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SYSTEMATIC REVIEW

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Assessing modalities used to alleviate postoperative pain in children receiving dental treatment under general anaesthesia: a systematic review

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Abstract

Postoperative pain is generally a novel experience among paediatric patients. Topical anaesthetics, distraction procedures, and buffering of anaesthetic solutions have been used in reducing the postoperative pain. In this review, the authors assessed various modalities used to alleviate postoperative pain in children's dental treatment under general anaesthesia. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol were strictly adhered to in this systematic review. Specific keywords including postoperative pain, general anaesthesia, children, and dental extraction were used in the search for relevant randomized control trial studies in Web of Science, Scopus, and PubMed, and included articles published until June 2021. From a total of 191 abstracts, 21 were reviewed. From the six studies with the usage of non-steroidal anti-inflammatory drugs (NSAIDs) alone or in combination with paracetamol, four observed that the preoperative use of NSAIDs alone or in combination was better than paracetamol alone, one discovered preoperative intravenous paracetamol was better than postoperative intravenous paracetamol, and the remaining study found no difference among various groups. Of two studies comparing the usage of non-steroidal anti-inflammatory drugs with opioid analgesics, one stated intravenous fentanyl in combination was better, while the other study found no difference among groups. The results obtained in this review can be utilized by physicians to control postoperative pain in children undergoing dental treatment under general anaesthesia.

Keywords

Postoperative pain; General anaesthesia; Dental extraction; Children

1. Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience" by an individual and is subjective in nature [1]. Pain is described by McCaffery and Pasero's (1979) Clinical Manual as "whatever the experiencing person says it is and exists whenever he says it does" [2] which further highlights its subjective nature. Pain is multifaceted, causes significant distress to the patient and has potential adverse effects on the social, functional and psychological well-being of an individual [3, 4]. Despite the availability of local anaesthesia (LA) and conscious sedation, most children undergo general anaesthesia (GA) due to the lack of cooperation, multiple extractions, dental anxiety, pain, younger age, intellectual disability, previous history of lack of cooperation, acute abscess, parents request, facial swelling, and in some cases allergy to local anaesthesia [5, 6].

Postoperative pain is the most common postoperative complication observed in the American Society of Anaesthesiologists (ASA) I, II and III groups of children [7, 8]. Postoperative pain is acute and is present in over 80% of individuals [9]. The majority of paediatric patients receiving comprehensive dental treatment under GA experience sore mouth, difficulty eating, sobbing on the way home, and expressing distress with persistent bleeding and nausea [10, 11]. In addition, bad dreams, increased anxiety, altered behaviour, mental discomfort, and enuresis are related to children having postoperative pain under GA [12]. The emotional distress of children undergoing dental treatment under general anaesthesia will be increased multiple fold with increased postoperative pain [13].

The ASA practice guidelines for postoperative acute pain management refer to actions taken "before, during, and after a procedure that is intended to reduce or eliminate postoperative pain before discharge" [14]. Hence, effective management of postoperative pain control is mandatory for children undergoing dental treatment under GA to prevent prolonged hospitalization, reduce economic burden, and increase patient satisfaction [7]. Studies have also shown that age, the anxiety level of the patient, existing preoperative pain and the type

of surgery predict postoperative pain [15]. Identification of patients based on the predictors mentioned above is essential to customize pain relief for patients. The purpose of this systematic review is to assess the various pharmacological modalities used to manage postoperative pain in children and identify the frequency and incidence of postoperative pain in children undergoing dental treatment under GA. Thus, aiding physicians to determine the best analgesia for effective postoperative pain control.

2. Materials and methods

2.1 PRISMA protocol

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols were strictly adhered in this systematic review (Fig. 1). The study protocols were developed prior to data collection and were registered in the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42021275625).

2.2 Search strategy

Specific keywords were used in the search in Web of Science, Scopus and PubMed, and included articles published until June 2021. The keywords utilised in data mining were "children", "general anaesthesia", "postoperative pain" and "dental extraction".

2.3 Inclusion and exclusion criteria

The inclusion criteria were children and adolescents between 0 and 18 years of age who received comprehensive dental treatment under GA which consisted of a combination of preventive, restorative and exodontia procedures. The search was limited to randomized control trials and case-control interventional studies with modalities or interventions used to manage postoperative pain. Children with ASA physical status I, II and III groups were included in the review. Studies involving adults or a combination of adults and children were eliminated along with studies involving children exclusively treated under local anaesthesia or conscious sedation. Other studies such as observational, cohort studies, narrative reviews, systematic reviews with or without meta-analysis, case reports/case series, letters to editor, editorials, conference proceedings, book chapters and commentaries were eliminated. Only articles written in the English language were selected.

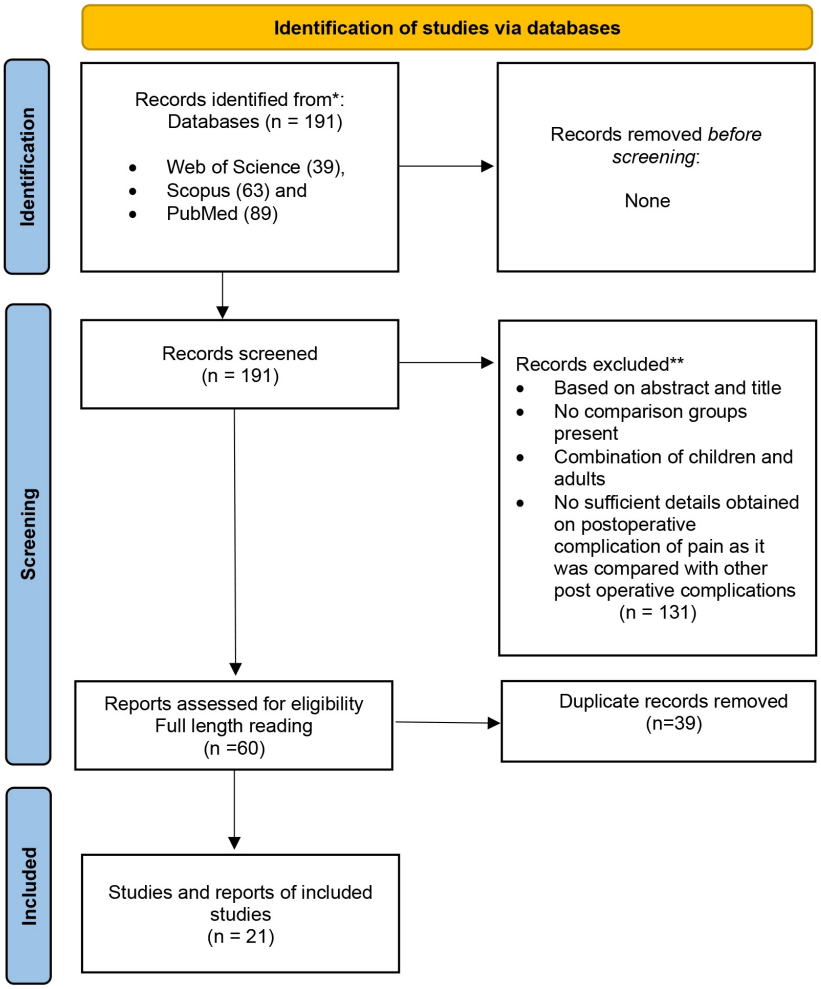

FIGURE 1. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols used in this study.

2.4 Focused question

The study protocol asked the following question "What are the various pharmacological modalities used to control postoperative pain in children undergoing dental treatment under general anaesthesia?". The framework of the population (P), intervention (I), comparison (C) and outcome (O) were used for this focused question. The participants were the children undergoing dental treatment under GA who received modalities to alleviate postoperative pain, while the control group consisted of children undergoing dental treatment under GA without any modalities. The interventions were the modalities alleviating postoperative pain. The outcome of the study focused on the frequency, incidence, and need for intervention with rescue analgesics in children receiving dental treatment under GA.

2.5 Studies selection and data extraction

Two independent reviewers extracted the data to reduce the risk of bias, and any arising disagreement was resolved with a third reviewer. The data extracted included authors' names, year of publication, country of origin, type of study, characteristics of demography, treatment modalities, preoperative and intraoperative pharmacological agents used, its frequency, duration of procedures, intensity of postoperative pain, postoperative analgesia used, route of administration and results.

2.6 Risk of bias assessment

Joanna Briggs Institute critical appraisal checklist was used to assess the risk of bias for the randomized control trial studies.

3. Results

Overall, 191 abstracts from the Web of Science (39), Scopus (63), and PubMed (89) were found. Of 191 abstracts, another 131 were eliminated based on the inclusion and exclusion criteria. Of the 60 abstracts selected for full-length reading, only 21 were selected for the systematic review after 39 duplicates were removed.

The pharmacologic modalities to relieve postoperative pain were divided based on the use of NSAIDs alone or in combination, with opioid analgesics and LA. All the studies in this systematic review utilized rescue analgesics by assessing the pain score of the patient, or as a routine regimen, except for a randomized control trial by Gazal *et al*. [16].

3.1 Usage of non-steroidal anti-inflammatory drugs alone or in combination with postoperative analgesia

The study by Gazal *et al*. [17] observed that preoperative ibuprofen alone or in combination with paracetamol provided better pain relief than groups where only paracetamol was administered. Similar results were obtained in the randomized clinical trial performed by El Batawi [18] which found that 93.8% of the children had varying degrees of postoperative pain, and diclofenac provided better pain relief than acetaminophen. The retrospective audit conducted by Marshall *et al*. [19] also found that the combination of paracetamol with non-steroidal anti-inflammatory drugs as recommended by the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) had lower postoperative pain.

The study conducted by O'Donnell *et al*. [20] found that preoperative administration of rectal Voltarol was better than preoperative oral paracetamol in providing pain relief to children. In the randomized study by Kharouba *et al*. [21], it was observed that the preoperative intravenous (IV) paracetamol group reported lower pain score when compared to the group with IV paracetamol postoperatively. However, a study done by Jensen [22] contradicts with other studies as there was no difference in postoperative pain scores among intra-operative paracetamol alone, NSAIDs, opioids and combination groups.

The majority of the studies recommended that the preoperative administration of NSAIDs in combination with paracetamol was effective in reducing postoperative pain scores. The demography, type of study, treatment procedures, diagnostic modality, results, and inferences on the usage of postoperative analgesics among the non-steroidal anti-inflammatory studies are displayed in **Supplementary Table 1**.

3.2 Comparison of the usage of non-steroidal anti-inflammatory drugs with opioid analgesics in postoperative analgesia

The prospective service evaluation by Alohali *et al*. [12] found that IV fentanyl, a short-acting opioid, in combination with paracetamol decreased postoperative pain with an odds ratio of 0.17 when compared to IV fentanyl, IV paracetamol, and control group, although 98.6% of their study population were given rescue analgesics due to postoperative pain. In contrast, the study by Littlejohn *et al*. [23] showed no significant difference in the pain scores between IV nalbuphine, IV diclofenac suppositories, and the control groups. As these were the only two studies which compared the usage of opioid analgesics with non-steroidal anti-inflammatory drugs, further studies are warranted to be conclusive and the results are shown in **Supplementary Table 2**.

3.3 Usage of opioids in postoperative analgesia

The randomized control trial conducted by Sheta *et al*. [24] compared preoperative intranasal midazolam with intranasal dexmedetomidine and found decreased postoperative pain in the latter. Around 86.1% of the children in this study experienced postoperative pain and were given rescue analgesics. Another randomized control trial conducted by Roelofse *et al*. [25] observed that the intranasal sufentanil and intranasal midazolam group experienced less postoperative pain when compared to the intranasal ketamine and intranasal midazolam group. A randomized control trial by Roelofse *et al*. [26] showed that IV tramadol provided better postoperative analgesia than the control group. **Supplementary Table 3** compared the various opioids used in studies for postoperative pain relief in children. The randomized control trial by McIntyre *et al*. [27] showed no difference in pain scores between the dexamethasone and normal saline group.

3.4 Usage of local anaesthesia alone or in combination with paracetamol and NSAIDs in postoperative analgesia

The randomized control trial by Coulthard *et al*. [28] compared LA with the group that received saline and found that the former was not effective in decreasing postoperative pain in children. Almost 84.9% of their study group received rescue analgesics. A randomized control study by McWilliams *et al*. [29] found no significant difference in postoperative pain scores between local anaesthesia and the group without local anaesthesia. Although this study stated that their study population experienced decreased postoperative pain due to usage of preoperative paracetamol and NSAIDs combination. This study recorded the postoperative analgesics administered but no attempt was made to randomize or systematically allocate patients to different study groups. A randomized prospective study by Townsend *et al*. [30] observed no significant pain score difference between groups receiving IV ketorolac with oral infiltration of LA and IV ketorolac group alone.

On the other hand, Jürgens *et al*. [31] compared LA injections with IV fentanyl alone or in combination with paracetamol, and stated that LA had a better analgesic effect postoperatively when compared to systemic analgesics. Another randomized control trial conducted by Leong *et al*. [32] compared various techniques of LA administration, such as the intra-ligamental injection technique with infiltration, to the control group and found no significant difference in postoperative pain, despite there being a decrease in pain scores in all groups. Another randomized control trial by Sammons *et al*. [33] observed a reduction in pain score in the intra-ligamental injection group when compared to the control group, although a reduction in pain was noticed in the first hour postoperatively. Thus,the role of LA in decreasing pain scores was insignificant, even though a decrease in postoperative bleeding was reported in most of these studies. The comparison for the randomised control trials involving the use of local anaesthesia is mentioned in **Supplementary Table 4**.

3.5 Usage of topical local anaesthesia alone in postoperative analgesia

A randomized control trial by Andrzejowski *et al*. [34] stated no difference in pain scores between the topical bupivacaine and saline group. Furthermore, a similar randomized control trial by Gazal *et al*. [16] also observed that topical bupivacaine did not provide an efficient analgesic effect postoperatively. From these studies, the exclusive use of topical bupivacaine did not reduce pain scores for children undergoing comprehensive dental treatment under GA. The comparison of these two randomized control trials for topical anaesthesia is shown in **Supplementary Table 5**.

3.6 Risk of bias

The Joanna Briggs analysis was used in this study to measure the risk of bias in the selected randomized control trials. The risk of bias is considered low if the score of the analysis is more than 9, moderate between 7–9 scores, and high if the score is less than 7. Fifteen studies were categorised under low risk of bias [12, 16–18, 21, 23–28, 30, 32–34] while four under moderate risk [20, 22, 29, 31] and two studies with high risk of bias [19, 35], respectively. The latter recorded the postoperative analgesics were administered, but that the patients were not randomized or systematically allotted into different analgesic groups [29].

The time point of postoperative pain assessment varied among the studies, with the lowest postoperative assessment conducted 15 minutes after recovery, while others made observations for a few hours post general anaesthesia recovery, and some extended their follow-up to a week. In these studies, adequate post-operative pain follow-ups were done for a week [12, 35], until 4 days [22] and up to 3 days [32, 33]. There were four studies which had post-operative pain follow-ups of up to 24 hours [21, 27, 28, 31], followed by studies which recorded follow-ups of up to 4 hours [25, 30], up to 2 hours [18, 26], up to 60 minutes [24], up to 45 minutes [23], and up to 30 minutes [34]. Some studies had less than 15 minutes of postoperative pain follow-up [16, 17, 20], while no post-operative pain observations were observed in two studies [19, 29].

Children gaining consciousness from GA are often disoriented. Therefore, self-reported pain scores obtained at arousal and 30 minutes would not be meaningful [28]. There is a significant correlation between pain scores obtained by patients and research nurses, whereas there was a significant deviation of scores when the parents are involved [28, 36, 37].

4. Discussion

The preoperative use of ibuprofen alone or in combination with paracetamol had reduced pain scores than paracetamol alone groups as stated by Gazal *et al*. [17] and Marshall *et al*. [19]. This is in agreement with the systematic review in which six studies had decreased postoperative pain scores with paracetamol in combination with NSAIDs in general surgical procedures [38]. This is also similar to the study done by McGaw *et al*. [39] which compared the use of ibuprofen to paracetamol in children undergoing extraction of their permanent teeth. Pickering *et al*. [40] reported that the use of ibuprofen in combination with paracetamol reduced postoperative pain in children undergoing tonsillectomy. A study by Dionne [41] also stated that the use of ibuprofen in combination with paracetamol provided better postoperative analgesia. One possible reason for the better analgesic effect of ibuprofen in combination with paracetamol is that it inhibits prostaglandin release centrally and peripherally at the site of injury [42–44].

In the study by Gazal *et al*. [17], there was a higher pain and distress score in 2 to 7 years old children when compared to 8 to 12 years old children. This was in agreement with studies by Gazal *et al*. [16] and Coulthard *et al*. [28]. Higher pain scores and distress were also observed in children who had 7 to 14 teeth extracted in comparison to between 1 and 6 extractions [17, 28, 45, 46]. The reason behind the increased in pain is due to an increase in the synthesis of prostaglandin which is directly associated with the increase in the number of surgical areas [11, 38, 47]. Other studies by Woolf [48] and Gill *et al*. [49] stated that an increase in tissue injury causes an increase in dorsal

horn neurons excitation, which could contribute to an increase in the duration of postoperative pain. Furthermore, the distress could be related to intraoral bleeding, an uncomfortable taste of blood, delayed calling of parents after arousal, and decreased cognitive development in younger children [16, 31, 50].

Two studies by Batawi [18] and O'Donnell *et al*. [20] which compared rectal Voltarol and oral diclofenac with paracetamol, found that NSAIDs have decreased pain scores postoperatively when compared to acetaminophen. This finding is in agreement with the study by Baygin *et al*. [51] which stated that preoperative use of diclofenac provided more analgesia when compared to paracetamol at $p < 0.001$ and $p < 0.009$ at 15 mins and 4 hours post-extraction for children undergoing extraction in dental clinic setup. This is also similar to the study by Olson *et al*. [52] which compared ibuprofen, ketoprofen and acetaminophen for faster onset of postoperative pain relief. Better postoperative analgesia was obtained with IV administration of diclofenac, especially in cases with more than 3 traumatic dental extractions, because of its anti-inflammatory and analgesic effect on acute neurogenic nature of injury [18, 53]. This could be due to the onset of action of diclofenac at 20 to 24 minutes in rectal administration, where the first-pass metabolism of the drug is avoided [54]. Whereas for oral paracetamol, the onset is at least 1 hour and the bioavailability of paracetamol after first-pass metabolism is only 60% in its active form [52, 53, 55, 56].

The rationale for decreased pain score with preoperative use could be because most studies used paracetamol through the oral and rectal route. The peak effect takes at least an hour, so administering it at the end of the procedure delayed the analgesic effect in recovery. To prevent this, it can either be administered preoperatively or IV paracetamol could be used intra-operatively as it has a rapid onset of 15 mins [57]. An earlier study by Romej *et al*. [58] stated that preoperative oral acetaminophen patients required less rescue morphine postoperatively when compared to the group with rectal acetaminophen at the end of the procedure. Another study stated that a better preoperative analgesic effect of paracetamol could be due to its serotonergic pain pathway mechanism which interrupts the repeated firing of neurons from the surgical site [59]. A similar study by Reuben *et al*. [60] observed that preoperative administration of rofecoxib required less postoperative analgesics when compared to the intra-operative group ($p < 0.001$), and rectal diclofenac reached peak analgesic effect at 30 mins. However, this was contradicted by a meta-analysis done by Ashley *et al*. [61] which showed no sufficient evidence to warrant the benefit of preoperative analgesics for children treated under LA in dental clinics. The side effects of NSAIDs include asthma, gastric bleeding, hepatotoxicity and nephrotoxicity, and caution should be warranted in children [62].

In a study by Alohali *et al*. [12], they found that combining fentanyl, a short-acting opioid with NSAIDs decreased the pain score postoperatively in children, whereas the study by Littlejohn *et al*. [23] lacked significant differences. Further studies are warranted in this area of dentistry. The decision to utilize IV fentanyl depends largely on the anaesthetist or the dentist, based on the treatment provided [12]. The respiratory depression caused by fentanyl plays an important role hence rarely utilized in children receiving comprehensive dental treatment under GA [63].

Nalbuphine hydrochloride, a partial opioid agonist, provided a better analgesic effect than morphine in children, especially in cases with dental extractions [64–67]. Although they are believed to have low incidences of side effects like nausea and vomiting, a study by Littlejohn *et al*. [23], showed that two patients developed laryngospasms in comparison to none in the NSAIDs and control group [68]. Sheta *et al*. [24] observed more compliance to sedation, decreased postoperative pain score, and distress among children with the use of dexmedetomidine than midazolam. Midazolam is benzo diazepam, a sedative given as premedication to calm children, reduce anxiety, emotional trauma, and facilitate a smooth induction. However, 36.1% of the children experienced adverse effect of nasal irritation in this study [69]. Dexmedetomidine is an α2A adrenoreceptor agonist which has sedative and analgesic effects, and acts on the locus coeruleus by mimicking arousal from natural sleep rather than from sedation [70]. Although intranasal sedation of dexmedetomidine has a rapid onset of action, non-invasive and has a higher compliance rate in younger children, the adverse effects such as hypotension, bradycardia and hemodynamic disturbances pose a limitation on its use [71–73]. A previous study by Roelofse *et al*. [25] observed that the intranasal sufentanil and intranasal midazolam group had a decreased postoperative pain score when compared to intranasal ketamine and intranasal midazolam group. Sufentanil is an opioid agonist analgesic which is twice as potent as fentanyl in providing postoperative analgesia and reducing separation anxiety due to unfamiliar surroundings. Although no respiratory depression was seen in this study, the limited studies with the intranasal use of sufentanil pose a barrier to reach a conclusion [74]. Intranasal analgesia has been recommended in the above studies [24, 25] because of its rapid absorption, skipping the first-pass metabolism through the liver, increased bioavailability compared to oral dosing, and increased compliance [75, 76].

Tramadol is a centrally acting opioid agonist which inhibits noradrenaline and serotonin (5HT) reuptake, providing analgesia from 20 minutes onward up to six and nine hours with peak serum at two hours [77, 78]. Even though it provides analgesia for prolonged hours, it has adverse effects such as nausea, vomiting, dizziness and respiratory reactions. An earlier study by Roelofse *et al*. [26] highlighted that IV tramadol provides better postoperative analgesia than the control saline group. The systematic review by Schaffer [79] and Schnabel *et al*. [80] involving 20 randomized control trials showed no significant evidence of reduction of postoperative pain in children with the usage of tramadol.

The use of LA to relieve post-operative pain may lead to increased distress in young children due to its numbing effect [29, 81–83]. The distress was evident to parents despite being blinded to the usage of LA [30]. The distress can be prevented in older children by preoperatively counselling them on the numbing sensation of lips [29]. The application of intraligamental technique is encouraged to eliminate numbness of lips and tongue, and potential self-injury of lips in younger children [33]. Alternatively, the use of morphine with or without IV NSAIDs caused less distress as reported by post-

anaesthesia care unit (PACU) nurses [30]. Moreover, a study done by Sammons *et al*. [33] showed that the analgesic effect of LA only lasts for one hour, and the children subsequently needed rescue analgesics to overcome their postoperative pain. Although the use of LA is essential to reduce postoperative haemorrhage in children, LA is inefficient when used for postoperative pain control. Furthermore, the topical use of bupivacaine had no effect on reducing postoperative pain [16, 34], similar to the study by Quirke *et al*. [84].

4.1 Clinical significance

It is been reported that 80–95% of the children receiving dental treatment under general anaesthesia experience post-operative pain. In some cases, it leads to prolonged hospitalization and increased distress in patients. Despite multiple literature being present the problem is still existing. This systematic review aims to identify and compare the various modalities used to control postoperative pain in children and present the result which can be employed by physicians to reduce the postoperative pain experience in children.

4.2 Future recommendations

1. For future studies, post-operative inflammatory markers like C-reactive protein could be used as an adjunct to subjective measurements to avoid bias.
2. Separate subgroup analysis could be done based on the age of the children for all studies as the pain perception tends to vary in children under 6 years and up to 14 years old.
3. The follow-up period for postoperative pain should be increased until the recall visit to comprehend the full extent of the post-operative co-morbidities experienced by the patients.
4. Further studies are warranted in paediatric dentistry regarding the usage of opioids especially Fentanyl, a short-acting opioid in combination with paracetamol for effective management of postoperative pain in children receiving dental treatment under general anaesthesia.

4.3 Limitations

Several works of literature have shown there are inconsistencies between self-reported pain and observational measurement of pain [37, 84]. There is a descriptive bias in this study as the incidence and frequency of postoperative pain are not assessed by a standardized individual but rather described by various individuals like parents, caregivers, self-reported by the child, PACU nurses or a combination of the above. The other confounding factors such as parental anxiety with the procedure, the anticipation of pain, and observation of different techniques utilized by recovery staff may affect pain scores by parents as well as have a parental influence on the child's pain score [27]. There is also a bias in the measurement of pain in these children undergoing dental treatment under general anaesthesia as all these studies have utilized subjective measurements for scoring postoperative pain. Another major limitation in the present systematic review was that the variables including diagnosis, corresponding to the treatment could have influenced both the incidence and the intensity of pain post-general anaesthesia. Furthermore, the duration of anaesthesia and the length of surgery are not mentioned in all articles as studies show that an increase in the above could lead to increased postoperative pain. In self-reported scoring of post-operative pain, there could be potential bias in cases of children below six years old as there are other confounding factors that could cause increased anxiety and distress to the child, like separation from parents among others. Reliability testing among evaluators is not done, it may cause a difference in scores. The interrater reliability test could have ensured consistent evaluation of postoperative FLACC (Face, Legs, Activity, Cry, Consolability) scores. Quantitative analysis or meta-analysis was not possible in this study because the pain score data was not coherent due to the utilization of various diagnostic modalities used to score pain.

5. Conclusion

In conclusion, ibuprofen in combination with paracetamol given preoperatively and through an intravenous route provides better postoperative pain relief in children. There is a lack of coherent studies on the usage of local anaesthesia infiltration alone or in combination with paracetamol and NSAIDs to reach a conclusion. Topical local anaesthesia or injection of LA alone does not provide sufficient postoperative pain relief although there is insufficient literature to be conclusive.

ABBREVIATIONS

ASA, American Society of Anaesthesiologists; GA, General Anaesthesia; LA, Local Anaesthesia; IASP, International Association for the Study of Pain; NSAIDs, Non-steroidal anti-inflammatory drugs; IV, Intravenous; FLACC scale, Face, Legs, Activity, Cry, Consolability scale; PACU, Post-Anaesthesia Care Unit.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

SS, AV and SM—designed the study. SS and AV—performed the study. SS, AV, MAR and SM—analysed the data; wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The clinical protocol was authorized by the Ethical Review Board PROSPERO International Prospective Register of Systematic Reviews (No. CRD42021275625).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/1785196361582297088/attachment/Supplementary%20material.docx.

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