Section: Research Paper

ISSN 2063-5346

Dexmedetomidine and midazolam, as intranasal conscious sedative agents in pediatric dental practice: A systematic review and meta-analysis

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ABSTRACT

Objectives:

Main purpose: The wide range of sedatives impose challenges to the pediatric dentist in choosing the appropriate drugs. The ideal selection can be made depending upon the efficacy and the adverse effects of the drug.

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Research question: Dexmedetomidine or Midazolam, which one is better as an intranasal conscious Sedative agent for Pediatric Dental Practice?

Materials and Methods:

Research protocol: The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42021261330(Visit https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021261330 to access the review protocol).

Literature search: Electronic searches were performed in PubMed, Medline, Cochrane, and LILACS from the date of inception up to March 2023.

Data extraction: Reviewers extracted the data from the included studies using the pre-defined data extraction form and have presented in "Characteristics of Studies Table". Data was extracted in terms of type of study, details of participants, details of intervention, outcomes reported.

Quality appraisal: To assess the caliber of the evidence, the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) working group approach was employed.

Data analysis: Methodological quality of evidence was evaluated using the Cochrane Collaboration's risk of bias tool and a comprehensive meta-analysis was performed for homogenous outcomes.

Results: Among 19 trials (N = 2841), six were included in the quantitative meta-analysis. IND had an onset of sedation ranging from 5 to 20 min. Satisfactory behavior was higher with IND than that with INM. The only adverse effect of IND reported in these trials was post-operative vomiting. Adverse events such as respiratory depression or cardiovascular changes requiring resuscitative measures were not reported with the use of IND.

Conclusions: IND is more effective at sedating children compared to INM. However, larger trials involving IND as a monotherapy in children are required.

Clinical Relevance: This review recommends the use of intranasal administration of dex as monotherapy which is the most effective and noninvasive approach for conscious sedation during pediatric dental treatment.

Keywords: Conscious sedation, Intranasal administration, Dexmedetomidine, Midazolam, Pediatric dentistry.

INTRODUCTION

Dentistry has been closely associated with primary emotional components such as pain, fear, and anxiety.[1] According to the study by Humphris et al., dental anxiety was more common among these and could lead to a reduction in the standard of care given or the early termination of therapy.[1] Modern pediatric dentistry describes a wide range of non-pharmacological and pharmacological behavior management approaches to aid in reduction of emotional components.[2] The use of pharmaceutical methods, such as sedation or general anesthesia, is advised when nonpharmacological techniques are ineffective.[3]

Current understanding

Preoperative drugs that are fast-acting, neuroprotective, dependable, quickly metabolized, and sustain patient respiratory function with little to no cardiovascular side effects are ideal sedatives.[4] Among drugs used in conscious sedation, midazolam **(midaz)**, a member of the benzodiazepine family, has gained much attention as a good sedative agent for pediatric dental patients since 1983.[5] It produces anterograde amnesia, drowsiness, muscle relaxation, and anticonvulsant actions with a rapid start and quick recovery.[6]
To reduce the adverse effects of varying drugs, one newer promising drug, which is used in dentistry for sedation is dexmedetomidine **(dex)** which has been registered in the United States of America (USA) since 1999 and is being used in clinical dental practice from 2005.[7] Dex, a selective agonist of the alpha-2-adreno receptor is gaining importance owing to its short action, and sedative and analgesic effects.[8] Dex-based sedation can be successfully used as an alternative to conscious sedation on grounds of its minimal effects on patient's respiration and demonstrates anti-salivation.[9]

Limitations in the existing literature

The administration routes are another element of sedation that has evolved. The oral route of administration has traditionally been the most accepted and recommended method in pediatric dentistry; however, it has certain drawbacks, such as slow beginning of the action, inconsistent efficacy owing to poor absorption, an inability to titrate, and patient resistance.[10] In contrast, intranasal administration is a parenteral approach that allows for exact dosage delivery and drug absorption through the nasal mucosa without the first-pass metabolism, producing bioavailability that is comparable to that of intravenous treatment. The intranasal route can be effectively used in a child who refuses oral administration.[4]

Therefore, this systematic review and meta-analysis aimed to identify the effectiveness of dex and midaz as intranasal conscious sedative agents for pediatric dental treatment, which could aid us in selecting an effective sedative drug; thereby, improving the quality of dental treatment.

Methods

A methodical strategy to search for publications that assessed the effectiveness of midaz or dex as an intranasal-conscious sedative drug in pediatric dental practice was employed. The Preferred Reporting Items for Systematic Review and Meta-Analysis **(PRISMA)** reporting items for systematic reviews and meta-analyses and Cochrane review methodologies served as the foundation.

Information sources

The protocol for this review was registered with the International Prospective Register of Systematic Reviews **(PROSPERO)** under the registration number CRD42021261330 (Visit https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021261330 to access the review protocol).

Data sources and literature sources

The electronic search was conducted from the date of inception using MEDLINE, Cochrane Controlled Trials Register, PubMed, and LILACS. A manual search of pertinent references from conference proceedings and abstracts was performed to further augment this search. Various searches, including bibliographies of relevant reference materials, journal and book searches, conference abstracts, contacting subject-matter experts, and other appropriate studies were referred. The present review only considered studies published in English language between 1992 and 2023. The keywords and MeSH terms used are mentioned in Appendix 1.

The results of the searches were imported to Mendeley desktop (version 1.18.9) to locate and remove duplicates.

Study selection

Using predetermined selection criteria, two reviewers independently identified each study. Disagreements that arose during the selection of the primary study were arbitrated by a third reviewer.

Eligibility criteria

Studies that met the following requirements were considered for this review:

Literature type: The randomized-controlled trials evaluated the outcomes using either the open or blinded method. All the trials conducted in pediatric dentistry using intranasal dexmedetomidine and midazolam, compared with any other sedatives in all published international journals were considered; the PICO strategy is elaborated in Table 1.

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Exclusion criteria - Studies involving either adults or adolescents, a combination of dex and midaz, use of these medications for procedures other than basic dental care, use of the substances as a premedication before general anesthesia or other similar operations, and the drug's pharmacokinetics and pharmacodynamics.

Data extraction

Based on the predetermined criteria, two reviewers independently extracted the data which was then verified by the third reviewer. The study variables extracted were as follows: 1) Study design and population; 2) Onset of sedation; 3) Behavior changes; 4) Adverse effects; and 5) Recovery from sedation. If the variables had missing data or incomplete results, the study was excluded from the review.

Risk of bias in individual studies The methodological quality of the studies was independently assessed by two reviewers using the Cochrane risk of bias domain-based, two-part technique as outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011). We assessed the Risk of Bias **(ROB)** under the following criteria: Sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias.

Quality of the evidence across the studies

To assess the caliber of the evidence used throughout the investigation, we employed the Grades of Recommendation, Assessment, Development, and Evaluation **(GRADE)** working group approach. Two reviewers independently evaluated the quality of each result. The five criteria employed for the GRADE quality assessment were study design, publication bias, indirectness, imprecision, and inconsistency. We used GRADE profiler **(GRADE pro)** software to create the ‘‘Summary of findings’’, which included the following outcomes: 1) Onset of sedation; 2) Operative effects; 3) Adverse effects; and 4) Recovery time.

Summary measures and synthesis of results

We pre-emptively considered meta-analyses if there was homogeneity in operative procedures and outcome measures. However, if there was substantial heterogeneity in the outcomes, meta-analyses were not performed. Instead, a descriptive analysis of each study's design, population, and the primary outcome was performed. We used ranges to describe the onset of sedation and recovery from sedation. A raw agreement was used to characterize the level of differences among the reviewers.

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Statistical analysis

With analyses employing weighted mean differences, which are obtained using the general inverse variance approach. The risk ratio for binary outcomes is presented with a 95% confidence interval. The I statistic was used to access the heterogeneity of the study. To demonstrate statistical heterogeneity, an I^2 statistic (50% with a p value of 0.10) was considered. When considerable statistical or clinical heterogeneity was detected, we used random effects models.

Publication bias

In this meta-analysis, the publication bias was evaluated using funnel plots.

Results

Identification of studies

A preliminary database search turned up 2841 publications; 356 duplicate articles were eliminated, and then 2456 articles were further rejected by analyzing their titles and abstracts. Subsequently, we identified 19 studies [11-29] describing possibly pertinent findings after reviewing the full manuscripts for the 45 publications that were still published. Consequently, six studies were included in this meta-analysis and are represented in a flow diagram (Fig. 1).

Study characteristics and patient populations

The characteristics of the included studies were featured between 1992 and 2023, from eight different countries: the United States of America (three), Syria (one), the United Kingdom (one), Saudi Arabia (two), India (seven), South Africa (one), Egypt (two), and Iran (two). Table 2 represents the summary of the study characteristics included in this review.

Risk of bias in individual studies

All the studies included in this review used a random allocation method. Only six studies gave a detailed explanation of the type of randomization used. The likelihood of inadequate outcome data and biased reporting was generally low in trials. Fig. 2A and 2B show graphs and descriptions of the risk of bias in individual studies.

Quality of the evidence across the studies

The GRADE system, which evaluated the certainty, classified the overall quality of the evidence as high (recovery time), moderate (onset of sedation), and poor quality (operative and adverse effects) (table. 3).

Publication bias

The results of the funnel plots did not exhibit a symmetrical shape; however, the accuracy of the funnel plots was undetermined as the number of studies included for meta-analysis was less than ten (added in electronic supplement source).

Onset of sedation

Ten trials [11-20] eported the onset of sedation ranging from 4 to 30, 5 to 20, and 10 to 50 min for intranasal midazolam (INM), intranasal dexmedetomidine (IND), and other comparator drugs, respectively, and variations were attributed to the difference in the drug dosages. The comparator drugs identified through this review are ketamine, sufentanil, and fentanyl citrate. The onset of sedation is elaborated on in Table 4.

Recovery from sedation

Eleven trials [11-16,18,21-24] reported recovery from sedation ranging from 55 to 150 min in IND and 25 to 100 min in INM.

Pooled results for meta-analysis

Studies with both mean and standard deviation data were included for meta-analysis. All ratios that are frequently employed in meta-analyses as effect measures are relative measures. Individual studies reported a 95% confidence interval of one study overlapping 0 that was study 1, while the other studies did not overlap 0. Therefore, all studies were statistically significant except study 1. Overall studies reported that the heterogeneity was 99%; therefore, we considered the random effects model. The overall random effect model at 95% confidence intervals overlapped 0, which represented no statistical significance in the overall study (Fig. 3, 4).

Operative effects

Behavior changes

Behavior changes were reported in nine out of 19 trials [11-14,17,19,21,23,24,25] Eight studies assessed behavior changes using Houpt's scale, [11-13,17,19,23,25,29] while one used the Ohio state behavior rating scale.[14] Psychological characteristics were assessed in a trial by Kattayoun et al using the strengths and difficulties questionnaire (SDQ)

Degree of pain was assessed only in one study conducted by Khalil et al. using the Wong-Baker FACES pain rating scale.[27] A detailed summary of the behavior changes is presented in Table 2.

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Clinical anxiety changes. Anxiety changes were reported in five of 19 trials. [16,20,24,26,28] Four studies assessed anxiety changes using Venham's clinical anxiety scale. [16,20,24,28] A study conducted by Shanmugavel et al**.** assessed anxiety changes by evaluating salivary cortisol levels.[26] A study conducted by Kattayoun et al evaluated Dental fear through the Persian version of children's fear survey schedule-dental subscale (CFSS-DS).[29]

Depth of sedation

Five of 19 trials reported the depth of sedation.[11,14,15,21,24] Abrams et al. reported the mean sedation score for INM as 4, which denoted acceptable sedation with minor fussing and no struggle.[21] Al-Rakaf et al. reported the depth of sedation by evaluating the level of drowsiness for INM, which ranged between 92 and 100%, yet none of the children slept.[11] Heard et al. used Michigan Sedation Score and reported higher sedation in the INM+ oral transmucosal fentanyl citrate (OTFC) group only than that in INM.[14] Bahetwar et al. evaluated the depth of sedation using separate five-point scale and reported an adequate depth of sedation of 84% in INM.[15] Peerbhay et al. evaluated the depth of sedation using the Wilson sedation score and reported that 96.6% of children were drowsy, while 3.4% had their eyes closed but were arousable.[24]

Adverse effects

Adverse effects were reported in 13 of 19 trials. Abrams et al. and Al-Rakaf et al. reported 0% desaturation using INM with no difference in diastolic blood pressure.[11,21] Furthermore, Al-Rakaf et al. reported diplopia in 62% with fasting and 69% without fasting and 8–17% of sneezing and coughing in children administered with INM, which was similar to that reported by Shashikiran et al. with 30% of sneezing and coughing.[11,12] No vomiting, seizures, allergic reactions, or respiratory depression were observed while using INM by Al- Rakaf et al. and Shashikiran et al.[11,12]Moreover, Heard et al. and Johnson et al. reported airway complications and desaturation using INM.[14,23] Nasal irritation was one of the major adverse effects reported with the use of INM. To overcome this Khalil et al. used local anesthesia before the administration of INM.[27] Headaches and hiccups were reported by Peerbhay et al.[24] Trials using IND reported vomiting in one study with no vital changes.[16]

Discussion:

Decreasing the level of anxiety and pain in children undergoing dental procedures has been a challenge for pediatric dentists. Sedation is regularly used by clinicians, certain domains like the ideal choice of drug and method of administration for children remain ambiguous. In this review, IND and INM when used as a conscious sedative agent were evaluated in children undergoing dental treatment. Thus, this systematic review and meta-analysis was conducted with the methodological approach to reflect the highest available evidence. A total of 19 trials based on the prespecified inclusion and exclusion criteria were included. The qualitative syn-

thesis of the present systematic review compared the operative effects, which included the depth of sedation, behavior changes, and anxiety levels. Depth of sedation with INM was acceptable in trials conducted by Abrams et al. Al- Rakaf et al. reported no variation in depth of sedation irrespective of fasting; however, drowsiness increased with an increase in dosage with respect to INM.[11] Christopher et al. reported increased depth of sedation when INM was used in combination with other drugs, yet none of the children were either deeply sedated or over-sedated (score 3 or 4 UMSS).[14] Bahetwar et al. reported adequate depth of sedation with anxiolysis and purposeful response to verbal commands using INM, yet it was less than intranasal ketamine.[15] The depth of sedation achieved using dex was assessed in only of the included trials by Kattayoun et al which reported increased acceptance in midaz than in dex group.[29] Behavior changes assessed using the Houpt's scale reported acceptable behavior with INM than that in the oral group in Johnson et al.'s study which was in accordance with the studies conducted by Chopra et al., Sunbul et al., and Mowafy et al.[17,19,23] Behavior changes of dex and midaz were compared by Natarajan et al. They reported significantly satisfactory behavior using dex.[16] Kattayoun et al reported more unacceptable behaviour in dex group.[29] An increase in clinical anxiety level was prevented using dex in a study reported by Mai et al.[20] Dex has been reported as an effective sedative to reduce the anxiety induced by dental treatment.[16,18] Although Midaz has increased evidence for successful dental sedation, considering the acceptance of the drug a higher incidence of nasal discomfort, burning sensation, increased degree of pain, and defiant behavior has been reported. However, the route of administration is in line with acceptance and the amount of drug to be used. In children, the intranasal or oral route is preferred over the intramuscular or intravenous route to avoid anxiety due to injection. The oral route has a disagreeable taste and undergoes the first-pass metabolism; thus, requires a higher dose for the desired action. An insulin syringe without a needle or an atomizer device with variable acceptance are generally administered using the nasal route. The trials of this systematic review safely employed IND dosage between 1.0–2.5 ug/kg. However, the trials included in this review have reported only vomiting as an adverse effect of IND without any changes in the vital parameters.[16] This is in line with a pediatric systematic study, where the authors reported no compromise in the respiratory system with IND. [30] INM reported with adverse effects such as nausea, vomiting, desaturation, aggressive behavior, diplopia, sneezing, coughing, headache, and nasal irritation. The quantitative meta-analysis from individual studies reported a statistically significant result favoring the experimental group at a 95% confidence interval for the onset and recovery from sedation. The overall studies reported 99% heterogenicity, which could be attributed to the variations in drug dosage. The onset of sedation is an important consideration in an over-embellishing dental setting. This review has recorded a wide range in the onset of IND (5–20 mins); INM (6–30 mins), which might be attributed to the heterogenicity in dosing or definition of sedation; however, are inconsistent with a previous pediatric systematic review by Poonai et al.[31] This review identified the only drawback of using dex is the pronged recovery time, which could necessitate the child to be under observation for a longer duration.

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The risk of bias in individual studies was graded well for four trials that met all the criteria according to the Cochrane ROB tool. Randomization, allocation concealment and blinding were not elucidated in other studies, which led to downgraded outcomes.

The certainty assessment of this review, revealed the overall quality of evidence as recovery time was high because the studies involved did not have any serious considerations. The evidence was graded moderate for the onset of sedation as there was a serious indirectness owing to variations in the mode of delivery of intranasal agents using either insulin syringe or atomizer, which could affect the rate of absorption in the nasal mucosa, where some amount of the drug might be swallowed by the patient. The certainty of operative and adverse effects was low, as there was serious inconsistency and impression as the outcomes could not be pooled statistically owing to heterogenicity among the studies. This was attributed to differences in the comparator drugs and variations in the scales used for assessing the behavior changes. The overall certainty assessment was graded critical for operative and adverse effects, as the changes in the behavior after sedation was the most essential factor for providing dental treatment to a child from a pediatric dentist's viewpoint. We downgraded the level of certainty of the evidence for some outcomes owing to the asymmetry in the funnel plot, which had arisen possibly owing to publication bias. By assessing the certainty, this review gives a precise interpretation of the results.

A large number of studies included in this analysis had several methodological shortcomings, and the lack of a standardized approach for assessing behavioral changes may have influenced the reporting of results and other relevant outcomes, such as the onset and recovery of sedation. It was challenging to compare the behavioral changes between trials that employed validated sedation instruments and trials that did not due to the heterogenicity reported in dose and indications.

The most prudent strategy would be to confine the use of IND to children with any cardiac abnormalities, hypotension, bradycardia, or auxiliary use of sympatholytic agents. [32] Based on existing literature, future studies should be utilized to identify adverse events with validated scales and their appropriate interventions.

This review protocol has minor modification from the PROSPERO registration for extending the year of studies including 2021-2023, hence this review has a upgraded research data upto march 2023.

Future agenda

Future studies should focus on reporting the concealment allocation and following proper blinding techniques as this can affect the primary outcomes of the study.

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The quality of evidence assessed for operative and adverse effects was low in this review. However, larger and more methodologically rigorous trials using objective validated and standard scales to record adverse effects in future studies would assist in definitive judgment.

Future trials should focus on involving dex as monotherapy for conscious sedation and assessing the depth of sedation. Whereas, trials using midaz should focus on a combination of drugs to overcome the adverse effects.

Limitations of this review

This review did not include behavior changes as an outcome in the meta-analysis. Instead, a descriptive analysis was performed, since there was a wide variation in the scales used and different comparator drugs in each trial. Moreover, a higher number of trials on dex was not available in the literature.

Highlights of this review

We included IND as a monotherapy for conscious sedation in pediatric dental treatment, which could aid in our routine practice, whereas, INM was more commonly used in combination with other drugs.

Clinically from the pediatric dentist's viewpoint, we believe that changes in behavior are the most relevant, pragmatic, and practical approach to describe the success of sedation. From a methodological perspective, we believe this to be a reliable technique to overcome the variations in behavior assessment scales.

To assess the overall success of the sedative, we included the onset of sedation, operative changes, depth of sedation, acceptance of the drug, anxiety changes, adverse effects, and recovery from sedation. By evaluating these parameters, we could derive a promising conclusion.

In conclusion, this review suggests that IND is well tolerated with minimal adverse effects for dental procedures in children. Midaz has a quick onset of sedation; however, its use is limited owing to its adverse effects. Thus, this systematic review and meta-analysis recommends the use of intranasal administration of dex as monotherapy for conscious sedation, to achieve the most effective and noninvasive pediatric dental treatment.

Acknowledgment: We would like to thank Editage (www.editage.com) for English language editing.

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Table 1- PICO strategy in evaluating the scientific evidence

Parameter	Evaluation
Population (P)	Paediatric patients with systemically healthy conditions (American Society of Anaesthesiologist's status I/II) indicated for treatment under conscious sedation will be included without any regard to racial or gender distinctions.
Interventions (I)	Trials evaluating the safety and efficacy of intranasal dexmedetomidine or intranasal midazolam as a conscious sedative agent in paediatric dental treatment.
Comparator (C)	Trials evaluating the safety and efficacy of any other sedative in paediatric dental treatment
Outcomes (O)	onset of sedation, operative effects, post-operative effects (adverse effects), and time of recovery are evaluated to measure the primary outcomes. The operative effects include behavior changes, level of anxiety, and depth of sedation. The outcomes recorded are either the incidence of events (primary outcome) or mean differences between groups.

Table 2: The characteristics of the included studies.

S.No	Source, trial design, country	Participants	Comparisons	Parameters assessed	Measure of effectiveness of sedation	Results	Summary
1.	Richard Abrams et al-1993, parallel group RCT, USA.[21]	30 patients of 17-62 months of age were divided into 3 groups.	IN Midaz - 0.4mg/kg; IN ketamine-3mg/kg IN sufentanil- 1.5 or 1 ug/kg.	Depth of sedation Intraoperative desaturation Recovery time	Depth of sedation based on mean sedation scored from1 to 10	INM and INK – scored 4 (acceptable sedation) INS- scored 7 (heavily sedated)	Favourable for INM followed by INK. INS is unacceptable.
2.	Al rakaf et al - 2001, Crossover group RCT, Saudi Arabia.[11]	38 patients of 2-5 years of age were divided into 3 groups.	IN Midaz- using atomizer First visit-fasting Second visit- without fasting Group1-0.3mg/kg; Group2-0.4mg/kg; Group 3- 0.5mg/kg	Onset of sedation Behaviour changes Depth of sedation Post-operative adverse reaction Recovery time	Depth of sedation evaluated based on drowsiness. Behaviour changes based on houpt scale scored from 1 to 7 for overall behaviour.	Depth of sedation A-79%, B-96%, C-100% Acceptable behaviour scored between 3-6 was noted in all the three groups.	Neutral for all the groups irrespective of fasting.

3.	Shashikiran et al 2006, parallel group RCT, India.[12]	40 patients of 2-5 years of age were divided into 2 groups	Group N- IN Midaz 0.2mg/kg-Using syringe; Group M- midaz IM	Onset of sedation Behaviour changes 5-self-designed dichotomised scales-allergic reactions. Recovery time	Behaviour changes based on houpt scale scored from 1 to 7 for overall behaviour.	Overall behaviour scored excellent IM-25%,IN-25% Unsatisfactory-IM-5%,IN-10%	Favours INM 0.2mg/kg than IMM.

4.	Gilchrist et al – 2007, parallel group RCT, United kingdom.[22]	20 patients of 2-9 years of age	IN Midaz 0.25mg/kg Using MAD	Post-operative adverse effects Recovery time	Compliance with full dose was achieved in 14 of 20 patients.	Nine patients had no resistance to drug administration. Five patients had verbal resistance.	Favoured adequate anxiolysis.

5.	Romania et al – 2007, parallel group RCT, Iran.[13]	30 patients of 3-5 years of age	IN Midaz 0.5mg/kg Using insulin syringe	Onset of sedation Behaviour changes Post-operative adverse reaction Recovery time	Behaviour changes based on houpt scale scored from 1 to 7 for overall behaviour.	Overall behaviour after drug administration scored unacceptable 23.5%, acceptable – 76.5%	IN Midazolam has successful sedation of significant percentage of children by increasing their general behaviour based on houpt scale.

6.	Christopher heard et al 2010, parallel group RCT, USA.[14]	102 patients of 1.8-12 years of age were divided into 4 groups	IN Midaz 0.7mg/kg-Oxygen via nasal cannula. Oral midaz IN midaz+ oral transmucosal fentanyl citrate IN midaz+ IN sufentanil.	Onset of sedation Behaviour changes Depth of sedation Post-operative adverse reaction Recovery time	Depth of sedation based on university of Michigan sedation score (UMSS) scored from 0 to 4 Behaviour changes based on Ohio state behaviour rating score (OSBRS) scored from 1 to 4	IN midaz+ oral transmucosal fentanyl citrate had increased depth of sedation. All the groups except IN midaz+ IN sufentanil had significant changes in behaviour.	All four sedation regimes were equally effective.

7.	Erin johnson et al 2010, Cross-over group RCT,USA.[23]	30 patients of 42-84 months of age into 2 groups	IN Midaz 0.3mg/kg; Oral Midaz 0.5mg/kg	Behaviour changes Respiratory depression Recovery time	Behaviour changes based on modified Houpt behaviour scale recorded during LA administration and after 20 minutes.	Overall behaviour was significantly higher in intranasal group.	Oral midazolam was considered to be effective than intranasal midazolam.

8.	Bahetwar SK et al- 2011, Crossover group RCT, India.[15]	45 patients of 2-6 years of age were divided into 3 groups	IN Midaz 0.3mg/kg; IN KETAMINE 6mg/kg IN KET+MIDAZ 4mg + 0.2mg/kg Using insulin syringe	Onset of sedation Depth of sedation Post-operative vomiting Recovery time	Depth of sedation based on separate 5 point rating scale.	Adequate depth of sedation was noted in INM with 84%.	Sedation was most successful with ketamine and least with midazolam.

9.	Chopra R et al-2013 Crossover group RCT, India.[25]	30 patients of 2-8 years of age were divided into 2 groups.	IN Midaz 0.25mg/kg; Buccal route midaz Using spray.	Behaviour changes Burning sensation	Behaviour changes based on houpt scale.	INM had good acceptance of 16.6%, with successful completion in 56.7%.	Buccal midazolam was well tolerated however effectiveness of sedation was not influenced by route.
10	Natarajan Surendar et al 2014, parallel group RCT, India.[16]	84 patients of 4-14 years of age were divided into 4 groups	D1- IN Dex- 1ug/kg; D2- IN Dex- 1.5ug/kg M1- IN Midaz-0.2mg/kg; K1- IN Ketamine-5mg/kg	Onset of sedation Behaviour changes Post-operative adverse reaction Recovery time	Behaviour changes based on venhaam's clinical anxiety scale and FLACC.	Satisfactory behaviour with 90.5% in D2 group and 71.4% in M1 group.	Dex produced greater analgesia than midazolam.
11.	Nada sunbul et al- 2014, Crossover group RCT, Saudi Arabia.[17]	25 patients of 36-72 months of age were divided into 2 groups	IN Midaz 0.3mg/kg Using MAD; Buccal midaz 0.3mg/kg Using MAD	Onset of sedation Behaviour changes Post-operative adverse reaction	Behaviour changes based on houpt scale scored from 1 to 7 for overall behaviour.	Overall behaviour scored excellent IN-16%; very good- 32%	Atomized intranasal midazolam is more acceptable.
12.	Shanmugavel et al 2016, parallel group RCT, India.[28]	48 patients of 3-7 years of age were divided into 2 groups	IN Midaz 0.2mg/kg Using MAD; sublingual midaz	Behaviour changes	Behaviour changes based on Venham's clinical anxiety scale	Anxiety reduced to 95% in INM and 100% in sublingual route.	Sublingual group is better accepted but both groups are equally effective.

13.	Fathima peerbhay et al – 2016, parallel group RCT, South Africa.[24]	118 patients of 4-6 years of age were divided into 2 groups	Group A -IN Midaz- 0.5mg/kg using MAD.0.5% lidocaine spray Group B -IN Midaz- 0.3mg/kg using MAD.0.5% lidocaine spray	Level of anxiety Level of sedation Post-operative adverse effects Recovery time	Level of anxiety based on venham scale, facial image scale.	No significant changes in anxiety levels.	0.5mg/kg INM was more effective.
14.	Shanmugavel et al 2016, parallel group RCT, India.[26]	20 patients of 3-7 years of age were divided into 2 groups	IN Midaz- 0.2mg/kg using MAD; Buccal midaz- 0.2mg/kg using MAD	Clinical Anxiety changes Changes in salivary cortisol level	Level of anxiety based on venham scale.	Significant decrease in anxiety levels in IN group.	Both IN and sublingual groups were equally effective.
15.	Vinod Patel et al – 2018, parallel group RCT, India.[18]	44 patients of 4-9 years of age	IN Dex- Group 1- 2ug/kg group 2- 2.5ug/kg; Oral Dex Group 3- 4ug/kg ; Group 4 - 5ug/kg	Onset of sedation Patients acceptance Recovery time	Patients acceptance based on OHIO State behaviour scale.	Acceptance was better in oral group. Successful treatment completion was high in IND group.	IN dex is safe and effective.
16.	Walla khalil et al – 2020, parallel group RCT, Syria.[27]	63 patients of 4-11 years of age were divided into 3 groups	IN Midaz- 0.5mg/kg using spray; IN midaz+ lidocaine 0.9% placebo	Degree of pain Nasal discomfort	Degree of pain based on WBFS scale Scored between 1to 8.	IN Midaz- 8 IN midaz+ lidocaine- 1	INM results in high level of pain.

17	Mowafy et al – 2021, Crossover group RCT, Egypt.[19]	36 patients of 3-5 years of age were divided into 2 groups.	IN Midaz- 0.3mg/kg using MAD; Buccal midaz-0.3mg/kg using MAD	Onset of sedation Overall behaviour.	Behaviour changes based on houpt scale scored from 1 to 7 for overall behaviour.	No significant changes.	Both aerosolized buccal and IN midazolam are safe and effective.
18.	Mai.A. et al-2021, crossover group RCT,Egypt.[20]	42 patients of 5-7 years of age were divided into 2 groups.	IN Dex- Group 1- 1ug/kg group 2- 1ug/kg; sublingual Dex	Onset of sedation Acceptance of drug Clinical anxiety changes.	Level of anxiety based on venham scale scored from 0 to 5.	Both routes prevented the increase in anxiety during LA administration.	Onset favoured IND; acceptance favoured sublingual group.
19.	Katayoun Salem et al- 2022, parallel group RCT, Iran.[29]	92 patients of 4-6 years of age were divided into 2 groups.	IN Midaz - 0.2mg/kg IN DEX - 1µg/kg. Using MAD	Dental fear psychological status Sedation assessment Drug acceptance	Persian version of children's fear survey schedule-dental subscale (CFSS-DS) strengths and difficulties questionnaire (SDQ) Houpt behavioral rating scale	There was no significant association between overall behavior and total difficulties, or strengths in either group. The lower acceptance rate of Midaz in comparison to DEX	IN sedation with Midaz results in more acceptable overall behavior than DEX in pediatric patients with high dental fear.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Dexmedetomidine or midazolam**	**other sedative**	**Relative (95% CI)**	**Absolute (95% CI)**		
onset of sedation												
6	randomised trials	not serious	not serious	serious[a]	not serious	none	287	287	-	SMD **0.12 SD lower** (0.32 lower to 0.08 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
operative effects												
18	Randomised trials	serious[b]	serious[c]	not serious	not serious	none	behavioural changes, level of anxiety, depth of sedation favours the experimental groups.				⊕⊕◯◯ Low	CRITICAL
adverse effects												
10	Randomised trials	serious[d]	not serious	not serious	serious[e]	none	varied effects like bradycardia, nausea, vomiting, oxygen desaturation, nasal discomfort, burning sensation has higher incidence in intranasal midazolam groups.				⊕⊕◯◯ Low	CRITICAL
recovery time												
5	Randomised trials	not serious	not serious	not serious	not serious	none	251	251	-	SMD **0.38 SD higher** (0.15 higher to 0.61 higher)	⊕⊕⊕⊕ High	IMPORTANT

Table 3: Overall quality of evidence based on the GRADE system

Table 3: Explanations- (**CI:** confidence interval; **SMD:** standardized mean difference) a. difference in the mode of delivery of drug; b. variations exist in the type of scales used across the studies. c. wide variance of results across studies; d. adverse effects were not defined using standardized criteria. e. only fewer events of adverse effects were recorded.

Table 4- Onset of sedation

Intranasal Midazolam	Intranasal dexmedetomidine
0.2mg/kg - 6 – 14 mins	1.0ug/kg- 9-20 mins
0.3mg/kg - 5 – 15 mins/10-30mins	1.5ug/kg - 16-20 mins
0.4mg/kg - 9- 12 mins	2.0ug/kg- 7-10 mins
0.5mg/kg - 4-5 mins	2.5ug/kg - 5-8 mins
0.7mg/kg - 9- 30 mins	

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ISSN 2063-5346

FIGURES

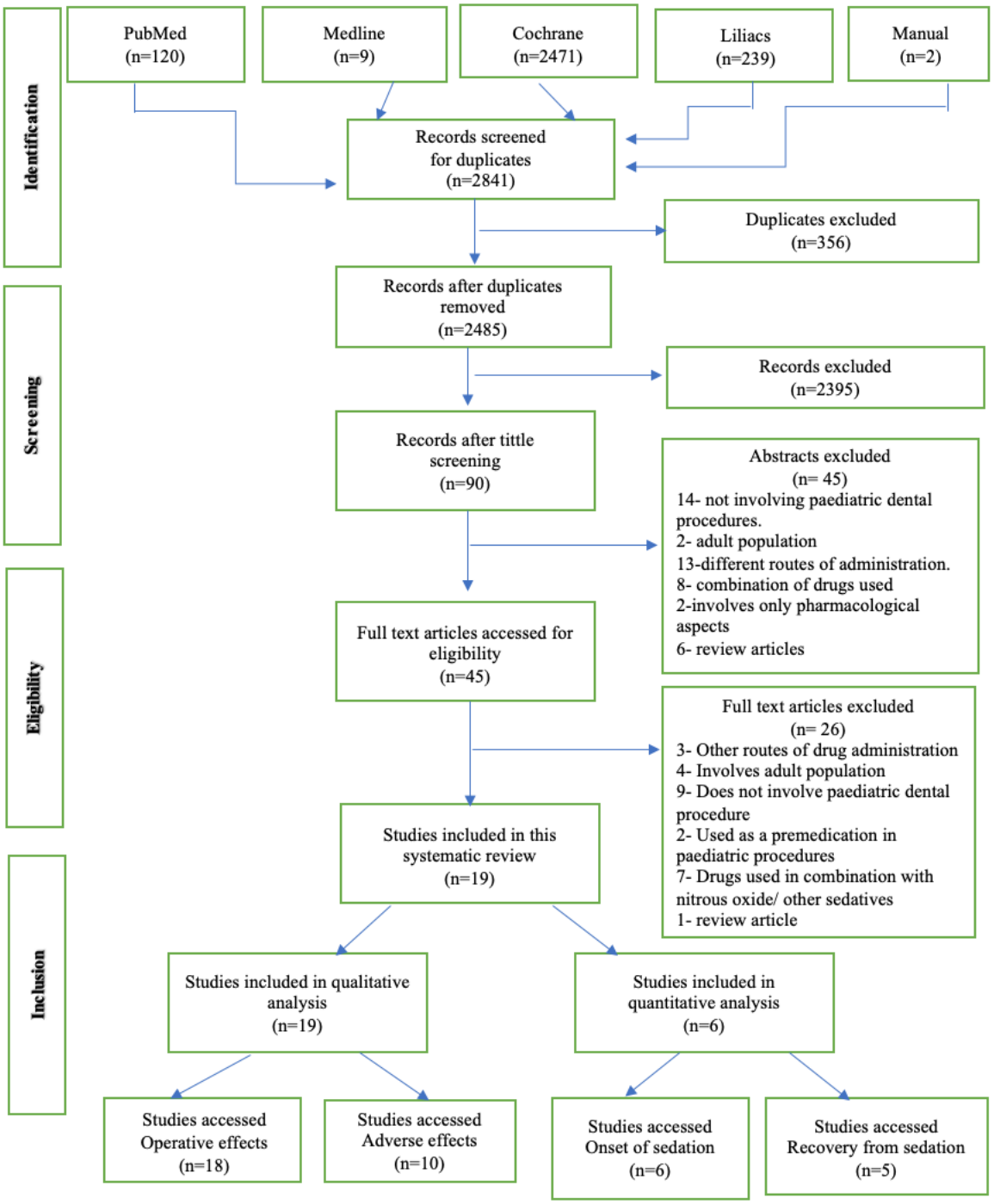

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Fig 1: PRISMA flow diagram of the literature search strategy.

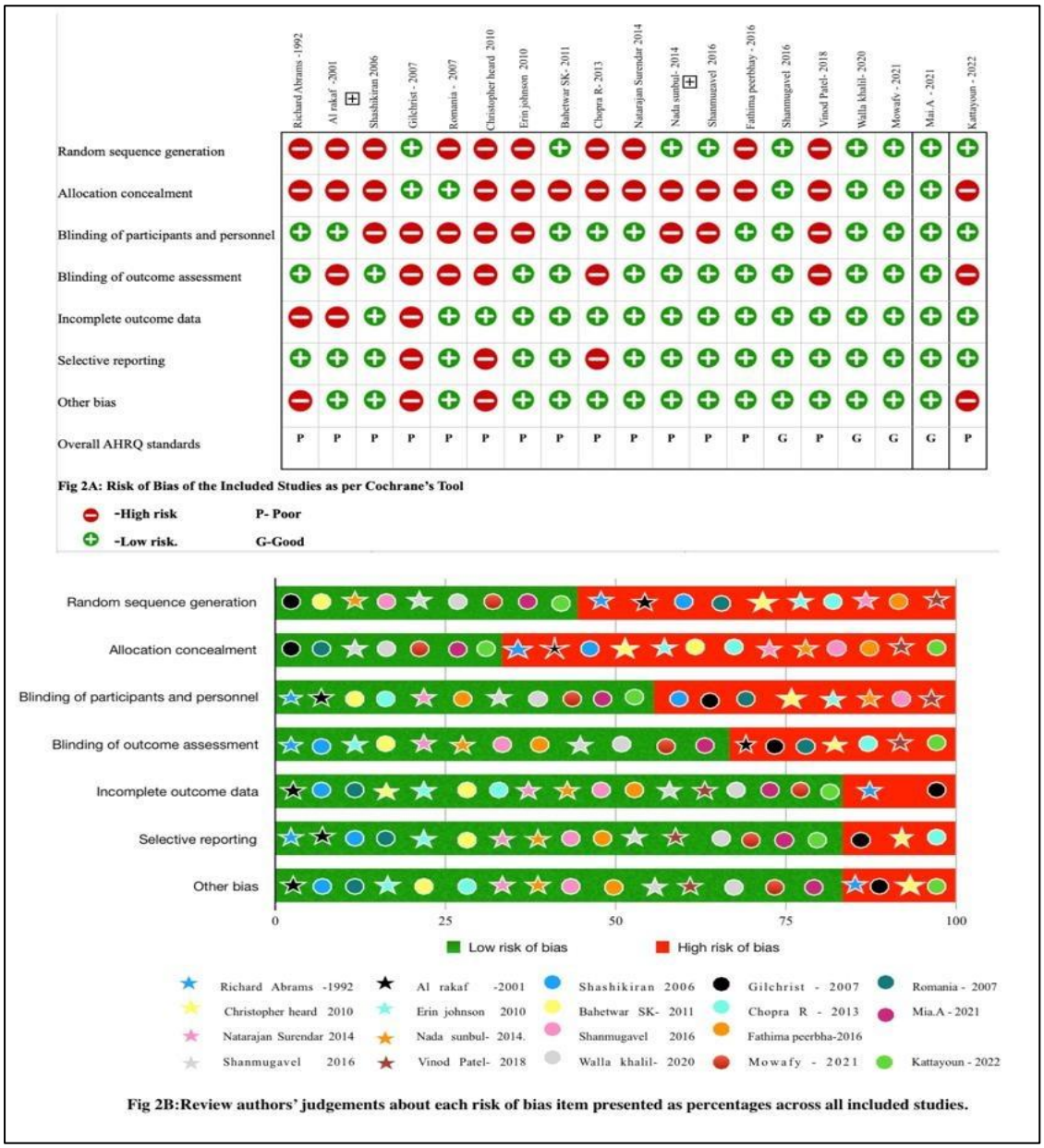

Fig 2A: Risk of bias of the included studies as per Cochran's tool; **Fig 2B:** Review author's judgements about each risk of bias item presented as percentage across all included studies

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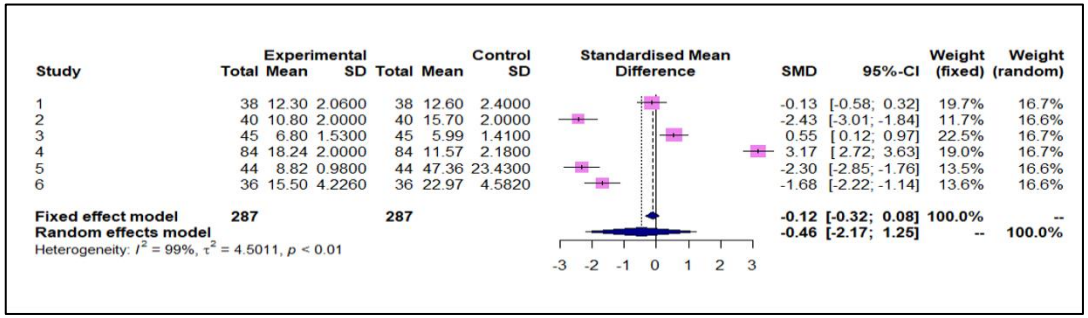

Figure 3. Synthesis forest plot. This forest plot summarizes the results of included studies for the onset of sedation (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

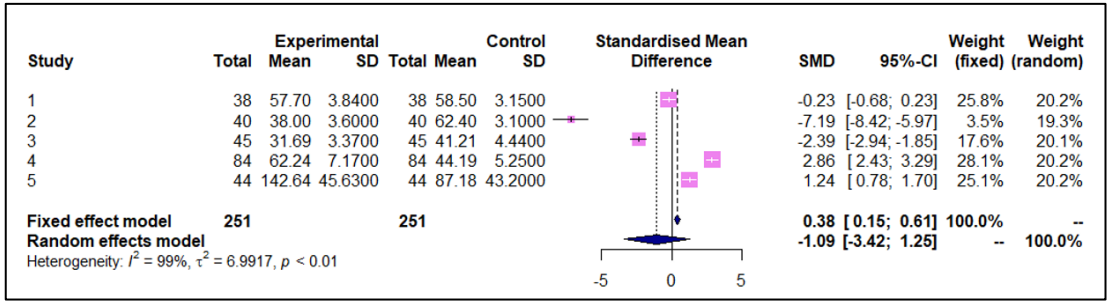

Figure 4. Synthesis forest plot. This forest plot summarizes the results of included studies for the recovery from sedation (sample size, standardized mean differences [SMDs], and weight). The small boxes with the squares represent the point estimate of the effect size and sample size. The lines on either side of the box represent a 95% confidence interval (CI).

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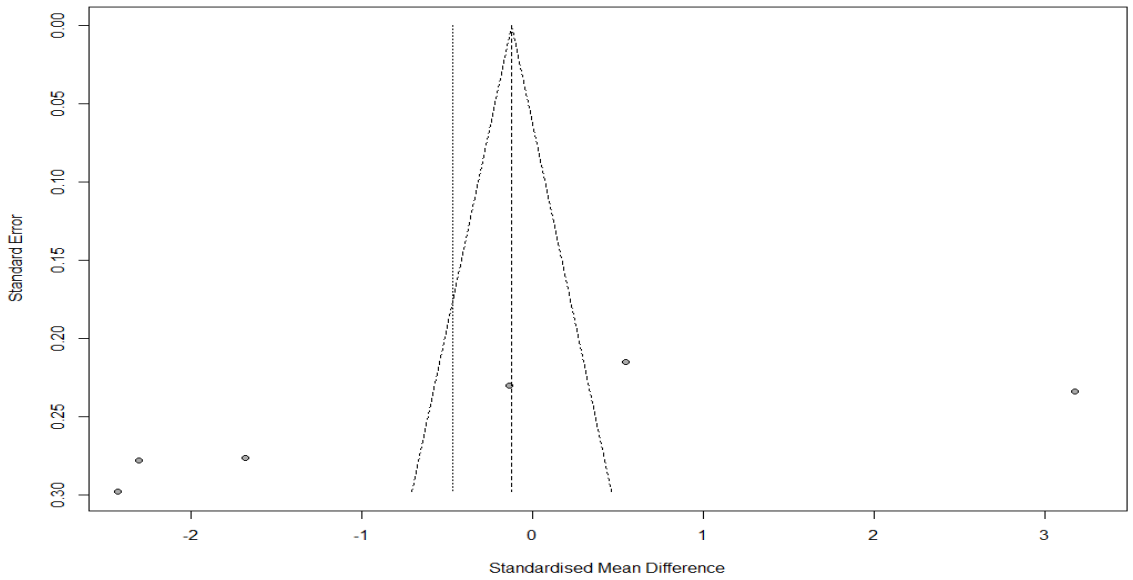
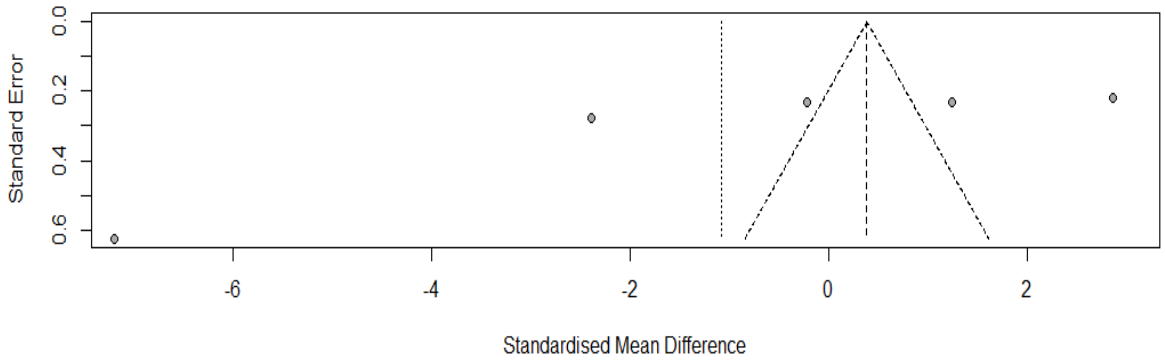
Supplementary data

Forest plot – onset of sedation



Forest plot –recovery from sedation



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ISSN 2063-5346

Supplementary data

Appendix 1- Database search strategy

The keywords and MESH terms used are ((((((("children*"[Text Word] OR "paediatric*"[Text Word] OR "pre schoolers*"[All Fields] OR "toddlers*"[Text Word] OR "uncooperative children*"[Text Word] OR "paediatric dental*"[All Fields] OR "Child"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR "Dental Care for Children"[MeSH Terms] OR "Paediatrics"[MeSH Terms:noexp]) AND ("nasal"[All Fields] OR "atomizer*"[All Fields] OR "nasal spray"[All Fields] OR "nasal drops"[All Fields] OR "administration, intranasal"[MeSH Terms] OR "Nasal Absorption"[MeSH Terms] OR "Nasal Sprays"[MeSH Terms] OR "Nebulizers and Vaporizers"[MeSH Terms]) AND ("Midazolam"[All Fields] OR "short acting benzodiazepine"[All Fields] OR "imidazobenzodiazepine derivative"[All Fields] OR "Dexmedetomidine"[All Fields] OR "selective alpha-2 agonist"[All Fields] OR "alpha-2 adrenoceptor agonist"[All Fields] OR "alpha 2 adrenergic receptor agonist"[All Fields] OR "Midazolam"[MeSH Terms] OR "Dexmedetomidine"[MeSH Terms] OR "Anti-Anxiety Agents"[MeSH Terms] OR "Anti-Anxiety Agents"[Pharmacological Action] OR "Hypnotics and Sedatives"[MeSH Terms] OR "Hypnotics and Sedatives"[Pharmacological Action] OR "Central Nervous System Depressants"[MeSH Terms]) AND ((("anxiolysis*"[All Fields] OR "sedation*"[All Fields] OR "natural sleep"[All Fields] OR "sedation"[All Fields] OR "anesthesia*"[All Fields] OR "analgesia*"[All Fields]) AND "dental sedation"[All Fields]) OR "moderate sedation"[All Fields] OR "procedural sedation"[All Fields] OR "paediatric dental sedation"[All Fields] OR "Conscious Sedation"[MeSH Terms] OR "Analgesia"[MeSH Terms])) NOT ("premedicate"[All Fields] OR "premedicated"[All Fields] OR "premedicating"[All Fields] OR "premedication"[MeSH Terms] OR "premedication"[All Fields] OR "premedications"[All Fields])) NOT ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR "icu"[All Fields])) NOT ("general anaesthesia"[All Fields] OR "anesthesia, general"[MeSH Terms] OR ("anesthesia"[All Fields] AND "general"[All Fields]) OR "general anesthesia"[All Fields] OR ("general"[All Fields] AND "anesthesia"[All Fields]))) NOT ("emerge"[All Fields] OR "emerged"[All Fields] OR "emergence"[All Fields] OR "emergences"[All Fields] OR "emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields] OR "emergent"[All Fields] OR "emergently"[All Fields] OR "emergents"[All Fields] OR "emerges"[All Fields] OR "emerging"[All Fields])) NOT ("urgent"[All Fields] OR "urgently"[All Fields]).