (1.9)|                             | implementation of ERAS protocols and the use of non-opioid analgesics after surgery.|
|            |                                | Hydromorphone, Sufentanil, remifentanil  |                   | morphine, sufentanil, or fentanyl and remifentanil.                        |               |      |                             |                                                                                     |
|            |                                |                                          |                   | Postoperative IV PCA*. Fentanyl, morphine, and hydromorphone were the       |               |      |                             | According to a multivariable linear regression model, age (P = 0.006), weight     |
|            |                                |                                          |                   | opioids administered to patients who received PCA. On the first or second   |               |      |                             | (P = 0.009), and postoperative day of transition from IV to enteral opioids were   |
|            |                                |                                          |                   | day postoperatively, the majority of patients were able to transition to    |               |      |                             | independent predictors of overall hospital stay length (P < 0.001).                |
|            |                                |                                          |                   | enteral formulation. Each patient receiving enteral opioids was prescribed   |               |      |                             |                                                                                     |
|            |                                |                                          |                   | oxycodone at a dose of 0.1 mg/kg (0.01 mg/kg), which was administered every 4 h. |               |      |                             |                                                                                     |
|            |                                |                                          |                   | Scheduled "around the clock" or "as needed" dosing of oxycodone basis.     |               |      |                             |                                                                                     |
|            |                                |                                          |                   | All patients received acetaminophen at a dose of 12.5 mg/kg every 4 h.     |               |      |                             |                                                                                     |
|            |                                |                                          |                   | Route of administration of acetaminophen varied; mostly orally, some        |               |      |                             |                                                                                     |
|            |                                |                                          |                   | rectally, and a few IV. Six patients received IV ketorolac, and 4 received  |               |      |                             |                                                                                     |
|            |                                |                                          |                   | Dexmedetomidine.                                                            |               |      |                             |                                                                                     |
| Reddy      | Complex cranial vault          | Dexmedetomidine, morphine                |                   | NA                                                                          |               |      |                             | There is still a need for further investigation into the relationship between      |
|            | reconstruction                 |                                          |                   | Both cohorts received morphine, one cohort (n = 39) also received dexmedetom |               |      |                             | dexmedetomidine and lower antiemetics use.                                          |
|            |                                |                                          |                   |idine                                                                  |               |      |                             |                                                                                     |
|            |                                |                                          |                   | Control = 4.2 ± 1.0, dexmedetomine cohort = 4.0 ± 0.8                     |               |      |                             | Ondansetron doses and intraoperative dexmedetomidine dosages (P = 0.017).           |
| Author        | Surgical intervention                  | Name of pain management drug                                      | Complete analgesic protocol                                                                 | Complications | LOS                  | Clinical recommendations                                                                 | Significant outcomes                                                                                                                                 |
|--------------|----------------------------------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------|----------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Festa [39]   | Mininvasive procedure: 6 in ST group, 7 in SB group, Open remodeling: 7 in ST group, 6 in SB group | Levobupivacaine, acetaminophen, tramadol, ketoprofene                 | Levobupivacaine 0.125% (total dose 2 mg/kg), acetaminophen 10 mg/kg every 8 h, tramadol 1 mg/kg every 12 h, ketoprofene 1 mg/kg every 8 h | None          | PICU = scalp block group: 21.1 — control group: 18.1 | A multimodal approach consisting of SNB + acetaminophen was effective for immediate postoperative pain control in pediatric patients aged less than 2 years who underwent cranioeplasty for craniosynostosis. | - Weak evidence in SNB group which showed a longer LOS ($P = 0.04$)  
- Strong evidence in SNB patients which showed earlier oral feeding for both clear fluid and milk ($P = 0.001$) |
| Knackstedt [34] | Fronto-orbital advancement               | Dexmedetomidine, acetaminophen, Ketorolac, ibuprofen, oxycodone and morphine | Acetaminophen (1.5 mg/kg IV q6h), Ketorolac (0.25 mg/kg IV q6h), Ibuprofen (10 mg/kg PO q6h), oxycodone (0.05 mg/kg PO q6h prn), morphine (0.05 mg/kg q4h prn) | Intraoperative: At closure, dexmedetomidine drips are started and continued postoperatively. During postoperative recovery, the drip is titrated to effect and maintained until the first morning following surgery. Postoperative: Every 6 h, 15 mg/kg of acetaminophen is administered intravenously. Every 6 h, ketorolac or ibuprofen are administered. Nurses have the discretion to choose one over the other. Oxycodone and morphine are available and may be given as needed. | NA            | ERAS group 2.3 control group: 3.6         | By using the ERAS approach, the overall as well as the intraoperative allogenic blood transfusion rates were reduced, narcotics were used less, and hospital stays were shorter. | - Patients in the ERAS protocol had a decreased overall LOS ($P = 0.02$)  
- Fewer patients in the ERAS protocol required intraoperative blood transfusion ($P < 0.0001$)  
- From the ERAS protocol patients who required morphine or PO narcotics, fewer doses were needed ($P = 0.0005$, $P = 0.007$, respectively). |

* NA Not available, IV Intravenous, N/V Nausea/vomiting, SNB Scalp nerve block, FLACC Face, Legs, Activity, Cry, Consolability, PCA Parent/patient-controlled analgesia, LOS Length of stay.
Table 3  An overview of characteristics and analgesic protocols for postoperative pain management

| Author      | Surgical intervention         | Name of pain management drug                                                                 | Dose of each drug                                                                 | Complete analgesic protocol                                                                 | Complications                      | LOS | Clinical recommendations | Significant outcomes          |
|-------------|--------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------|-----|--------------------------|-------------------------------|
| Jong [27]   | Cranioplasty                   | Isoflurane, Sevoflurane, Iso- and Sevo-flurane, Acetaminophen IV or supp, Remifentanil IV,  | Single dose                                                                     | 1- ‘M’ technique massage with carrier oil only, i.e., almond oil                          | NA                              | NA  | NA                      | NA                           |
|             |                                | Fentanyl IV, Sufentanyl IV, Propofol IV, Midazolam IV                                       |                                    | 2- ‘M’ technique massage with mandarin 1% in carrier oil                                 |                                 |     |                          |                               |
| Fearon [35] | All cranial vault remodeling   | Oral ibuprofen, acetaminophen, intravenous ketorolac                                           | Intravenous ketorolac 0.5 mg, oral ibuprofen 10 mg, acetaminophen 15 mg/kg       | Patients in the control group were given oral ibuprofen and acetaminophen only, while the treatment group was given IV ketorolac and acetaminophen only. Neither group received any postoperative narcotics, and the thresholds for the medications were determined by standard pediatric nursing assessments for discomfort. | Postoperative nausea and vomiting | 2   | Administer all nonnarcotic pain drugs IV | IV administration decreased severe vomiting significantly (P value < 0.001) compared to oral |
| Arts [29]   | Endoscopic strip craniectomy   | Acetaminophen, low-dose morphine                                                           | Acetaminophen 80 mg/kg/d, low dose morphine 5–40 mg/kg/h                        | Mainly acetaminophen, Morphine was started, when required, at 5 lg/kg/h and increased to a maximum of 40 mg/kg/h depending on the CHIPPS score. | Decline in hemoglobin and hematocrit, blood loss | NA  | NA                      | NA                           |
| Tuncer [37] | Anterior cranial vault, Posterior cranial vault remodeling | Ketorolac, ibuprofen, oxycodone, morphine                                                  | Morphin, Acetaminophen. Before skin incision, either a scalp block or local anesthetic infiltration was performed with 1 mL/kg of 0.2% levobupivacain, associated with epinephrine (0.01 mg/mL) in case of infiltration | 10 mg/kg ibuprofen; 0.25 mg/kg IV ketorolac | The discharge hemoglobin is lower in the ketorolac group compared to the control group | NA  | NA                      | NA                           |
| Chiaretti [10] | NA                           | Remifentanil                                                                                | Remifentanil 0.25 mg/kg/min                                                      | RF was delivered at 0.25 µg/kg/min via continuous infusion, 1 h after admission to the pediatric intensive care unit (PICU). The treatment was continued for 12 h postoperatively | 1 episode of urinary retention | NA  | NA                      | NA                           |
| Author       | Surgical intervention                      | Name of pain management drug                  | Dose of each drug                                                                 | Complete analgesic protocol                                                                 | Complications | LOS | Clinical recommendations | Significant outcomes |
|-------------|--------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------|-----|--------------------------|----------------------|
| Warren [31] | NA                                         | Morphine                                      | Morphine 10 to 40 μg/kg/h                                                         | 10 to 40 μg/kg/h on a continuous morphine infusion order form. The infusion was titrated by the nurses within the rate parameters, based on the patient’s level of pain. | N/V           | NA  | NA                      | NA                   |
| Xu [2]      | Posterior cranial vault expansion           | Morphine, dexmedetomidine, acetaminophen       | For patient 1: 1 mg morphine, dexmedetomidine 0.5 mcg/kg/h, acetaminophen 75 mg Q6H For patient 2: dexmedetomidine 0.2 mcg/kg/h, IV acetaminophen 86 mg Q6H, and morphine 0.4 mg Q3H PRN. | No clear protocol due to the study design                                                   | None          | NA  | NA                      | NA                   |
| Zubovic [33] | Endoscopic repair & open cranial vault remodeling | Acetaminophen, acetaminophen & ibuprofen, oxycodone | Oxycodone 5 mg/5 mL                                                               | Oxycodone 5 mg/5 mL suspension was the only opioid prescribed at discharge. The most common dosing applied was 0.05 mg/kg | NA            | NA  | NA                      | NA                   |
| Marel [28]  | NA                                         | Acetaminophen                                  | Orally 20 mg/kg, rectal 40 mg/kg                                                   | Patients received 20 mg/kg acetaminophen either orally \(n = 20\) or rectally \(n = 20\) every 6 h after a rectal loading dose (40 mg/kg) | NA            | NA  | NA                      | NA                   |

NA Not available, LOS length of hospital stay
According to Fearon et al., the average hospital stay was two days [35]. Arts et al. found that hospitalization lasted 2.6 days [29], Kattail et al. found that it lasted 3.7 days [14], and Zubovic et al. found that it lasted one day [33].

Parental satisfaction
There was only one study that reported parental satisfaction. A study by Festa et al. found that parental satisfaction levels were similar for both groups (Scalp block versus control group) [39].

Quantitative data analysis
Meta-analysis was not possible due to the heterogeneity of the included articles.

Identifying biases, quality assessment, and level of evidence
All included studies were evaluated based on the methodology of these studies. The bias risk was assessed separately and concurrently by two reviewers for the case series studies. The methodological quality and synthesis of the case series and case report was used, and the assessment tool is divided into four domains: selection, ascertainment, causation, and reporting (Table 4) [25]. The risk of bias assessment of eligible RCTs was done independently by two reviewers using the Cochrane Risk of Bias Assessment Tool for Randomized Trials (RoB 2). All of the three included RCTs were considered low risk of bias by the Revised Cochrane tool (Fig. 4) [26]. A Newcastle Ottawa Scale was used for the retrospective and prospective cohort studies. According to the Newcastle–Ottawa scale, case–control and cohort studies scored 7 out of 9, indicating a high quality (Table 5) [24]. According to the level of evidence and grading recommendations of the American Society of Plastic Surgery, two of the articles were level I, eleven articles level II, two articles level III, and one article level IV (Table 1) [23] (Table 6).

Discussion
Postoperative analgesia following open craniosynostosis repair is considered a challenge among plastic and reconstructive surgeons [15]. There is a persistent problem with pediatric patients suffering from acute postsurgical pain that is poorly treated [40–42]. Although numerous studies describe the etiology, evaluation, and treatment of craniosynostosis, few describe its pain management, even though some studies indicate a high prevalence of moderate to severe pain postoperatively [6]. In this systematic review, we compared the literature on perioperative pain management regarding potential clinical outcomes, recommendations, administration methods, and outcomes for different options for managing pain following craniosynostosis surgery.

A substantial amount of variability has been observed in the published data on intraoperative analgesia for craniosynostosis surgery. Among the seven studies, we found describing intraoperative pain management, each used a different protocol, from IV opioids alone to IV opioids combined with other drugs (e.g., Acetaminophen, NSAIDs, Gabapentin, and Dexmedetomidine). Thus, a unified intraoperative pain management protocol should be established through more studies in the future. As for postoperative analgesia, most studies used multimodal analgesia, with opioids (e.g., Morphine, Tramadol) and Acetaminophen being the most commonly used.

The known side effects of opioids range from nausea, vomiting, and urinary retention to more serious adverse effects such as respiratory depression, oversedation, and hypotension [10]. Dexmedetomidine has been used in some studies as a substitute for opioids to minimize these effects. A study by Reddy et al. in which the author

Table 4  A qualitative assessment of the case series included

| Reference | Selection | Ascertainment | Causality | Reporting |
|-----------|-----------|---------------|-----------|-----------|
|           | Q. 1      | Q. 2          | Q. 3      | Q. 4      | Q. 5      | Q. 6      | Q. 7      | Q. 8      |
| Xu [2]    | Yes       | Yes           | Yes       | Yes       | No        | No        | No        | Yes       |

Selection: [question 1]. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentations may not have been reported?

Ascertainment: [question 2]. Was the exposure adequately ascertained? [question 3]. Was the outcome adequately ascertained?

Causality: [question 4]. Were other alternative causes that may explain the observation ruled out? [question 5]. Was there a challenge/rechallenge phenomenon? [question 6]. Was there a dose–response effect? [question 7]. Was follow-up long enough for outcomes to occur?

Reporting: [question 8]. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?
describes using Dexmedetomidine as an opiate-sparing agent revealed that Dexmedetomidine was not associated with reduced opioid requirements by children postoperatively. The study also compared postoperative acetaminophen requirements, in which it found no significant difference between the group that received Dexmedetomidine versus the control group. However, patients who received Dexmedetomidine intraoperatively showed a significant reduction in their need for rescue medication for nausea and vomiting postoperatively [32]. Nonetheless, Fearon et al. pointed out that despite opioid avoidance, some craniosynostosis patients in their center who were given oral non-narcotics still suffered from nausea and vomiting [35]. Regarding respiratory depression and oversedation, the few reports that describe their occurrence in craniosynostosis patients treated with IV opioids suggest that these major complications are unlikely to occur [14, 31, 43].

In cranioplasty procedures, scalp nerve blocks (SNBs) have been reported to be adjuncts to traditional postoperative analgesia and as interventions for reducing intraoperative blood loss [38]. Guilfoyle et al.’s systematic review and meta-analysis found reduced postoperative pain when using regional SNBs in pediatric patients undergoing craniotomy [44]. However, current studies showed that the duration of postoperative opiate use following SNBs has not been found to be reduced [45]. Remifentanil is a potent synthetic opioid with a marked postoperative analgesic effect. Chiaretti et al. found that children who had a postoperative infusion of Remifentanil showed improvement in hemodynamic and behavioral parameters and pain control with no significant side effects, apart from one case of

Table 5 The Newcastle–Ottawa Scale for the included cohort studies

| Article       | Selection | Comparability | Outcome | Quality Score |
|---------------|-----------|---------------|---------|---------------|
|               | Q1 Q2 Q3 Q4 | Q5 | Q6 Q7 Q8 |               |
| Arts [29]     | *          | * *          | *       |               |
| Reddy [32]    | *          | * *          | *       |               |
| Kattail [14]  | *          | * *          | *       |               |
| Tuncer [37]   | *          | * *          | *       |               |
| Knackstedt [34]| *          | * *          | *       |               |
| Chiaretti [10]| *          | * *          | *       |               |
| Warren [31]   | *          | * *          | *       |               |
| Bracho [36]   | *          | * *          | *       |               |
| Bronco [30]   | *          | * *          | *       |               |
| Zubovic [33]  | *          | * *          | *       |               |

Selection: Q1. Representativeness of the exposure cohort? Q2. Selection of the non-exposure cohort? Q3. Ascertained measurement? Q4. Demonstration that outcome of interest was not present at the start of the study?

Comparability: Q5. Comparability of cohort on the basis of the design or analysis?

Outcome: Q6. Assessment of outcome? Q7. Was follow-up long enough for outcomes to occur? Q8. Adequacy of follow-up of cohorts?
As a result, the children required further analgesia [12].

Furthermore, regarding the length of stay (LOS), one study demonstrated that the total doses of opioids administered postoperatively was not associated with the overall LOS [6]. On the other hand, Festa et al. found that adding SNB to the anesthetic protocol could potentially decrease the overall LOS compared to using general anesthesia alone [39]. However, LOS has not been explored in further depth. Therefore, more studies should explore the effect of various anesthetic and analgesic protocols on the length of stay in the field of craniosynostosis.

Strength and limitations

This review has several limitations. Due to the heterogeneity of the included studies, no conclusions could have been drawn in the aggregate. In addition, meta-analysis was not possible. Also, the lack of consistency in the used pain medications, as well as their dosage, route of administration, and outcomes measured by the studies, prevents the development of substantial quantitative conclusions. Moreover, there is a scarcity in the available high-quality body of literature that looks into the pre-, peri-, and postoperative management of craniosynostosis. However, to the authors’ knowledge, this is the only systematic review that summarizes the use of analgesic agents in the pre-, intra-, and post-craniosynostosis repair surgery in the area. As part of our review, we focused on highlighting the fact that perioperative pain control for pediatric craniosynostosis patients is variable. In our study, the importance lies primarily in the usefulness of the tables and graphs used to report the different perioperative pain management options and the protocols for their application in clinical practice. Further comparative randomized controlled trials are required to determine the benefits and side effects of each agent. By comparing the intervention to the golden standard of care and to other interventions as well, we will be able to draw better, more accurate conclusions. For the management of postoperative pain after craniosynostosis surgery, standardized trials with clear, consistent, and non-biased outcomes can facilitate meta-analyses. To reduce the methodology disparity and improve the validity of the article by adding meta-analysis, we recommend that future studies focus mostly on prospective studies and RCTs. Studies are needed to compare the advantages and disadvantages of analgesia accurately. Also, future high-quality studies with large sample sizes are encouraged to establish a standard protocol for craniosynostosis perioperative pain management.

Conclusion

The perioperative pain management plan is essential for any surgeon to decide prior to any major procedure, especially for pediatric patients undergoing invasive procedures such as craniosynostosis repair, which requires special considerations and regular adjustments. Based on this systematic review, the authors identified the most commonly used analgesics for pain control in pediatric patients undergoing cranioplasty, along with common side effects, length of hospitalization, and postoperative pain scores. Morphine is the most commonly used opioid as a single treatment, in combination with ketorolac, as it is found to have the shortest length of hospitalization and the lowest dose of opioids to control the pain. Second, SNB should be added to the intraoperative regimen as it is found to influence the length of hospitalization as well. Future clinical trials comparing the different types of analgesic combinations are recommended to further advance the understanding and practice of craniosynostosis pain management.

Abbreviations

NSAIDs: Nonsteroidal anti-inflammatory drugs; PICUs: Pediatric intensive care units; IV: Intravenous; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: Prospective Register of Systematic Reviews; CHEOPS: Children’s Hospital of Eastern Ontario Pain Score; FLACC: Face, Legs,
Activity, Cry, Consolability, OPS: Objective pain scale; CC: Case—control; CS: Case series; R: Retrospective cohort; P: Prospective cohort; M: Male; F: Female; NA: Not available; USA: United States of America; N/V: Nausea/vomiting; SNB: Scalp nerve block; PCA: Parent/patient-controlled analgesia; LOS: Length of stay.

Acknowledgements
This work was supported by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia.

Authors’ contributions
H.M.: concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript editing, and manuscript review. R.A.: concept, design, definition of intellectual content, literature search, manuscript editing, and manuscript review. N.A.: literature search, clinical studies, manuscript preparation, manuscript editing, and manuscript review. H.A.: literature search, clinical studies, manuscript preparation, manuscript editing, and manuscript review. G.A.: concept, design, definition of intellectual content, literature search, manuscript, manuscript editing, and manuscript review. S.A.: literature search, clinical studies, manuscript preparation, manuscript editing, and manuscript review. K.A.: concept, design, definition of intellectual content, literature search, manuscript editing, and manuscript review. The authors have read and approved the manuscript.

Funding
The authors declare that there is no conflict of interest or funding source.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was waived due to the nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Surgery, Division of Plastic Surgery, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. 2 Department of Plastic Surgery & Burn Unit, King Saud Medical City, Riyadh, Saudi Arabia. 3 Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. 4 College of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia. 5 Department of Plastic Surgery and Burn Unit, Security Forces Hospital, Riyadh, Saudi Arabia. 6 Division of Plastic Surgery, Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

Received: 2 September 2022   Accepted: 5 October 2022
Published online: 14 October 2022

References
1. Abdel-Aziz M, Ahmed A, Naguib N, Abdel-Khalik MI (2012) The effect of steroid injection of the tongue base on reducing postoperative airway obstruction in cleft palate repair. Int J Oral Maxillofac Surg 41(5):612–615
2. Arts S, Delye H, van Lindert EJ, Blok L, Borstlap W, Driessen J (2018) Evaluation of anesthesia in endoscopic strip cranietomy: a review of 121 patients. Pediatr Anesth 28(7):647–653
3. Bernie KA, Chambers CT, Fernandez CV, Forgeron PA, Latimer MA, McGrath PJ et al (2014) Hospitalized children continue to report undertreated and preventable pain. Pain Res Manage 19(4):198–204
4. Boku A, Hanamoto H, Oyamaguchi A, Inoue M, Morimoto Y, Niwa H (2016) Effectiveness of dexmedetomidine for emergence agitation in infants undergoing palatoplasty: a randomized controlled trial. Rev Bras Anestesiol 66:37–43
5. Bracho GFP, de Souza Neta EP, Grousset S, Mottolense C, Dailler F (2014) Opioid consumption after levobupivacaine scalp nerve block for craniosynostosis surgery. Acta Anaesthesiol Taiwan 52(2):64–69
6. Bronco A, Pietrini D, Lamperti M, Somaini M, Tosi F, Minoglu del Lungo LS et al (2014) Incidence of pain after craniotomy in children. Pediatr Anesth 24(7):781–787
7. Brown S, Yao A, Sanati-Mehrzy P, Zackai SP, Taub PJ (2019) Postoperative pain management following craniosynostosis repair: current practices and future directions. J Craniofac Surg 30(3):721–729
8. Cercueil I, Migeon A, Desgranges FP, Chassard D, Bouvet L (2018) Postoperative analgesia for craniosynostosis reconstruction: scalp nerve block or local anesthetic infiltration? Paediatr Anaesth 28(5):474–475
9. Chiaretti A, Pietrini D, Piastra M, Polidor S, Gavoli A, Velardi F et al (2000) Safety and efficacy of remifentanil in craniosynostosis repair in children less than 1 year old. Pediatr Neurosurg 33(2):85–88
10. De Beer D, Mackerie A (2001) Safety and efficacy of remifentanil infusion in craniosynostosis repair in infants. Pediatr Neurosurg 34(6):327–327
11. Fearon JA, Dimas V, Dithakhase K, Herbert MA (2015) A randomized controlled trial of oral versus intravenous administration of a non-narcotic analgesia protocol following pediatric craniosynostosis corrections on nausea and vomiting rates. J Craniofac Surg 26(6):1951–1953
12. Festa R, Tosi F, Pusateri A, Mensi S, Garra R, Mancini A et al (2020) The scalp block for postoperative pain control in craniosynostosis surgery: a case control study. Childs Nerv Syst 36(12):3063–3070
13. Groenewald CB, Rabbits JA, Schroeder DR, Harrison TE (2012) Prevalence of moderate–severe pain in hospitalized children. Pediatr Anesth 22(7):661–668
14. Guiffoyle MR, Helmy A, Duane D, Hutchinson PJ (2013) Regional scalp block for postcranioanatomy analgesia: a systematic review and meta-analysis. Anesth Analg 116(5):1093–1102
15. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al (2011) The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 343:d5928
16. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ et al. (2019) Cochrane handbook for systematic reviews of interventions. Wiley
17. Hoeftiffin SM (1998) The extended supraplatysmal plane (ESP) face lift. Plast Reconstr Surg 101(2):494–503
18. Jong M, Lucas C, Boelhouwer H, Adrichem L, Tibboel D, van Dijk M (2012) Does postoperative ‘M’ technique (R) massage with or without mandarin oil reduce infants’ distress after major craniofacial surgery? J Adv Nurs 68(8):1748–1757
19. Kattail D, Macmillan A, Musavi L, Pedreira F, Faateh M, Cho R et al (2018) Pain management for nonsyndromic craniosynostosis: adequate analgesia in a pediatric cohort? J Craniofac Surg 29(5):1148–1153
20. Kayyal TA, Wolswinkel EM, Weathers WM, Capehart SJ, Monson LA, Buchanan EP et al (2014) Treatment effects of dexmedetomidine and ketamine on postoperative analgesia after cleft palate repair. Craniomaxillofac Trauma Reconstr 7(2):131–138
21. Knackstedt R, Patel N (2020) Enhanced recovery protocol after fronto-orbital advancement reduces transfusions, narcotic usage, and length of stay. Plast Reconstr Surg Glob Open 8(10):e3205
22. Kozlowski LJ, Kost-Byerly S, Colantuoni E, Thompson CB, Vasquesna KJ, Rothman SK et al (2014) Pain prevalence, intensity, assessment and management in a hospitalized pediatric population. Pain Manag Nurs 15(1):22–35
23. Lee Steely R, Collins DR, Cohen BE, Bass K (2004) Postoperative nausea and vomiting in the plastic surgery patient. Aesthetic Plast Surg 28(1):29–32
24. Mathijssen IM (2015) Guideline for care of patients with the diagnoses of craniosynostosis: working group on craniosynostosis. J Craniofac Surg 26(6):1735
25. Maxwell LG, Buckley GM, Kudchadkar SR, Ely E, Stebbins EL, Dube C et al (2014) Pain management following major intracranial surgery in pediatric patients: a prospective cohort study in three academic children’s hospitals. Pediatr Anesth 24(11):1132–1140
26. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
27. Murad MH, Sultan S, Haffar S, Bazerbachi F (2018) Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 23(2):60–63
28. Ouzzani M, Hammady H, Fekrazad Z, Elmagarmid A (2016) Rayyan—a web and mobile app for systematic reviews. Syst Rev 5(1):1–10
29. Park KM, Tripathi NV, Al-Mufarrij F (2021) Quality of life in patients with craniosynostosis and deformational plagiocephaly: a systematic review. Int J Pediatr Otorhinolaryngol 149:110873
30. Peng W, Zhang T (2015) Dexametomidine decreases the emergence agitation in infant patients undergoing cleft palate repair surgery after general anesthesia. BMC Anesthesiol 15(1):1–7
31. Pietrini D, Ciano F, Forte E, Tosi F, Zanghi F et al (2005) Sevoflurane–remifentanil vs isoflurane–remifentanil for the surgical correction of craniosynostosis in infants. Pediatr Anesth 15(8):653–662
32. Redley SK, Jones JJ, Gordish-Dressman H, Pestieau SR (2020) Dexametomidine as an opioid-sparing agent in pediatric craniofacial surgery. Children 7(7):68
33. Rothera E, Chumas P, Liddington M, Russell J, Guruswamy V (2014) Scalp blocks in nonsyndromic craniosynostosis surgery-a retrospective case series review. Paediatr Anaesth 24(8):894–895
34. Schiavo JH (2019) PROSPERO: an international register of systematic review protocols. Med Ref Serv Q 38(2):171–180
35. Senders CW, Emery BE, Sykes JM, Brodie HA (1996) A prospective, double-blind, randomized study of the effects of perioperative steroids on palatoplasty patients. Arch Otolaryngol Head Neck Surg 122(3):267–270
36. Srivatsa S, Heiman AJ, Gray MC, Carpenter C, Patel A (2021) Variations in postoperative management of pediatric open-vault craniosynostosis. J Craniofac Surg 32(1):305–309
37. Sullivan D, Chung KC, Eaves FF III, Rohrich RJ (2011) The level of evidence pyramid: indicating levels of evidence in Plastic and Reconstructive Surgery articles. Plast Reconstr Surg 128(1):311–314
38. Turnel U, Turan A, Bayraktar MA, Erkorkmaz U, Kostakoglu N (2013) Efficacy of dexamethasone with controlled hypotension on intraoperative bleeding, postoperative oedema and ecchymosis in rhinoplasty. J Cranio-Maxillofac Surg 41(2):124–128
39. Tuncer F, Knackstedt R, Murthy A, Patel N (2019) Postoperative ketorolac administration is not associated with hemorrhage in cranial vault remodeling for craniosynostosis. Plast Reconstr Surg Glob Open 7(8):e2401
40. van der Marel CD, van Lingen RA, Pluim MA, Sooones G, van Dijk M, Vaandrager JM et al (2001) Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther 70(1):82–90
41. Warren DT, Bowen-Roberts T, Ou C, Purdy R, Steinbok P (2010) Safety and efficacy of continuous morphine infusions following pediatric cranial surgery in a surgical ward setting. Childs Nerv Syst 26(11):1535–1541
42. Weber CR, Griffin JM (1994) Evaluation of dexamethasone for reducing postoperative edema and inflammatory response after orthognathic surgery. J Oral Maxillofac Surg 52(1):35–39
43. Wells GA, Shea B, O’Connell D, Peterson J, Welch, V, Losos M, et al (2000) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. In: Oxford
44. Xu H, Bui A, Brown S, Sanati-Mehrizy P, Zacker SP, Taub PJ (2020) The role of precededex in post-operative pain management following craniosynostosis repair. J Craniofac Surg 31(6):e669–e672
45. Zubovic E, Skolnick GB, AuBuchon JD, Waters EA, Snyder-Warwick AK, Patel KB (2022) Variability and excess in opioid prescribing patterns after cleft and craniosynostosis repairs. Cleft Palate Craniofac J,10556656221083082

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.