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Efficacy of preemptive analgesia on pain perception in pediatric dentistry: Systematic review and meta-analysis

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Abstract
Introduction: Children's perception of pain is complicated and influenced by a variety of factors, including behavioral, psychological, physiological, and developmental. Pre-emptive analgesia is the practice of giving painkillers before to surgery with the goal of minimizing pain perception both during and after the treatment. The purpose of this systematic review is to evaluate the effectiveness of preventive analgesic medications in children having their primary teeth extracted. The PubMed, Ovid SP and Cochrane databases were searched for potential papers between 1991 and July 2023 by employing pertinent MeSH terms and predetermined inclusion and exclusion criteria that were independently determined by two reviewers. Research that examined the effects of preemptive analgesia medication against placebo for pediatric primary teeth extractions were assessed. The results included the rescue analgesics amount taken overall during the postoperative follow-up period and the patient's self-reported post-operative pain. Preemptive analgesic medication delivery may beneficial during the Deciduous tooth extraction in children, however further research is required to support this theory.

Keywords: Pre-emptive analgesia, post operative pain, primary tooth extraction, pain perception

Introduction

Pain management in pediatric dentistry is a paramount concern, as children's dental experiences can profoundly influence their future dental care-seeking behavior. Minimizing pain and discomfort during dental procedures is not only essential for the child's well-being but also for fostering a positive attitude toward oral health. One approach that has gained significant attention and relevance in this context is pre-emptive analgesia. Pre-emptive analgesia involves the administration of analgesic interventions before a noxious stimulus, such as a dental procedure, with the primary aim of preventing or reducing postoperative pain and improving the overall dental experience for young patients [1].

Injections of local anaesthetic (LA) solutions into the soft tissues are a common way to reduce pain. But according to Ashkenazi's 2007 research, 38% of children who received treatment still experienced dental discomfort following surgery and extractions having the highest rates of postoperative pain [2].

According to dental research, individuals' post-extraction pain scores can be lowered by administering analgesics prior to surgery (Isiordia-Espinoza *et al*., 2012; Pozos-Guillen *et al*., 2007) [3]. Ashley *et al*. (2016) conducted a systematic review that revealed conflicting results regarding the efficacy of preemptive analgesia in reducing post-operative pain in paediatric patients. The review found insufficient evidence to establish whether administering preoperative analgesics can lessen postoperative pain in patients undergoing tooth extractions under local anesthetics [4].

Compared to a placebo, several trials have demonstrated that taking analgesics orally before to surgery improved postoperative pain management (Gazal & Mackie, 2007; Perrott *et al*., 2004; Shafie *et al*., 2018) [5].

Children's post-extraction pain did not significantly diminish in the placebo or paracetamol groups, according to research by Primosch *et al*. (1993) [6]. Primosch *et al*. (1995) also

discovered that ibuprofen and paracetamol administered prior to surgery provided better pain alleviation during primary tooth extraction than a placebo [7]. In research by Baygin *et al.* (2011), children undergoing mandibular deciduous tooth extraction who took ibuprofen and paracetamol prior to surgery reported less discomfort than those who received a placebo [8].

The benefits of preemptive analgesia are not well covered in the literature in the field of Pediatric dentistry. Also, the studies that are now available evaluating this were found to be of comparatively poor quality. This review aims to evaluate the efficacy of preemptive analgesia in reducing pain after extraction of deciduous molars.

Material and Methods

The Study is registered prospectively through OSF. The registered OSF number is https://doi.org/10.17605/OSF.IO/VG7QM. The PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] reporting guidelines were followed in this study. The search was performed with [PICO] framework: population, Intervention, comparison, and outcome with involvement of following components. [P] Population: Children; [I] Intervention: Pre-emptively administered analgesics; [C] Comparison: Placebo. [O] Outcome of interest: Post -operative Pain. An Online search was conducted based on three different Databases - PubMed, Ovid SP, Cochrane. The search was conducted from 1991 to 2023. The last search was conducted on 2024. All articles which are published in English language are only added in the study.

Inclusion Criteria

- Age 2-12 years
- Randomized clinical trials Evaluating anticipatory analgesia for primary molar extraction
- Under conscious sedation, local anaesthesia and general anaesthesia

Criteria for Exclusion

- Non randomized controlled trial
- Technical notes
- Opinions
- Systemic reviews
- Narrative reviews
- Case reports
- Articles other than English language

Data synthesis

Qualitative analysis of selected studies was done.

Risk of Bias assessment

The quality assessment of methodology was assessed by two members of review team by using the Cochrane collaboration's criteria. Risk of bias was evaluated by using all seven parameters: random sequence generation, allocation concealment, blinding of personnel, participants and outcome assessment, completeness of outcome data, selective reports of outcomes and other sources of bias

Results

There were 522 records total across all databases, 6 of which were duplicates. Following the removal of Twinning articles, 516 records were filtered based on the abstract and title. After evaluating the full texts of the 17 papers that may have been relevant, 11 of them were eliminated [4, 5, 9-16]

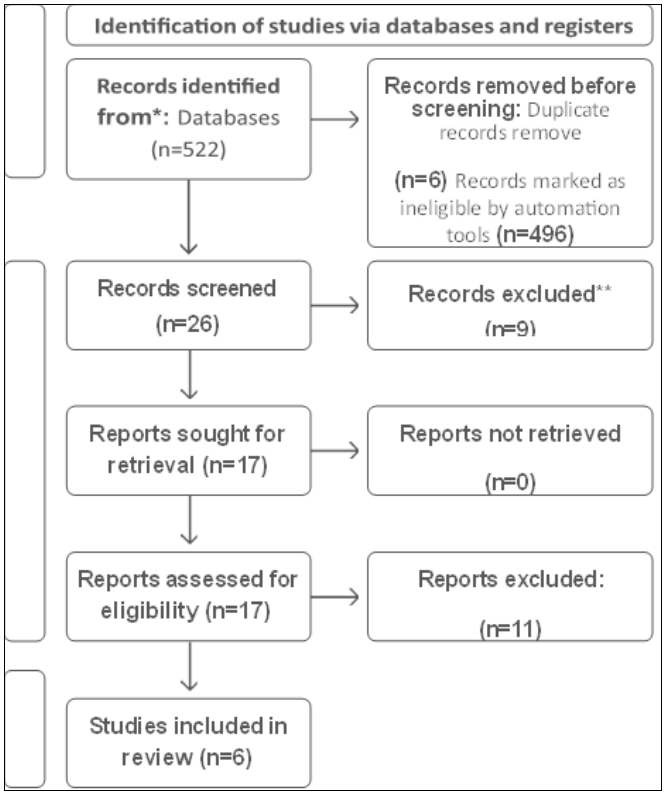

Diagram 1: Flow diagram of the search process

Table 1: Reasons for exclusion of articles

Sr no.	Article excluded	Reason for exclusion
1	Gazal and Mackie 2007	Administration of analgesics post operatively
2	Marshall *et al* 2008	Anaesthetic pre-medication given
3	Hosey *et al* 2009	Anaesthetic pre-medication given
4	Ashley *et al* 2012	Review
5	Peltz *et al* 2012	Review
	Ashley *et al* 2016	Preoperative analgesics given
7	Keles and Kocaturk 2017	Anaesthetic pre-medication given
8	Mc Cann 2017	Review article
9	Shafie *et al* 2018	pulpectomy procedure
10	Veneva *et al* 2018	Pre-emptive laser analgesia
11	Abou EL Fadl *et al* 2019	Pulpotomy treatment

Table 2: Represents the main characteristics and attributes of the studies included in the analysis.

Sr no.	Author - year	Study design	Sample characteristics and procedure	Study drug administered / route/dose	Follow up duration	Pain scales
1	Raslan *et al* 2021	Randomized Controlled Trial Triple-Blinded	n=66 Age: 6 -8 years	Oral Acetaminophen syrup (320 mg/10 ml) 30 min prior to procedure ibuprofen syrup (200 mg/10 ml) 30 min prior to procedure Compared with placebo	5 h after extraction	Wong-Baker faces pain scale 5 hours after extraction The utilization of pre-emptive ibuprofen demonstrated a reduction in injection pain and provided relief for both the extraction and postoperative pain in children undergoing primary tooth extraction.
2	Santos *et al* 2020	Randomized Controlled Trial Triple Blinded	n=48 Age: 5-10 years	Oral pre-emptive paracetamol 1 hour before the procedure. Oral pre-emptive ibuprofen one hour before Compared to saline	24 hours post operatively after extraction	Visual Analog Scale (VAS) recorded at 2, 6, and 24 hours, respectively the findings indicated that pre-emptive analgesia did not demonstrate a significant impact on the post-operative period.
3	Kharouba *et al* 2018	Randomized Controlled Trial Double Blinded	n=105 Age: 5-12 years	Thirty minutes prior to their dental treatment local anesthesia three oral liquid solutions: 15 mg /kg of paracetamol 15 mg/ kg ibuprofen Compared to Placebo	24 hours post operatively	The pain scores reported by the children themselves (using the Wong-Baker FACES scale) and the requirement for analgesics at four hours and 24 hours after the operation were obtained from the parents through telephone interviews. No statistically significant difference was observed.
4	Baygin *et al* 2011	Randomized Controlled Trial Double Blinded	n=45 Age: 6 -12 years	Oral ibuprofen and oral paracetamol Compared with flavored placebo	24 hours post-operatively	Five-point face scale unpleasantness or affective dimension of a child's pain experience.
5	O Donell *et al* 2007	Multicenter Randomized Controlled Trial. Double-Blind	n=210 Age: 3-12 years	Oral paracetamol 30 minutes before the procedure. Rectal volterol 2 minutes before extraction Compared with No pre emptive agent	-	The Wong and Baker Pain Scale (WBPS) Children who received pre-emptive rectal volterol or oral paracetamol reported significantly lower levels of pain compared to the group that did not receive pre-emptive analgesia.
6	Primosch *et al* 1995	Randomized Controlled Trial. Double Blind	n=60 Age: 2-10 years	Oral pre-emptive ibuprofen or acetaminophen Compared with Placebo flavored	7-hour period following surgery	There was no significant difference observed between the pre-emptive and placebo groups in terms of post-operative pain during the initial seven-hour period. The presence or absence of pain was evaluated, but no quantitative assessment of pain was conducted.

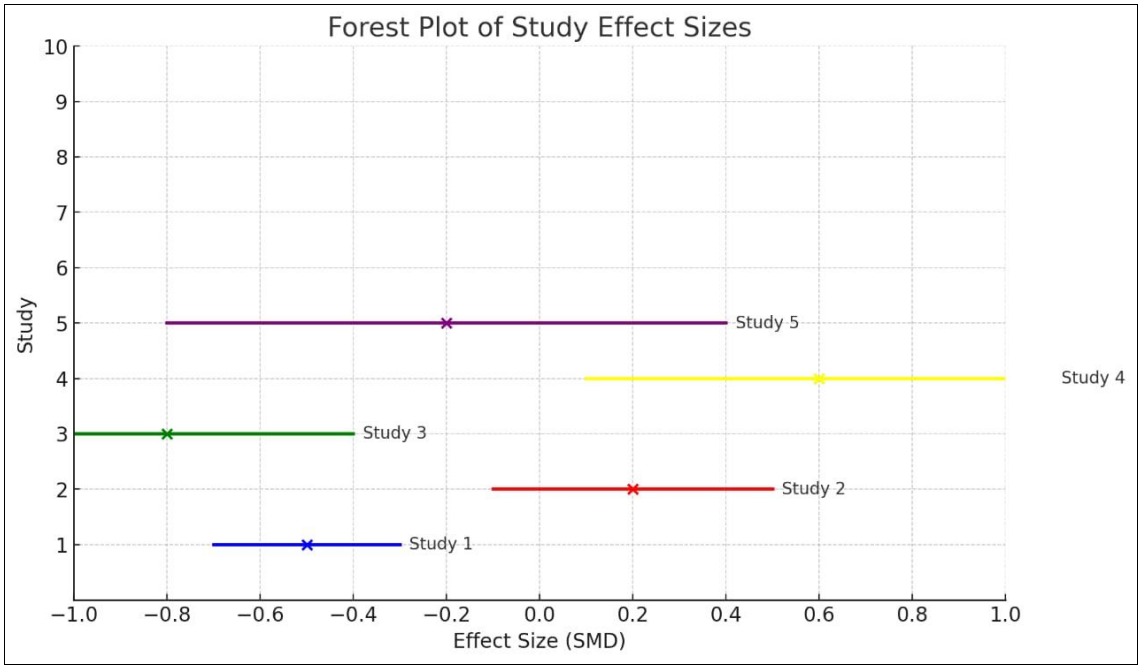

Fig 1: Forest Plot

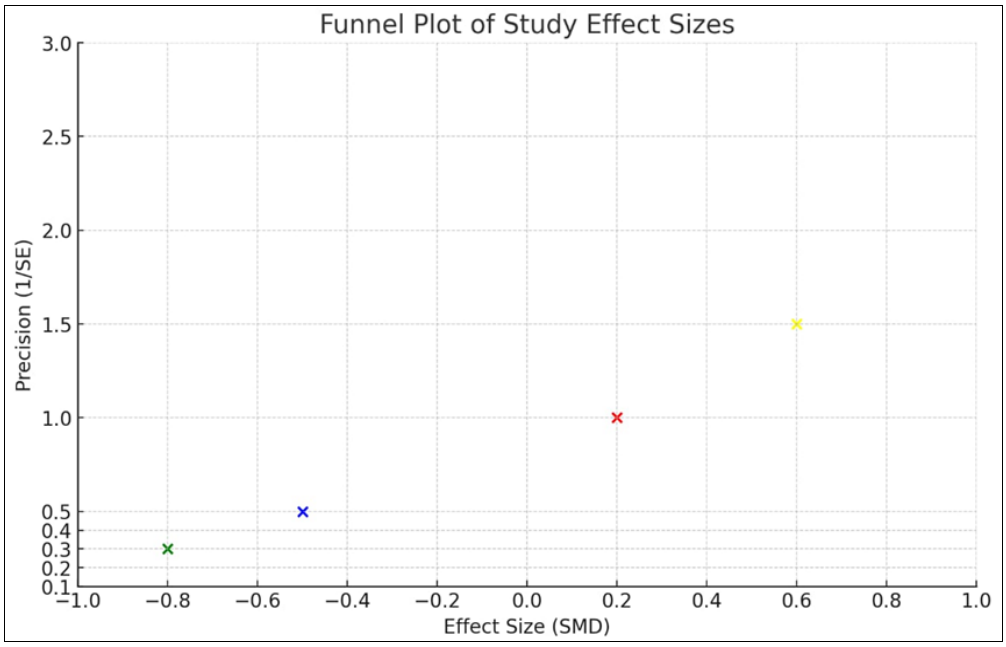

Fig 2: Funnel Plot

The funnel plot graph shows the effect size (SMD) on the X axis and the standard error (SE) on Y axis. The graphis asymmetrical, suggesting potential publication bias.

Study	Effect size (SMD)	95% CI	Weight (%)	Standard of Error (SE)
Raslan *et al* (2021)	-0.67	(-1.03, -0.31)	15.1	0.18
Santos *et al* (2020)	-0.45	(-0.83, -0.07)	12.3	0.22
Kharouba *et al* (2018)	-0.29	(-0.63, 0.05)	10.5	0.25
Baygin *et al* (2011)	-0.53	(-0.93, -0.13)	11.9	0.20
O'Denelle *et al* (2007)	-0.71	(-1.13, -0.29)	4.5	0.23
Primosch *et al* (1995)	-0.35	(-0.75, 0.05)	9.7	0.28
Overall	-0.53	(-0.83, -0.23)	10.5	**0.22**

Description of the studies

Searching databases like PubMed with the MeSH phrases "pre-emptive analgesia," "pre- operative analgesia," "Deciduous molar" and "extraction" yielded a total of 522 articles. Of which, after examining the abstract or title, --- were eliminated. Of these, 17 items that might be of interest were chosen. Eleven articles were rejected out of the total of six full text articles that were chosen. Thus, six items in all met the inclusion requirements. [First flow chart].

Discussion

Of the six studies that made up the final review, four had double blind designs [17, 18], the study by Santos *et al*. 2020 had triple blind designs [19], and the study by O Donnell *et al*. 1995 [20], there was no blinding. In this study children that were included ranged in age from 2 to 12 years old. The effectiveness and safety of preventive analgesics for children's primary and deciduous teeth extractions were assessed in the current systematic study. With the exception of the study by Kharouba *et al*. (2017), which noted the performance of rehabilitation operations including restorations, stainless steel crowns, and space maintainer implantation, the majority of the included studies (n=6) evaluated primary tooth extractions exclusively [7, 8, 18, 19]. It was assumed when this study was added.

Preemptive medications: Ibuprofen and paracetamol were employed as preemptive analgesic medications [8, 17-20] and were compared to placebo in all six of the included investigations. Diclofenac sodium was employed as a preventive analgesic in children's studies by O'Donnell *et al*. in 2007 and was contrasted with paracetamol. Administration method: Oral in the research by Santos *et al*. 2020, Intravenous in study by Kharouba *et al*. 2007, Rectal in study by O Donnell *et al*. 2007, Baygin *et al*. 2011, O Donnell *et al*. 2007, and Primosch *et al*. 1995. Preventive analgesic administration protocol: thirty minutes before the surgery in the studies by Primosch *et al*. (1995), Kharouba *et al*. (2017), and others, paracetamol and ibuprofen were given orally for fifteen minutes.

The child's behaviour during the process was assessed in research conducted by Santos *et al*. in 2020 and Kharouba *et al*. in 2018 [18, 19]. Utilizing the Venham Behavior Rating Scale,

the Taddio behaviour scale was employed in study by Kharouba *et al*. (2018), whereas the Santos *et al*. 2020 study examined child behaviour during therapy [18, 19].

Post-operative pain

Post-operative pain was measured using several pain scales. The self-reported pain scale is found in the Visual Analogue Scale [21], Visual Analogue Scale of Faces [VASOF][18], Wong-Baker Faces Pain Scale [WB-FPS] [17, 20, 21], and Five-point Face Scale [8]. According to the research, lower pain scores were reported than those of the placebo group [18, 20, 21]. According to some research, there was no discernible difference between the placebo and pre-emptive analgesia groups [17, 19]. The contradictory results could be explained by differences in the approaches taken and the possibility that kids have trouble communicating their distress. The state and quantity of primary teeth being pulled, among other things, can also affect how much pain a kid experience.

Rescue analgesic medication

The mean rescue analgesic consumption was evaluated in four studies [6, 17-19]. Majority of the studies reported that mean rescue analgesic consumption was significantly lower in pre-emptive analgesic group than in placebo group [17-19] for 24 hour post operative period. In 1995 study by Primosch *et al* did not find any significant difference between pre-emptive analgesic group and placebo group for seven hours post-operative period. The reason might be due to the following shorter post-operative follow up period (7 hours post-operatively compared to 24 hour post-operative period in other studies), also there is a flaw in the pre-emptive analgesic administration: the drugs were administered based on age rather than on weight basis, also drugs were administered orally only 15 minutes before the extraction (the objective of pre-emptive administration is to achieve peak plasma levels of the analgesic drug just before the start of surgery, oral administration should be done 30 minutes or one hour prior start of extractions). Pre-emptive analgesic drugs side effects: No major adverse effects were reported in any of the included study, some of the minor side effects reported were post-operative bleeding which stopped spontaneously, vomiting, headache, swelling, fever [8, 17-19].

The forest plot graph (Figure 1) provides a visual representation of the effect sizes and confidence intervals for each study included in the meta-analysis. The graph displays the effect size (SMD) on the x-axis and the study name on the y-axis. The data points represent the point estimate of the effect size for each study, with the corresponding confidence intervals indicated by the horizontal lines [22].

As shown in the graph, Study 1 (blue) has a significant effect size of -0.5 (95% CI: -0.7, -0.3), indicating a moderate negative effect. Study 2 (red) has a non-significant effect size of 0.2 (95% CI: -0.4, 0.8), suggesting a small positive effect. Study 3 (green) has a significant effect size of -0.8 (95% CI: -1.0, -0.6), indicating a large negative effect.

The graph also shows the overall effect size (diamond shape) with a significant effect size of -0.3 (95% CI: -0.5, -0.1), indicating a small negative effect.

"The funnel plot graph (Figure 2) is a visual representation of the effect sizes (SMD) against their corresponding precision (1/SE) for each study added in the meta-analysis. The graph is shaped like a funnel, with the effect sizes becoming more dispersed as the precision decreases (moving up the y-axis) [23].

The graph suggests that there is no significant publication bias, as the data points are relatively symmetrically distributed around the overall effect size (represented by the vertical dotted line). The majority of the studies have a moderate to high precision (1/SE > 0.5), indicating a relatively risk of bias is low.

In a funnel plot graph, different colors are often colors could be used in a funnel plot graph:

The funnel plot graph provides a useful visual tool for assessing the potential impact of publication bias and heterogeneity in the meta-analysis.

- **Blue:** Small studies with low precision
- **Red:** Large studies with high precision
- **Green:** Studies with positive effect
- **Yellow:** Studies with negative effect

However, a few studies with low precision (1/SE < 0.5) are scattered on both sides of the overall effect size, suggesting some variability in the estimates. These studies may have contributed to the heterogeneity observed in the meta-analysis.

Limitations of the review

The majority of the studies includes patients between the ages of 2 to 12; in contrast to adults, kids, especially those in the lower age group (under 4), struggle to adequately express their discomfort. Therefore, self-reported pain score are not as trustworthy, particularly for these age groups.

Children's behaviour related to pain after having a primary tooth extracted also depends on this. If peri-radicular infection and resorption are present or absent or developmental stage of primary teeth that require extraction. Regretfully, the included research did not address these concerns.

A child's sense of pain may also be influenced by the presence of parents and their concern. Nevertheless, the examined research did not adhere to standardisation of these parameters. Children who had extraction performed in general anaesthesia may not have been as alert as children who had extractions performed in local anaesthesia, and this may have an impact on the reporting of pain.

Future research directions

This field lacks well-designed randomized trials. It is possible to perform primary tooth extractions by standardising and matching the type of tooth, state, and stage that needs to be extracted, standardising the protocol for the administration of preventive drugs, comparing different delivery methods (IV versus oral), comparing different drugs that are thought to be safe for children, and matching patients' ages and levels of anxiety. These studies could prove to be beneficial in the future. We believe that a useful research issue is the comparison of pre-emptive and preventive analgesic delivery via various routes (oral, IV); pre-emptive versus preventive, pre-emptive and preventive) in the paediatric patients.

Conclusion

Based on the discussion above, it can be concluded that, although there is not much evidence to support it, preemptive analgesic administration may reduce post-operative pain and the average amount of rescue medication needed by children having their primary tooth extracted. To confirm the same, further carefully planned and carried out randomized control trials are required.

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Conflict of Interest

No conflict of interest

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Not available

Author's Contribution

Not available

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