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Comparision of intransal or oral dexmedetomidine and midazolam for pre-medication in pediatric dental patients: Systemic review and meta analysis

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Abstract

Background: The present study was conducted to evaluate comprehensively the efficacy and safety of dexmedetomidine and midazolam for the management of pediatric patients in the dental clinic.

Methods: Relevant material was discovered using PubMed (Medline), Google Scholar, Cochrane Library databases, SCOPUS, and LILACS. Electronic databases and manually searching for pertinent publications were used until all articles published between January 2012 and October 2022 were comprehensively reviewed. Randomised controlled trials comparing oral or intranasal midazolam, intranasal or oral dexmedetomidine sedatives, or placebos during paediatric procedural sedation were included. The study did not include reviews, editorials, letters, or case reports. The key result was the success of the scheduled procedure.

Results: Five randomised control trials were analysed: Three trials with total 214 comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures found out that significant difference was seen in parental separation among midazolam and dexmedetomidine group. Overall, pooled data failed to show any conclusive evidence in favour of midazolam or

dexmedetomidine: (MD 0.55; 95% CI -0.06 to 5, 05; p=0.60).

Conclusion: Intranasal dexmedetomidine and Oral Midazolam is a safe and effective sedative for minor paediatric procedures. However, compared with midazolam, the superiority of dexmedetomidine in providing adequate sedation at mask induction and postoperative analgesic effects has not yet been defined.

Keywords: Dentistry, Dexmedetomidine, Midazolam, Pediatric, Premedication.

Introduction

Dental fear and anxiety are widely recognized problems affecting young children and are considered the global barrier in pediatric dentistry. Common anxieties among children include fearing the unknown and being worried about a lack of control – both of which can occur with dental examination and treatment. However, the oral health of young children specially preschoolers can have a significant effect on their wellbeing and their families welfare, and affect their quality of life.[1] Pediatric anesthesiologists strive to minimize distress for children in the operating room (OR) environment and to provide a smooth induction of anesthesia.[2] Premedication is commonly used to reduce preoperative anxiety, to facilitate separation from parents, and to promote acceptance of mask induction. Among the different goals that can be achieved with premedication, the primary objective in children is anxiolysis. Premedication that effectively calms the child also minimizes parental anxiety.[3,4] A plethora of sedative agents have been in used in pediatric dental settings i.e. midazolam, ketamine, propofol, chloral hydrate, promethazine, hydroxyzine, nitrous oxide and sevoflurane. Each of these has its own sets of limitations,[5] the deep sedation state being provided by them requiring a high dosage of these sedatives;[6] which may often lead to potential complications such as nausea, vomiting, hallucinations, hypoxemia, and even catastrophe during the period of pediatric sedation.[7] Benzodiazepines, and midazolam in particular, are the most frequently used premedications in pediatric patients.

Midazolam, in the oral route, is a common pre-anesthetic medication.[8] This would involve understanding of the pharmacodynamics and pharmacokinetics of the sedative drug used, careful pre - sedation airway evaluation, and appropriate monitoring and emergency equipment.[9] It is an effective anxiolytic, muscle relaxant, and amnesic drug.[8]

Dexmedetomidine is a recently introduced sedative agent in pediatric dentistry. It was approved by the Food and Drug Administration in 1999 for the sedation of intensive care unit patients and for premedication. In 2005, it was introduced in dentistry.[10] It is a highly selective α-2 adrenergic receptor agonist with sedative, anxiolytic, and mild analgesic properties.[11] The sedation produced by dexmedetomidine is compliant and semi-arousable, similar to natural sleep,[12] indicating that it has minimal influence on respiration. It maintains spontaneous respiration during sedative action and reactivity to CO_2 increase, reduces dose of anesthetic drug required, and inhibits tachycardia.[13]

Although some randomized controlled trials (RCTs) have compared the efficacy of DEX versus MDZ in paediatric anaesthesia, the sample size in all of these trials was too small to provide a definite conclusion. Moreover, some of their results were inconsistent. Therefore, the present meta-analysis was performed to confirm their conclusions using a large sample size.

Method

Inclusion and exclusion criteria

To be eligible for this systematic review and meta-analysis, publications were required to meet the

following inclusion criteria: (1) studies published between the year 2012 and 2022, (2) studies comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures, (3) studies in which the age of the participants was between 2 and 12 years, (4) studies design: Randomized control trails, and (5) disclosure of at least one of the following outcome measures: quality of separation from parents, effect on behavior management, success rate of sedation, effect on vital parameters following sedation, postoperative nausea and vomiting, shivering, and other possible untoward events. Studies with any of the following characteristics were not included: (1) studies carried out in animals,(2) studies not available in English language, (3) free or full text not available, (4) studies in which the age of the participants was >12 years, (5) studies not involving any dental procedures, and (6) abstracts,reviews, editorials, letters, and case reports.

Data sources and search strategy

Three independent reviewers (RA, BM,KP) performed the literature search. Searching of electronic databases as well as hand searching for relevant articles was carried out until October, 2022. Electronic database searched included PubMed (Medline), Google Scholar, Cochrane Library databases, SCOPUS, and LILACS. Medical Subject Headings terms used were "(Oral or Intranasal dexmedetomidine) AND (Intranasal or Oral midazolam). Filters were applied during the search, so as to access only those articles published from January 2012 to October 2022, with the language limited to English. Relevant references were manually searched to identify additional studies. No ethical approval was necessary, as this study was a review of the previously published literature.

Data extraction and risk of bias assessment

A standardised record form was used to extract data from the included studies. Three authors (RA, BM, KP) independently evaluated the inclusion criteria, risk of bias and data extraction using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.[23] The Cochrane Collaboration tool [16] was used to assess the risk of bias in the studies included in the meta-analysis. Possible disagreements were discussed, and consensus was reached. Original data were collected from the included studies without any modifications. If the relevant data were not reported in the papers, the principal investigators were contacted for the missing data.

Results

A total of 1700 articles were identified initially. Eight hundred forty-four studies were excluded by duplicate removal and seven hundred studies by reviewing the titles and abstracts using selection criteria. Of which, 8 eligible abstracts were identified for full – text review. Finally, five studies fulfilled the selection criteria [Figure 1]

Characteristics included in study

The following data from the included studies were extracted and tabulated: author, year of publication, sample size, age range of the participants, drug administered for sedation along with its route of administration and dosage, type of procedure, and any outcome that met the inclusion criteria. The characteristics of these six studies are summarized in [Table 1].

Risk of bias assessment

Three studies that were considered either had high, unclear, or low risk. Random sequence generation, participant blinding and allocation concealment were all graded as low risk for the included RCTs. RCT by Sheta

and Wang et al showed incomplete outcome data and selective reporting were rated as a high risk, whereas study conducted by Sathyamoorthy et al. showed incomplete outcome data and selective reporting and other bias were rated to be unclear biases [Figure 2 and 3].

The software RevMan version 5.4 (Review Manager; The Cochrane Collaboration, 2020) was used for the synthesis. (I) Continuous variables were reported using weighted mean difference (WMD) and 95% confidence interval (CI) as statistics. Statistics were presented in the form of forest plot; (III) Test level $\alpha=0.05$; (IV) Literature heterogeneity was analyzed using I2 analysis, and heterogeneity of the results was indicated by $I2>25\%$ or $P<0.1$; (V) If heterogeneity existed between studies, the random effects model analysis was used; if heterogeneity did not exist, fixed effects model analysis was used.

Risk of bias was assessed using version 5.3 of the Cochrane Collaboration Review Manager (RevMan), and results were synthesized in a narrative summary.

Parental separation

Three studies with total 214 participants comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures found that no significant difference was seen in parental separation among midazolam and dexmedetomidine group. Study by Sheta SA favoured midazolam and study by Sathymoorthy et al favoured dexmedetomidine. Overall, pooled data failed to show any conclusive evidence in favour of midazolam or dexmedetomidine: MD 0.55; 95% CI -0.06 to 5,05; p=0.60; 214 participants [Figure 4].

Acceptance of mask induction

Three studies with total 205 participants comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures found out no significant difference was seen in mask induction among midazolam and dexmedetomidine group. Overall, pooled data failed to show any conclusive evidence in favour of midazolam or dexmedetomidine : MD 0.57; 95% CI -0.28 to 1.16; p=0.41; 205 participants [Figure 5].

Onset of sedation (min)

Two studies with total 145 participants comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures found out that significant difference was seen in onset of sedation among midazolam and dexmedetomidine group. Study by Sheta SA favoured dexmedetomidine and study by Ek Khatib et al favoured midazolam. Overall, pooled data failed to show any conclusive evidence in favour of midazolam or dexmedetomidine : MD 3.11; 95% CI -13.6 to 19.38; p=0.71; 145 participants [Figure 6].

Discussion

Pediatric sedation is always served as one of conundrums during diagnostic and surgical procedures, such area changes rapid and engenders several debates among the anaesthesiologists and pediatric specialists.[17] Premedication is the most common way to minimize distress for children entering the dental clinic and to facilitate the smooth induction of anaesthesia. It can be accomplished using various sedative drugs.[18]

Midazolam, which is an anxiolytic, sedative, hypnotic, and amnesic drug, has been widely used for premedication via several routes. But studies have shown that midazolam was ineffective in preventing emergence delirium when compared to other drugs such

as propofol, ketamine, α2 agonist, and fentanyl.[19] Despite their efficiency, associated adverse effects limit their use in pediatric dental procedures.[10]

Dexmedetomidine, α2-adrenoreceptor agonists cause sedation, anxiolysis, analgesia, an antisialogogue effect, sympatholytic, and postoperative reduction of nausea and vomiting better than benzodiazepines.[10] Due to its low effect on respiratory function, dexmedetomidine is a very valuable pediatric sedative.[20]

According to a study on dexmedetomidine as a premedication by Peng K. et al., it results in higher preoperative sedation and less postoperative pain when compared to midazolam.[21] Another study, by Chue PS et al. found that dexmedetomidine had a similar effect on postoperative pain, a considerable reduction in the doses of rescue analgesic medicines, less anxiety with parental separation, and less postoperative agitation when compared to midazolam.[22]

According to a study conducted by Goswami, et al. there was no significant difference between dexmedetomidine and midazolam premedication of pediatric patients in the dental clinic with regards to the behaviour of the child, successful parental separation, and mask induction following sedation. However, the occurrence of emergence delirium was significantly lower with dexmedetomidine than with midazolam.[23]

However, the results of individual studies that were included in this study were compared and it was observed that in the study conducted by Waly et al. in 2019[24] in which both dexmedetomidine and midazolam were administered by intravenous route, as well as in the study conducted by Surendar et al. in 2014[25] in which both dexmedetomidine and midazolam were administered by intranasal route, the time of onset of sedation following administration of midazolam was shorter than that following administration of dexmedetomidine. This difference was statistically significant in the study conducted by Surendar et al.[25] in 2014 ($P < 0.001$). This explains why intranasal dexmedetomidine is commonly administered 45–60 min before induction of surgery, because of the relatively slow onset of maximal sedation.[21]

In the present study, comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures found out that significant difference was seen in parental separation among midazolam and dexmedetomidine group. Study by Sheta SA et al.[26] favoured midazolam and study by Sathymoorthy et al.[27] favoured dexmedetomidine. When comparing the effectiveness and safety of sedation with dexmedetomidine to that with midazolam in pediatric patients undergoing dental procedures it was found out that no significant difference was seen in mask induction among midazolam and dexmedetomidine group. When the effectiveness and safety of sedation with dexmedetomidine were compared to that with midazolam in pediatric children undergoing dental procedures, a significant difference was found in the onset of sedation between the midazolam and dexmedetomidine groups. Moreover, dexmedetomidine being odorless, colorless, and tasteless had greater acceptability by most children compared to midazolam due to its poor palatability and bitter taste. Midazolam has also been shown to be associated with other disadvantages such as cognitive dysfunction, staged behavioural abnormalities, hiccups, and respiratory depression.[29]

These results imply that dexmedetomidine and midazolam give sufficient sedation to control anxiety and irrational behaviour in children undergoing dental

procedure. Furthermore, compared to midazolam, dexmedetomidine exhibits a greater margin of safety.

Conclusion

For modest paediatric procedures, intranasal dexmedetomidine and oral midazolam were a safe and effective sedative. However, the efficacy of dexmedetomidine over midazolam in providing sufficient sedation at mask induction and postoperative analgesic effects has yet to be established.

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Legend Figures and Tables

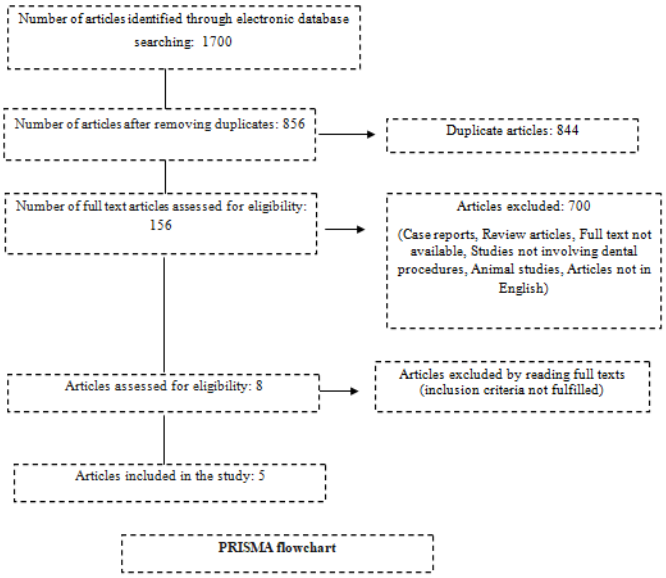

Figure 1: Flow of selection of studies for Meta – analysis

Table 1: Characteristics of the studies

Sn.	Author and year	Study design	Number of participants and age (years)	Drug administered (with route of administration and dosage)	Dental procedure done/ intervention	Outcomes measured
1	Salem K. 2022	Double – blind randomized clinical trial	92, 4-6	0.2 mg/kg intranasal midazolam 1 µg/kg dexmedetomidine	Not specified	Time of onset, recovery time, vital parameters
2	El Khatib 2021	Randomized clinical trial	72, 3-6	control group received 0.5mg/kg MDZ, study group I received 5µg/kg DEX, and study group II received 0.3mg/kg MDZ followed by 3µg/kg DEX	SS crown, Pulpotomy, extraction	Onset and duration of the effect of sedative drugs, vital parameters
3	Wang L 2020	A randomized clinical trial	60, 3-6	Oral midazolam, 0.5 mg/kg Intranasal dexmedetomidine, 2 µg/kg	Not specified	Ramsay sedation score, parental separation anxiety scale, mask acceptance scale, pediatricanesthesia emergence delirium scale, and hemodynamic parameters were recorded
4	Sathyamoorthy M 2019	A randomized controlled study	75, > 5	Oral midazolam at a dose of 0.5 mg/kg (max 15 mg) or intra- nasal	Not specified	' Level of sedation when separated from their parents, acceptance of mask

				dexmedetomidine at a dose of 2 mcg/kg (max 100 mcg).		induction, vital parameters pre-anesthetic behavior, time from pre-medication to anesthesia induction, and surgical time
5	Sheta SA 2014	double-blinded randomized controlled trial	72,3-6	Group M received intranasal midazolam (0.2 $mg \cdot kg^{-1}$)and group D received intranasal dexmedetomidine ($1 \mu g \cdot kg^{-1}$).	complete dental rehabilitation	Patients' sedation status, mask acceptance, and hemodynamic parameters

Figure 2: Cochrane risk assessment figure defining the assessment questions

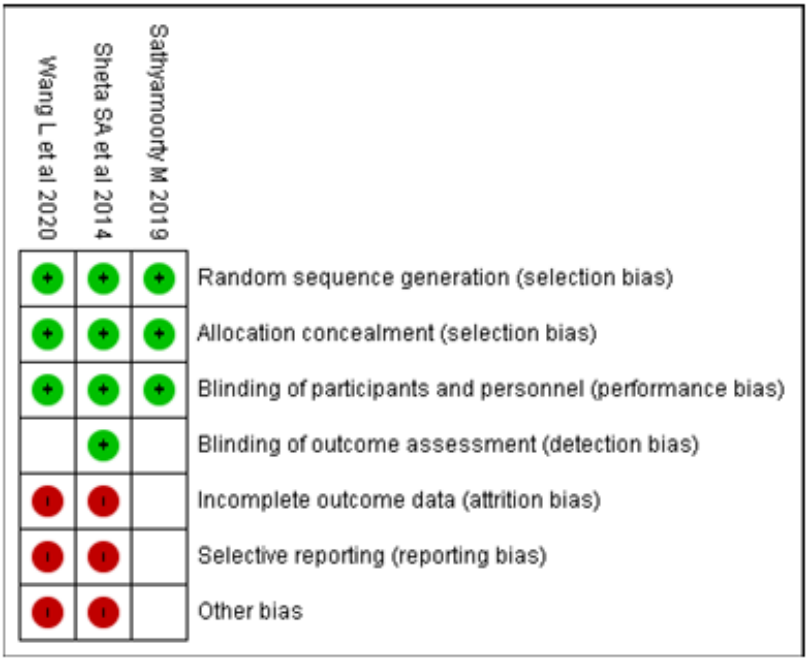

Figure 3: Risk bias assessment of the screened articles according to Cochrane risk assessment

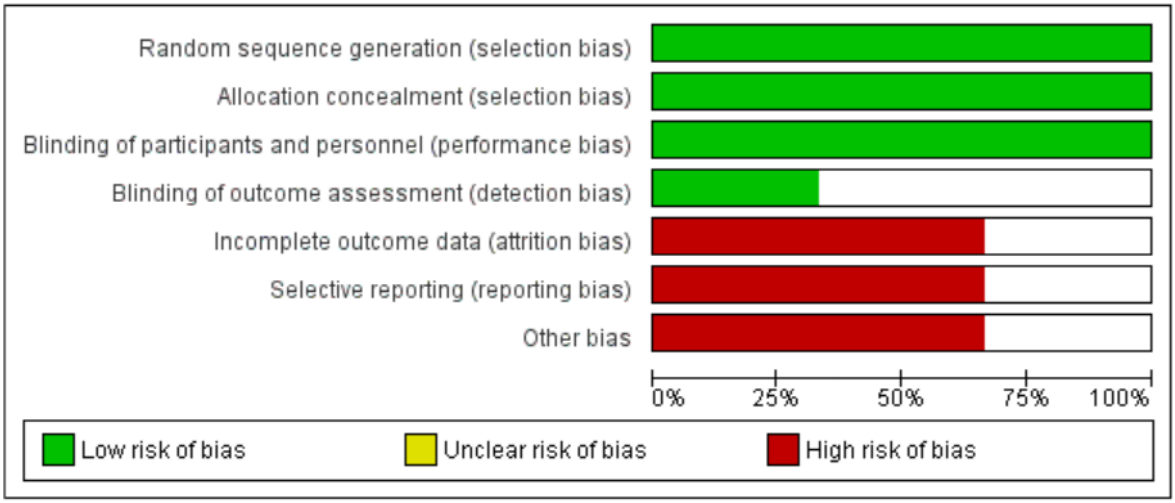

Figure 4: Forest plot depicting study specific effectiveness of dexmedetomidine v/s midazolam against parental separation parameter in pediatric patients

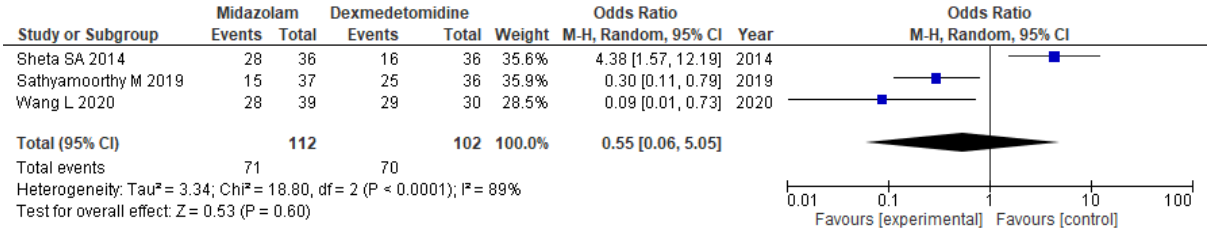

Figure 5: Forest plot depicting study specific effectiveness of dexmedetomidine v/s midazolam for Acceptance of mask induction parameter in pediatric patients

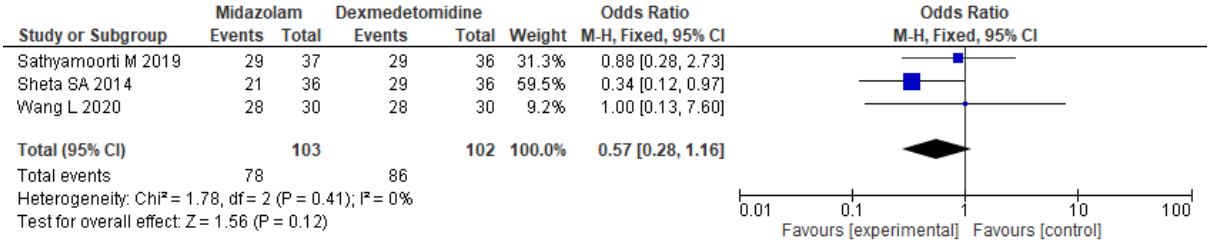

Figure 6: Forest plot depicting study specific effectiveness of dexmedetomidine v/s midazolam for onset of sedation in pediatric patients