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Effectiveness of dexmedetomidine and midazolam for pediatric dental procedures: A systematic review and meta-analysis.

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Background / Introduction: Pediatric dentistry has long been associated to pain, fear, and anxiety. It typically takes a variety of behavioural management techniques that are communicated by the entire dental team to get a child to cooperate with a procedure. Beyond non-pharmacological methods, there are pharmacological methods using sedative agents used in dental practise to provide analgesia and anxiolysis to help children behave appropriately for dental treatment. This makes treatment more patient-friendly and efficient.
Aim: The current study was aimed to determine the efficacy of Dexmedetomidine and Midazolam as sedative agents and the effective route of administration.
Methodology: A thorough literature search was conducted on PubMed, MEDLINE, Google Scholar, and Cochrane's database for randomized controlled trials that compared sedative efficacy of dexmedetomidine (DEX) with midazolam (MDZ) in children of 0–15 years of age undergoing dental procedures. This systematic review and meta-analysis has been registered at the International Prospective Register of Systematic Review- PROSPERO- CRD42023449821. This review follows the guidelines of preferred reporting items in systematic review and meta-analysis (PRISMA) guidelines. Sedation in children during procedure, when used as a sedative agent, hemodynamic stability, onset time, duration of anesthesia, were evaluated.
Result: Significant difference was noted for onset time with DEX group having a higher mean time, at p=0.005. The duration between the two agents were not significantly different at p=0.43. Dexmedetomidine administered children clearly took greater time to recover as compared to Midazolam group. Blood pressure did not vary between groups, SpO2 was better in Midazolam group, but heart rate was also increased in the Midazolam group.
Conclusion: The nasal route of administration may be the most effective method of drug delivery. The use of midazolam might be more beneficial for short procedures carried out in busy outpatient centers, but the use of dexmedetomidine is more effective for long extensive dental treatment.

Keywords: Sedation, intra nasal, oral route, sedative agents, anxiolysis

INTRODUCTION:

It's no surprise that most young patients experience anxiety before their dental procedures. When the time comes to separate from their parents, receive anesthesia, or even just have a simple procedure done, children can become uncooperative. But here's the thing: ignoring this anxiety can cause all sorts of problems.[1] Kids may squirm and move around during their procedures, leading to more pain and even complications. They may need stronger analgesics afterward, and they could experience agitation or behavioral issues post-operation. That's why it's important to address preoperative anxiety head-on and make sure our little patients feel as comfortable as possible.[2]
When it comes to keeping fidgety kids calm in the dental chair, we've got two options: nonpharmacological behavior management and pharmacological sedation. While we always aim to use nonpharmacological techniques first, sometimes they just aren't enough to ease a child's dental anxiety. That's where sedation comes in - it can make a world of difference in helping uncooperative children receive the care they need. By optimizing their comfort level, we can ensure successful dental treatment that's efficient and effective.[6]

When it comes to keeping kids calm during dental procedures, sedative agents can be a lifesaver. There are a variety of options out there, including midazolam, ketamine, propofol, chloral hydrate, and nitrous oxide.[6] But here's the catch: each of these agents comes with its own set of limitations. When we need to achieve a deep sedation state for uncooperative children, we often have to use higher doses of these sedatives - and that can lead to some unwanted side effects.[7] Think nausea, vomiting, hallucinations, and even hypoxemia. That's why we take extra care when using sedative agents in pediatric patients and always closely monitor for any potential complications.[9]
In the world of pediatric dentistry, dexmedetomidine is a bit of a game-changer. This sedative agent is a highly selective α2 adrenergic receptor agonist, which basically means that it's really good at calming down anxious child.[5] Originally approved by the Food and Drug Administration in 1999 for use in intensive care units and as a premedication, dexmedetomidine made its way into dentistry in 2005. One of the coolest things about dexmedetomidine is that it produces a sedative state that's similar to natural sleep - meaning it has minimal impact on breathing.[10] That's a big deal, especially when it comes to keeping little ones safe during dental procedures. Dexmedetomidine also has some other nifty benefits, like reducing the need for other anesthetic drugs, inhibiting tachycardia, and even causing preoperative sympatholytic effects (which is just a fancy way of saying it helps calm nerves).[11] Of course, like any medication, it's not without its potential side effects - it can cause hypotension, for example. But overall, dexmedetomidine is a promising option for sedation in pediatric dental patients.[5]
Dexmedetomidine is a sedative agent that works differently from midazolam. It doesn't affect gamma-aminobutyric acid or opioid receptors, which means it doesn't cause respiratory depression.[5] Another benefit of dexmedetomidine is that it can be administered in various ways, including orally, intranasally, intravenously, and intramuscularly, and it takes effect quickly. These factors make it an excellent choice for dental procedures in children as it enables fast and easy control of sedation levels and rapid recovery after sedation, with no risk of respiratory depression.[13] However, the use of dexmedetomidine as a sedative for pediatric dental procedures is relatively new, and there is limited data on its safety and effectiveness compared to other drugs such as midazolam. Therefore, this systematic review aims to determine the efficacy of Dexmedetomidine and Midazolam as sedative agents and their effective route of administration.

Materials and Methods

This systematic review and meta-analysis has been registered at the International Prospective Register Of Systematic Review- PROSPERO- CRD42023449821. This review follows the guidelines of preferred reporting items in systematic review and meta-analysis (PRISMA) guidelines.

Eligibility criteria

Inclusion criteria
1. Studies comparing the effectiveness of sedation with dexmedetomidine to that with midazolam as sedative agent in pediatric patients undergoing dental procedures
2. In vivo studies
3. Randomised control trials
4. Disclosure of at least one of the following outcome measures,

Efficacy, Onset & Recovery time, effect on vital parameters following sedation.

Exclusion criteria
1. Studies not involving any dental procedures
2. Studies in which the age of the participants was >14 years
3. Animal studies
4. In vitro studies

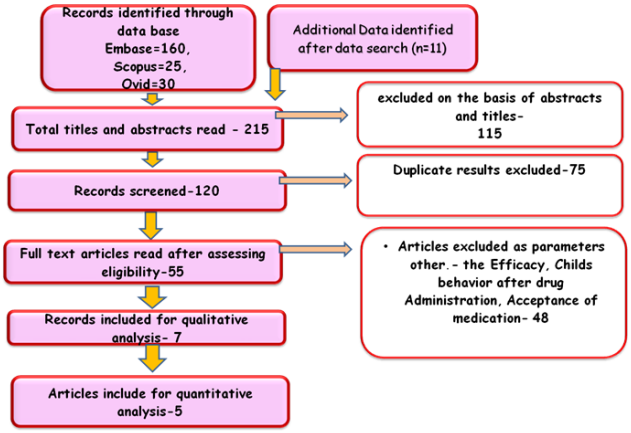
Information sources and search strategy

Searching of electronic databases as well as hand searching for relevant articles was carried out until May 20, 2023. Electronic database searched included Ovid, Google Scholar, Cochrane Library databases, SCOPUS, and Embase. Medical Subject Headings terms used were "(dexmedetomidine OR midazolam) AND (sedation) AND (Pediatric dentistry OR dentistry in children OR dentistry). Filters were applied during the search, so as to access only those articles published from January 1, 2009, to January 1, 2023.

A total of 215 articles were recorded from electronic databases. The articles provided by Embase were 160, Scopus provided 25, and Ovid provided 30 articles. Eleven articles were identified from additional Data identified after data search. Duplicate articles were identified and removed manually.

Study selection

One hundred and twenty articles were left after removal of the duplicate articles. Their titles and abstracts were evaluated thoroughly, and full manuscripts were carefully assessed according to the inclusion and exclusion criteria to finalize eligibility. Only the articles fulfilling all eligibility criteria were selected. Finally, Seven articles were selected to be included in this systematic review. A PRISMA flow diagram depicting the trial selection process is shown in Flowchart 1.



Flowchart 1: PRISMA FLOWCHART explaining the synthesis of the data for systematic review.

Data extraction

The following data from the included studies were extracted and tabulated: author, year of publication, sample size, age range of the participants, Type of sedative agent along with its route of administration and dosage, and any Outcomes measured that met the inclusion criteria. The characteristics of these seven studies are summarized in Table 1.

Table 1: CHARACTERISTICS OF STUDIES FOR INCLUDED QUALITATIVE STUDIES

Study Id	Study sample	Type of sedative agent	Route of administration	Efficacy	Outcomes measured
Katayoun Salem et al, 2014	92, 4-6 years,	Dexmedetomidine- (N=42) 1 mcg/kg Midazolam- (N=50) 0.2 mg/kg	Intranasal	**HR**-Significantly decreased in both groups **Behavior**- More acceptable in the MDZ group than DEX group **Acceptance of medication**- Superior in DEX group than MDZ	Houpt sedation rating scale to check sedation level. Vital signs were recorded before and during sedation
Salwa H. Waly, 2014	60, 6–10 years	Dosage Dexmedetomidine- (N=30) 2 µg/kg Midazolam (n=30)- 0.2 mg/kg	Intranasal	**Time of onset of sedation**- more for DEX **Duration of Procedure**- more for DEX **Recovery time**- Highly significantly shorter in Dexmedetomidine.	Time of onset of sedation, recovery time, discharge time, hemodynamic stability.
Asiya Basheer,et.al. 2018	40, 4-10 years	Group I: 1 – 2 µg/kg (N=10) group II: 2.5 µg/kg (N=10) group III: 3 – 4 µg/kg (N=10) group IV: 4 – 5 µg/kg (N=10)	Group I: IN Dexmedetomidin group II: 2.5 IN Dexmedetomidin group III: Oral Dexmedetomidin group IV: 4 – 5 µg/kg	**Onset on time**- Significantly lower for IN DEX **Depth of sedation**- Significantly more for IN DEX **Drug acceptance**- Excellent in Oral DEX	Onset and depth of sedation, recovery time and drug acceptance

Mohamad Nabil Hamod. Et.al.2018	20, 5 to 11 years.	Dexmedetomidine -(N=12)- 1mcg/kg Midazolam (N=12)- 0.2mg/kg	Intranasal	**SBP-** Significantly greater in the DEX group **pulse rate -** Significantly greater in the midazolam group.	vital signs, behavioral response, Depth of Sedation Scale, Houpt General Behavior Scale
Natarajan Surendar M et.al 2019	84, 4 to 14 years.	D1-Dex- 1 µg/kg D2-Dex 1.5µg/kg, M1-Midazolam- 0.2mg/kg	intranasal	**SBP-**Significantly lower in IN DEX **onset & recovery time-** Significantly greater in the IN DEX group	time of onset, depth of sedation, vital signs, oxygen saturation levels, adverse effects, recovery time
Vinod Patel, et.al.2022	44, 4-9 years	Group 1 – 2 µg/kg Group 2 – 2.5 µg/kg Group 3 – 4 µg/kg Group 4 – 5 µg/kg of body weight.	Group 1 & Group 2- Intranasal DEX Group 3 & Group 4-Oral DEX	**Onset of sedation-** Faster with IN DEX group **Recovery time-** significantly longer with IN DEX than Oral DEX	onset of sedation, depth of sedation, ease of completion of treatment, recovery from sedation
Amira A. El-Khatib et al,2022	72, 4-6 years	Group 1 - 0.5 mg/kg Midazolam, group 2 - 5 µg/kg dexmedetomidine	Intranasal	**SBP-**Slightly decreased with IN DEX **HR-** Decrease in heart rates with DEX **Onset of action-** DEX had significantly delayed onset of action	Onset of Sedation, duration of sedation, Safety in terms of vital signs

Statistical analysis

For the statistical outcome, all results were shown in a forest plot based on standardized mean differences (SMD) with a fixed-effects model to respect heterogeneity of these studies. To assess the heterogeneity of the different trials, I^2-value was performed. Statistical heterogeneity was assessed using I^2 test, which is 97% in the present analysis, indicating higher heterogeneity, and hence fixed effect model was run for the connotation of treatment effects.

Quality assessment

Risk of bias (ROB) was assessed using ROB 2 a revised tool for assessing risk of bias, tool by Sterne JAC *et al*. (2019). Within studies risk of bias assessment for RCTs on five ROB2 criterias and overall bias. The risk of bias evaluation in the categories bias arising from the randomization process (all criterias) Red symbol- high risk of bias, yellow symbol- some concerns, green symbol- low risk of bias. From seven articles two articles showed some concerns while other five articles showed high risk of bias. The assessment was done by two trained and calibrated reviewers. Any disagreements were resolved by discussion with the third reviewer. (Table 2)

Results

Out of the seven studies that compared the sedation efficacy of dexmedetomidine and midazolam for the management of pediatric patients in the dental clinic, only five studies were selected for meta-analysis. Effect of dexmedetomidine and midazolam as a sedative agent was assessed with respect to the following outcomes:

Onset time

Comparison for the onset time between DEX and MDZ was analysed using Review Manager 5.4. The mean difference with 95% Confidence Interval was calculated and $p<0.05$ was considered significant. A total of 86 samples in each group were assessed. Significant difference was noted for onset time with DEX group having a higher mean time, at $p=0.005$. A mean difference of 0.49 (95% CI: 0.15; 0.84) suggested that DEX administered group took significantly longer time for onset of anesthesia as seen in Figure 1.

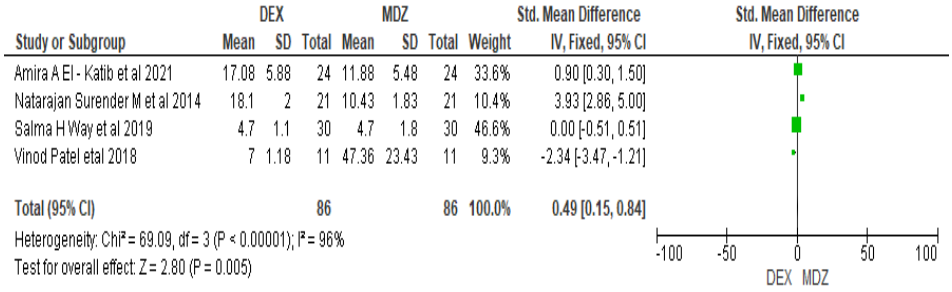


Figure 1: Forest plot for onset time between DEX and MDZ

Duration time

When compared between DEX and MDZ groups for duration time, 54 samples of two studies were analyzed. The duration between the two agents were not significantly different at $p=0.43$, as seen in Figure 2.

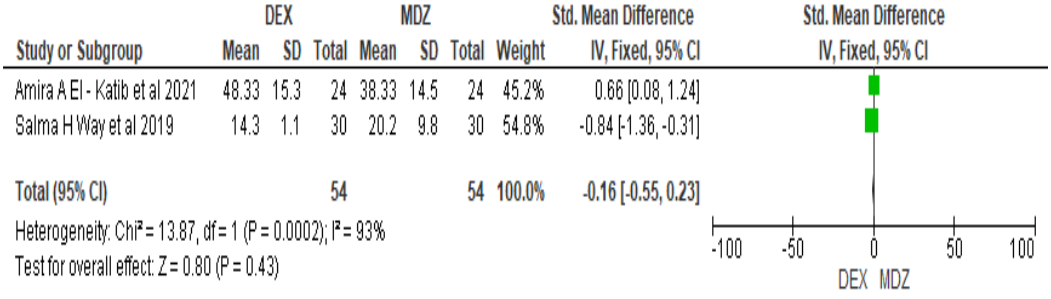


Figure 2: Forest plot for duration time between DEX and MDZ

Recovery time

Of the two studies assessed for recovery time between the two groups, DEX administered children clearly took greater time as compared to MDZ group. A mean difference of 2.37 (95% CI: 1.67; 3.07) was noted significant at p<0.00001 as seen in Figure 3.

Summative analysis for effectiveness of anesthesia showed superiority of MDZ for both onset and recovery time, but no difference was noted for length of duration.

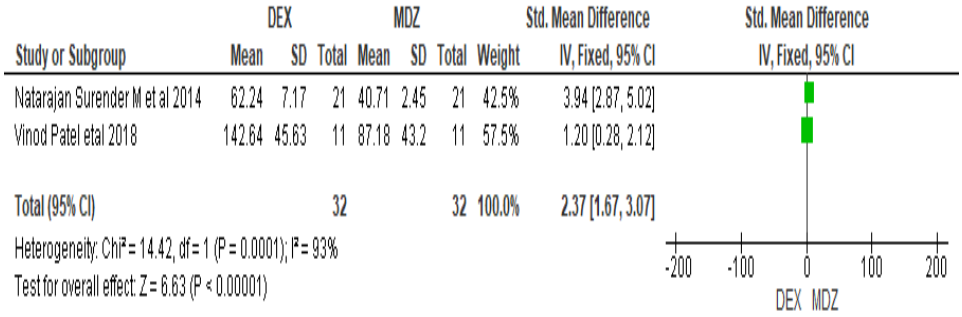


Figure 3: Forest plot for recovery time between DEX and MDZ

Systolic Blood Pressure & Diastolic Blood Pressure

Of the four studies analyzed with 97 samples in DEX group and 105 in the MDZ group, no significant difference was noted for SBP and DBP at p=0.49 and p=0.07 respectively as seen in Figure 4 and Figure 5.

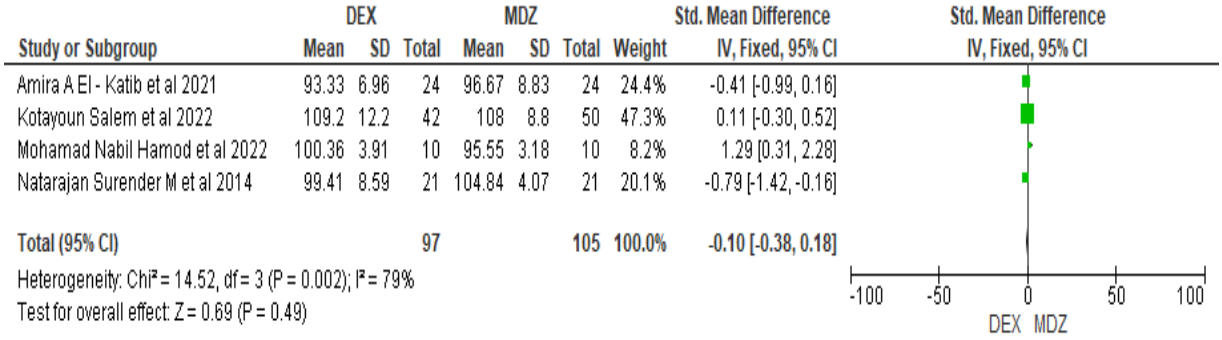


Figure 4: Forest plot for Systolic Blood Pressure between DEX and MDZ

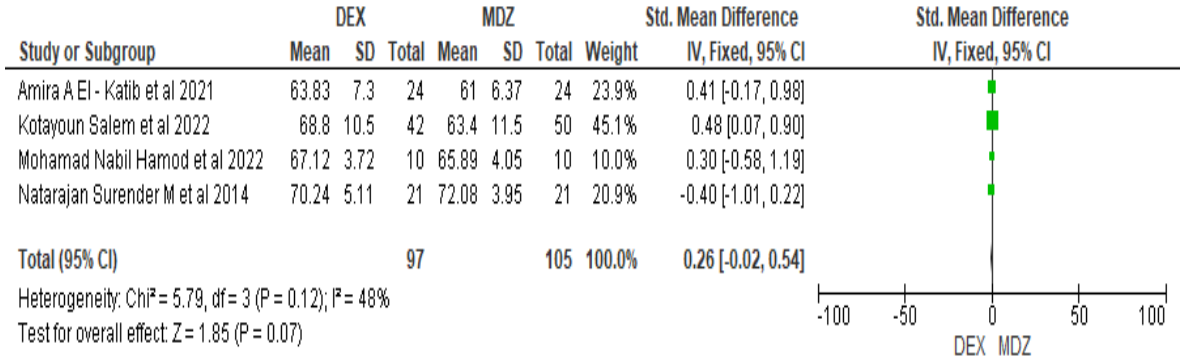


Figure 5: Forest plot for Diastolic Blood Pressure between DEX and MDZ

Oxygen saturation

Oxygen saturation levels were assessed in four studies with 84 children in DEX group and 92 in the MDZ counterparts. MDZ group subjects had significantly higher saturation levels with a mean difference of -0.36 (95% CI: -0.67;-0.06) at p=0.02 as seen in Figure 6

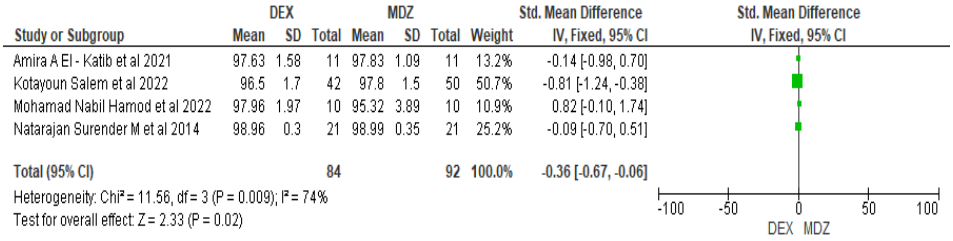


Figure 6: Forest plot for Oxygen saturation between DEX and MDZ

Pulse rate

Pulse rate was assessed in 97 children of DEX group and 105 children of MDZ group. MDZ administered group showed significantly higher pulse rate at a mean difference of -6.07, at p<0.00001 as seen in Figure 7.

Physiological parameters assessed were Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP), Pulse rate (PR) and Oxygen saturation (SPO2). Cumulatively, Blood pressure did not vary between groups, SpO2 was better in MDZ group, but heart rate was also increased in the MDZ group.

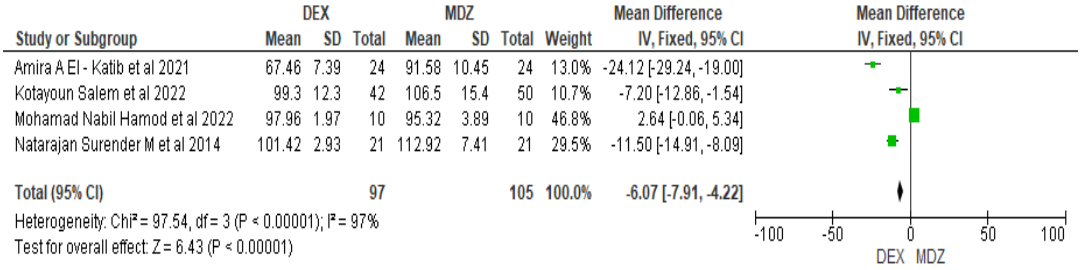


Figure 7: Forest plot for Pulse rate between DEX and MDZ

Discussion

Sedation is the most common way to minimize distress for children entering the dental clinic and to facilitate the smooth induction of anesthesia. It can be accomplished using various sedative drugs.[20] 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.[21] Therefore, different drugs, including α2 adrenoceptor agonists, which allow the child to remain cooperative or arousable and do not cause "clouding
of consciousness," are considered as alternatives for premedication in pediatric anesthesia.[22]

Dexmedetomidine is a highly selective α2 adrenoceptor agonist that provides sedation, anxiolysis, and analgesic effects without causing deleterious respiratory depression. Recently, it has been extensively explored in pediatric patients for premedication.[19] The meta analysis revealed that there was no significant difference between dexmedetomidine and midazolam premedication of pediatric patients in the dental clinic with regards to the behavior 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.

The results of individual studies that were included in this systematic review were compared and it was observed that in the study conducted by Waly in 2019,[14] in which both dexmedetomidine and midazolam were administered by intravenous route, as well as in the study conducted by Surendar in 2014,[16] 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[16] 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.[23]

In the study conducted by Waly[14] in 2019, both dexmedetomidine and midazolam were administered intravenously and recovery time was significantly shorter following administration of dexmedetomidine than following administration of midazolam, but when administered by intranasal route as in the study conducted by Surendar[16] in 2014, the recovery time was significantly shorter for midazolam than for dexmedetomidine. These results suggest that both dexmedetomidine and midazolam provide adequate sedation to control anxiety and unwanted movements in children undergoing dental procedures.

Limitations

The main limitation of this systematic review was that the sample sizes were highly variable among the included studies. Furthermore, as the number of studies for each outcome variable was not more than two, publication bias could not be assessed using funnel plot.

Conclusion

Midazolam is now commonly being used in pediatric dentistry for the sedation and behavior management of uncooperative patients. However, it is associated with respiratory depression and other adverse effects unlike dexmedetomidine. Although dexmedetomidine has comparable sedative efficacy to midazolam, it is difficult to find a lot of studies dealing with its use in children as it was approved by the Food and Drug Administration agency as a sedative for nonintubated patients only in late 2008. This systemic review provides pediatric dentists with a comprehensive comparison between dexmedetomidine and midazolam sedation to provide optimal and efficient dental treatment to uncooperative patients.

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Items evaluated	Katayoun Salem et al	Salwa H. Waly et al	Asiya Basheer et al
Source of information	+	+	+
Eligibility criteria	+	+	+
Time period evaluated	+	+	+
Consecutive population	+	+	+
Reporting of other aspects (of participants)	_	+	_
Quality assessment	_	_	+
Exclusion of participants in the analysis	_	+	+
Consideration of Confounding variables	_	_	_
Response rate	+	+	+
Handling missing data	_	+	_
Clarity follow-up	N/A	+	+

Table 2: RISK OF BIAS

Items evaluated	Mohammad Nahil Hamod et al	Natranjan Surendar M et al	Vinod Patel et al
Source of information	+	+	+
Eligibility criteria	+	+	+
Time period evaluated	+	+	+
Consecutive population	+	+	+
Reporting of other aspects (of participants)	_	+	_
Quality assessment	_	_	+
Exclusion of participants in the analysis	_	+	+
Consideration of Confounding variables	_	_	_
Response rate	+	+	+
Handling missing data	_	+	_
Clarity follow-up	N/A	+	+

Items evaluated	Amira El Khatib et al
Source of information	+
Eligibility criteria	+
Time period evaluated	+
Consecutive population	+
Reporting of other aspects (of participants)	_
Quality assessment	_
Exclusion of participants in the analysis	_
Consideration of Confounding variables	_
Response rate	+
Handling missing data	_
Clarity follow-up	N/A