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SYSTEMATIC REVIEW

Comparison of Efficacy and Safety of Midazolam versus Nitrous Oxide as Sedative Agents during Paediatric Dental Treatment: A Systematic Review

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ABSTRACT

Objective: To identify and study the existing literature on the efficacy and safety of midazolam compared to inhalation of nitrous oxide in children undergoing dental treatment. **Material and Methods:** Electronic resources such as PubMed Central, Cochrane Database of Systematic Reviews, Lilacs, Science Direct, and SIGLE were thoroughly searched. The title scan was used to find randomised controlled trials reviewed for inclusion by reading the abstract. Studies comparing the sedative, behavioural, and anxiolytic effects and safety in children undergoing dental treatment under midazolam and nitrous oxide inhalation were included. The Cochrane Reviews system software, Revman 5.4.1, was used to assess the quality of the included studies. **Results:** 11328 articles were identified by screening the electronic databases, of which 10906 were eliminated after titles were read and duplicates were removed. Ten full-text articles were examined, of which three were excluded as they did not match the eligibility criteria. Hence, a total of 7 studies were included. Midazolam and nitrous oxide inhalation were not statistically different in terms of the success of treatment and behaviour modification. However, midazolam showed a deeper level of sedation and resulted in amnesia in more children when compared to nitrous oxide sedation. All of the included studies were found to have a high risk of bias. **Conclusion:** Though all the studies included showed an increased risk of bias, midazolam and nitrous oxide inhalation seem equally effective sedative agents for controlling behaviour in children undergoing dental treatment. Midazolam shows a deeper sedation level when given orally and produces a higher rate of anterograde amnesia.

Keywords: Deep Sedation; Midazolam; Nitrous Oxide; Child.

Introduction

Horace Wells, who demonstrated nitrous oxide in dentistry in 1845 [1], is credited for being the first to demonstrate the use of sedatives in dentistry, following the development of drugs for conscious sedation. Nitrous oxide-oxygen is administered via the inhalation route [2,3], and according to the Council of European Dentists, it is the "standard sedative procedure" in pediatric dentistry [4]. This is due to the excellent sedative effects of this sedation procedure and the low risk of adverse reactions. In contrast to oral and rectal routes, inhalation bypasses the first-pass metabolism, thereby improving the drug's bioavailability [5]. The inhalation route has an advantage over other alternatives because the depth and length of the sedation can be monitored and controlled more accurately [6]. However, not only is the embracement of the nasal hood an obstacle in children [7], but nitrous oxide also entails specific health and safety risks [8].

On the other hand, midazolam is a "potentially ideal sedative agent" [9]. It is the most commonly used sedative agent because of its clinical therapeutic index and large safety margin [10,11]. Oral administration of midazolam is the most prevalent route, although other routes such as intranasal, intramuscular, transmucosal, and intravenous administration have also been identified [12]. Midazolam's short half-life allows for quick onset and recovery, making it ideal for ambulatory patients in dental practice. It does, though, have a limited action time and can lead to adverse effects such as hypoventilation and respiratory depression [13].

Many studies have been reported regarding the use of nitrous oxide and midazolam alone or in combination with other drugs [14-16]. Though there is literature available on nitrous oxide and midazolam sedation, an evidence-based comparison of the two agents still needs to be provided. Thus, the present systematic review evaluated the available literature on the efficacy and safety of midazolam sedation compared with nitrous oxide inhalation sedation in children undergoing dental treatment.

Material and Methods

Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed for this review. This study's protocol was filed with the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021248731.

Inclusion Criteria

1. Cross-over clinical trials comparing midazolam and nitrous oxide-oxygen inhalation;
2. Studies among children (below 17 years of age) undergoing dental treatment;
3. Studies published in the English language.

Exclusion Criteria

1. Studies involving the administration of midazolam or nitrous oxide in patients treated under general anaesthesia;
2. Comparison of any other drug to nitrous oxide-oxygen sedation;
3. Ongoing studies/trials;
4. Narrative reviews, short communications, letters to the editor, and case reports.

Literature Search Strategy

The following digital databases were accessed from 1984 until December 2022: MEDLINE - Medline (Medical Literature Analysis and Retrievel System Online (via PubMed), Cochrane Library, LILACS (Latin American and Caribbean Health Sciences Literature), ScienceDirect, and Google Scholar.

PubMed/Cochrane Search Strategy

((((((((((((((((((((((children) OR (kids)) OR (kid)) OR (child)) OR (pediatric dental patients)) OR (uncooperative children)) OR (anxious children)) OR (pediatric dentistry)) OR (medically compromised patients)) OR (children Down's syndrome)) OR (autistic children)) OR (children cerebral palsy)) OR (children physical disability)) OR (physically disabled children)) OR (mentally challenged children)) OR (anxiety)) OR (fear)) OR (fearful children)) OR (paediatric dental treatment)) OR (pediatric dental treatment)) AND ((((nitrous oxide sedation) OR (nitrous oxide inhalation sedation)) OR (nitrous oxide oxygen sedation)) OR (laughing gas))) AND (((((midazolam) OR (midazolam hydrochloride)) OR (dormicum)) OR (hypnovel)) OR (versed))) AND ((((((((((((((((((((((((((((behaviour) OR (behavior)) OR (management)) OR (behaviour management)) OR (managing)) OR (sedative effect)) OR (sedation level)) OR (procedural sedation)) OR (conscious sedation)) OR (mild sedation)) OR (minimal sedation)) OR (anxiolysis)) OR (houpt behaviour rating scale)) OR (houpt scale)) OR (Frankl behaviour rating scale)) OR (Frankl scale)) OR (FLACC)) OR (Venham's scale)) OR (visual analogue scale)) OR (VAS)) OR (behaviour profile rating scale)) OR (kurosu behaviour evaluation scale)) OR (Ramsay sedation scale)) OR (Richmond agitation sedation scale)) OR (state behaviour rating scale)) OR (bispectral index monitoring)) OR (North Carolina behaviour scale)) OR (safety)) OR (efficacy)) OR (toxicity))

LILICAS Search Strategy

children OR pediatric dental patients OR uncooperative children OR anxious children OR pediatric dentistry [Words] AND midazolam AND nitrous oxide [Words] and behaviour management OR behaviour OR management OR managing OR sedative effect OR sedation level OR procedural sedation [Words]

Science Direct Search Strategy

Children AND dental AND midazolam AND nitrous oxide AND (behaviour management OR sedation level OR anxiety OR efficacy OR safety)

Google Scholar

The database was searched using the following keywords: midazolam, nitrous oxide, sedation, behaviour, children, and dental.

Study Selection

One author was responsible for the search technique for each database (PJ). The acquired titles were browsed through and analysed separately by two writers (PJ and DG) to identify the pertinent research. Studies replicated in several databases were eliminated, and the differences between the two authors were settled through conversation (PJ and DG). When comprehensive information on the groups and people involved was not included in the title, the abstracts of the studies were assessed. Further, full-text articles were retrieved and screened thoroughly. A manual search was conducted, and the reference lists of all full-text papers were reviewed to identify any additional studies that were not found in the computerised search. Figure 1 gives the PRISMA

flow diagram. The final papers of both authors (PJ and DG) included in the discussion were appraised for study quality using the Cochrane Handbook of Systematic Reviews standards.

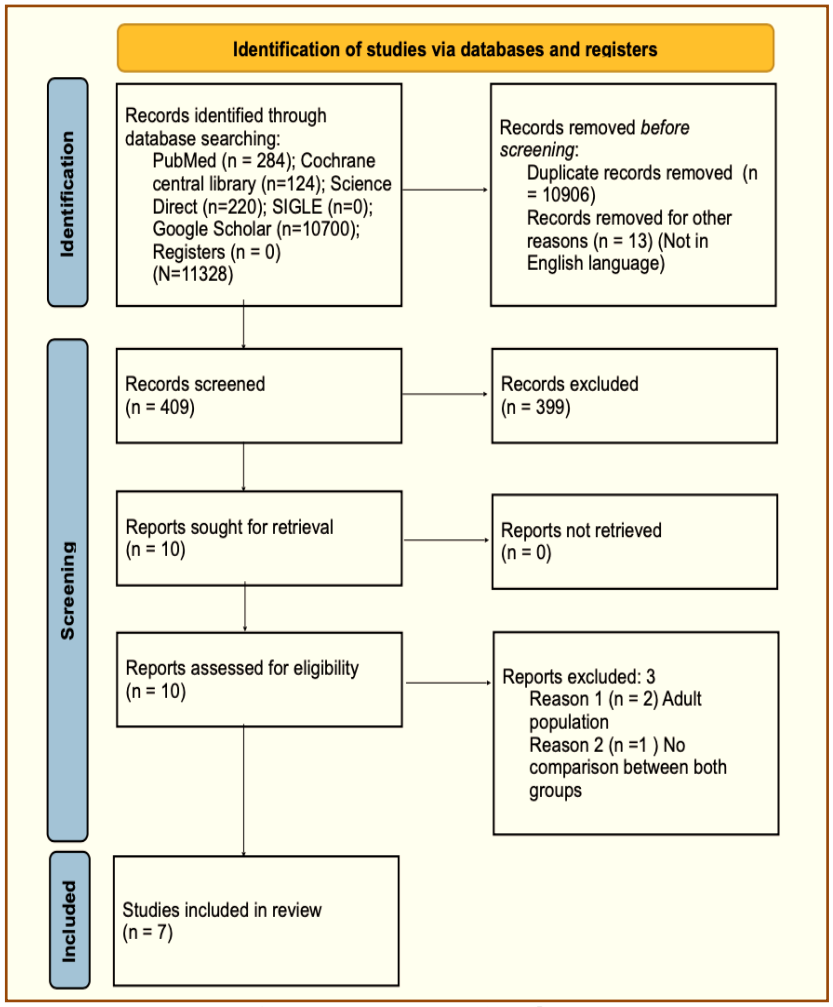

Figure 1. PRISMA Flowchart.

Data Extraction

The two authors (PJ and DG) independently read the full text of the included articles and then scrutinised them together using a data extraction form. The following information was methodically gathered: Author, year and country of study, study design, sample size, age group of the participants, procedure performed, dosage and route of administration, outcomes assessed, and their findings.

Quality Appraisal

The Risk of Bias tool for randomised trials provided by the Cochrane Handbook for Systematic Reviews was used to assess the quality of the included studies [17]. The included studies were evaluated using the RevMan 5.4.1 software for the following domains: random sequence generation and allocation concealment under selection bias, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), absence of incomplete outcome data assessment (attrition), bereft from baseline imbalance (reporting bias) and adequate reliability. The risk of bias evaluation was carried out independently by both authors (PJ and DG), who resolved any disagreement through discussions. The reliability between the two reviewers was good (k>0.88).

Results

Study Selection

A screening of the electronic databases identified 11328 records, of which 10906 were excluded after removing duplicates and title screening. Four hundred nine articles were screened, of which 399 were excluded based on their abstract. Ten text articles were assessed, of which three were excluded (Table 1) as they did not match the inclusion criteria. Seven full-text articles satisfied the eligibility criteria of the targeted research and were covered in this systematic review.

Table 1. List of excluded studies with reasons.

Sr No	Author and Year	Reason for Exclusion
1	J. M. Thompson et al., 1999	Study conducted in adults
2	Darklilson Pereira-Santos et al, 2013	Study conducted in adults
3	Sigalit Blumer et al, 2018	No comparison of midazolam and nitrous oxide

Descriptive Analysis

Two hundred sixty-two participants from all seven studies have been included, ranging from 4–16 years. The included studies were randomised, controlled, cross-over clinical trials conducted in the UK and India, published between 2002 to 20022. Of these, three studies used oral midazolam as the intervention [18-20], one utilised midazolam intravenously [8], one administered it buccally (transmucosal) [21], and two administered it intranasally [22,23]. All studies titrate nitrous oxide to a maximum dose of 30% and oxygen at 70%. Only one study extracted primary teeth [20], whereas four involved orthodontic extraction of premolars or canines [8,18,19,21]. Bilateral pulp therapy was performed in two of the included studies [22,23].

Six studies have assessed the overall behaviour using Houpts Behaviour Rating Scale [8,18-22], whereas one study did not evaluate the behaviour [23]. The level of sedation was evaluated using multiple tools; five studies used the classification of emotional status designed by Brietkopf & Buttner [8,18-21], one study used Elli's sedation scale [22], and one used the Modified Ramsay Sedation Scale [23]. Two of the included studies evaluated pre- and post-operative anxiety levels by Children's Fear survey schedule dental subscale. They also assessed the general anxiety levels by Spielberger state anxiety inventory [18,21].

The assessment of the risk of bias is presented in Figures 2 and 3. All seven selected studies were at high risk of bias because of insufficient outcome assessment blinding in all investigations. The study by Ann Preethy and Somasundaram [23] needed to be clearer on the blinding of participants and personnel, which may lead to performance bias. Two included studies were at risk of attrition bias [20,21].

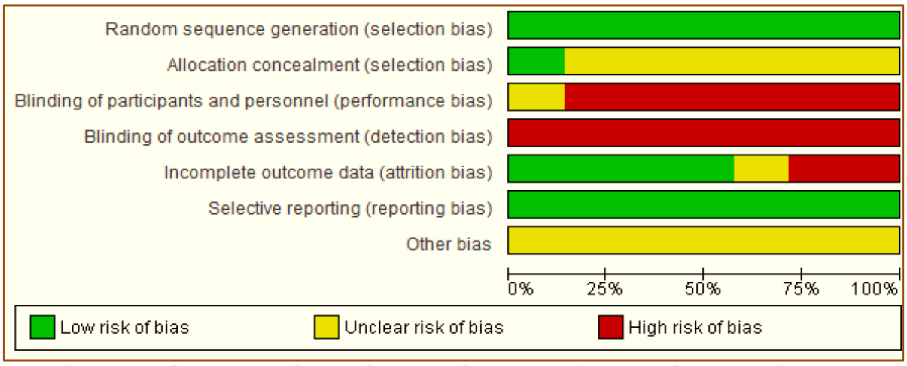

Figure 2. Risk of bias graph: review the author's judgments about each risk of bias item reported as a percentage across all included studies.

Table 2. Characteristics of included studies.

Author /Year	Country	Design, Sample Size & Age	Procedure	Intervention	Control (N2O/ O2 %)	Outcomes Variables	Outcomes Criteria	Main Findings	Conclusion
Wilson et al., 2002 [18]	UK	RCCT N=46 10-16 years	Orthodontic extraction of at least 4 teeth (premolars or canines)	0.5 mg/kg oral midaz	30/70%	i)Behaviour ii)Level of sedation iii)Physiologic status iv)Dental anxiety v)General Anxiety vi)Adverse effects	i)HBRS ii) Breitkopf and Buttner-Classification of emotional status iii)Pulse, respiratory rate, SPO2 iv)Children's fear survey schedule dental subscale v)Spielberger state anxiety inventory vi)Post-operative questions	i)Behaviour: The overall score was similar in both groups. 1 procedure in each group was aborted ii)Level of sedation: Higher in the midaz group than the N_2O group iii) Lowest median SPO_2: N_2O group - 98%, Midaz group - 95% ($p<0.001$)* Mean respiratory rate: N_2O group - 15.8 breaths/min, Midaz group - 15.5 breaths/min iv)Dental anxiety: For midaz - The mean score when used in 1st visit was 32, and 2nd visit was 30. For N_2O - Mean score in 1st visit 30 and 2nd visit mean score was 26 v)General anxiety: Score ranged from 20 to 73, but both groups showed a decrease in general levels of anxiety vi)Amnesia - Seen in 6 children in the nitrous group and 39 children in the midaz group ($p<0.001$)*	Oral midazolam is as effective as N_2O for controlling behaviour. Midaz shows higher levels of sedation and amnesic effects. SPO_2 levels for midaz were significantly lower than those of the N_2O group.
Wilson et al., 2002 [19]	UK	RCCT N=26 10-16 years	Orthodontic extraction of premolar or canines	0.5 mg/kg oral midaz	30/70%	i)Behaviour ii)Level of sedation iii)Physiologic status iv)Adverse effects	i)HBRS ii)Breitkopf and Buttner-Classification of emotional status iii)Pulse, respiratory rate, SPO_2 iv) Post-operative questions	i)Behaviour: N_2O - 21 children scored 6 (excellent), 3 scored 5 (very good),1 scored 4 (good), 1 aborted treatment Midaz-18 children scored 6(excellent), 3 scored 5 (very good),2 scored 4 (good), 2 scored 3 (fair), and 1 aborted treatment ii)Level of sedation: N_2O group - 24 children scored 2 (awake & calm), and 2 children scored 3 (tired, hardly moving) Midaz group - 7 children scored 2, 13 children scored 3, and 4 children scored 4(drowsy without reaction but arousable) iii)Lowest mean SPO_2: N_2O group - 97.7%; Midaz group - 95% Mean respiratory rate: N_2O group - 14.8 breaths; Midaz group - 14.6 breaths	Oral midaz is as effective as N_2O in controlling behaviour and sedation. One case of paradoxical reaction was reported with midaz, due to which treatment was aborted. Oral midazolam produces significant amnesic effects.

								iv) Amnesia - 3 children in the nitrous group and 20 children in the midaz group ($p<0.001$)* Sleepiness/dizziness/slight headache- reported in 19% of patients in both groups	
Wilson et al., 2003 [8]	UK	RCCT N=42 12-16 years	Orthodontic extraction of at least 4 teeth (premolars or canines)	Intravenous midaz (rate 0.5 mg min, max 5 mg)	30/70%	i)Behaviour ii)Level of sedation iii)Physiologic status iv)Adverse effects v)Onset of sedation vi) Recovery time	i)HBRS, Frankl Scale ii)Breitkopf and Buttner- Classification of emotional status iii)Blood pressure, Pulse rate, Ventilatory frequency, SPO_2 iv) Self- reported	i) Overall behaviour: No significant difference between both groups ii) Level of sedation: In the recovery phase, sedation levels of the midaz group were higher than those of the N_2O group. There is no significant difference between both in the other stages of treatment. iii)SPO_2: No significant difference between both groups iv) Adverse effects: 14 patients in the midaz group and 11 in the N_2O group reported effects including nausea, vomiting, drowsiness, headache, and sore mouth. v) Median onset to maximum sedation: N_2O group: 6 (2-18)min; Midaz group 8 (4-20)min ($p<0.001$)* vi) Mean recovery time: N_2O group: 23.3min (2-18); Midaz group - 51.6 min	Intravenous midaz is as effective as N_2O in providing satisfactory sedation and overall behaviour. It shows a slower onset of action than N_2O and a longer recovery time. Administration of IV midaz requires a specialist trained in pediatric sedation and life support.
Wilson et al., 2006 [20]	UK	RCCT N=42 5-10 years	Extraction of at least 4 primary teeth, one in each quadrant	0.3mg/kg oral midaz	30/70%	i)Behaviour ii)Level of sedation iii)Physiologic status iv)Adverse effects v)Time to max sedation	i)HBRS ii)Breitkopf and Buttner- Classification of emotional status iii)Heart rate, respiratory rate, SPO_2, Mean arterial blood pressure iv) Post- operative questions	i)Behaviour: No disruptive behaviour in the N_2O group. 5% of the children were uncooperative after oral midazolam. 3 and 2 children were unable to tolerate oral midaz and N_2O, respectively, and hence dropped out ii) Level of sedation: Midaz group: 70% were drowsy (score 4); N_2O group: 85% were tired (score 3)($p<0.001$)* iii) Vitals: Within acceptable limits in both groups iv) Adverse effects: 20% after midaz and 23% after N_2O showed drowsiness and headache. Procedural amnesia higher in midaz group ($p=0.031$)	Oral midaz produced greater levels of sedation and showed more procedural amnesia than N_2O. It may not be the preferred technique, but it may be more appropriate for some, depending on their treatment requirement and anxiety.
Wilson et al., 2007 [21]	UK	RCCT N=36 10-15 years	Orthodontic extractions of 4 premolars	0.2mg/kg transmucosal (buccal) midaz	30/70%	i)Behaviour ii)Level of sedation	i)HBRS ii)Breitkopf and Buttner's Classification of	i)Behaviour: No significant difference ii) Level of sedation: 36/36 in midaz and 35/36 in N_2O group scored 3 (tired)	Transmucosal midaz is as effective as N_2O in controlling behaviour and sedation. Anxiety

						iii)Pre- & post-op dental anxiety iv)General Anxiety v)Physiologic signs vi) Adverse effects	emotional status iii) Children's fear survey schedule dental subscale iv)Spielberger state anxiety inventory v)Blood pressure, pulse rate, respiratory rate, SPO_2 vi)Self-reported	iii)Dental anxiety: Mean score pre-op 31.9 Post-op score 27.1 ($p<0.001$)* iv)General anxiety: Mean pre-op score 45.5 Mean post-op score 39.4 ($p<0.001$)* v)Lowest SPO_2 in midaz group: 94% vi)Adverse effects: Sleepiness/headache/slight nausea seen in 16/36 under midaz & 14/36 under N_2O	decreased significantly throughout the study.
Srinivasan et al., 2021 [22]	India	RCCT N=35 4-7 years	Bilateral pulp therapy	0.3mg/kg intranasal midaz	30/70%	i)Behaviour ii)Pain iii)Level of sedation iv)Physiologic signs v)Adverse effects	i)HBRS ii)FLACC score iii)Ellis sedation scale iv)SPO_2, HR, RR v)Scale by Shashikiran et al.	i)Behaviour: Excellent behaviour of 57.1% under N_2O and 51.4% under midaz ii)Pain: Mean FLACC score 1.57 ± 2.6 for N_2O and 2.77 ± for midaz ($p<0.001$)* iv)Heart rate: 106.64 ±12.68 bpm for N2O and 103.29±12.69bpm for midaz when administering LA ($p<0.001$)* v)Adverse effects: N_2O - vomiting (2.2%) Midaz - sneezing/coughing/hiccups (n=4)	Intranasal midaz is as effective as N_2O in controlling behaviour and sedation. Dental treatment was successfully completed in both groups.
Ann Preethy and Somasundaram, 2022 [23]	India	RCCT N=35 4-8 years	Bilateral mandibular pulpectomy	0.3mg/kg intranasal midaz	30/70%	i)Level of sedation ii)Physiologic signs iii)Adverse effects iv) Onset of sedation	i)Modified Ramsay Sedation scale ii)Heart rate, respiratory rate, SPO_2 iii)Safety scale by Shashikiran et al.	i) Level of sedation: Moderate in both groups with no statistical difference ii)All vitals within acceptable limits with both agents. Heart rate: Statistically significant higher heart rate during LA administration in the midaz group than the N_2O group ($p=0.00$)* iii)Adverse effects: N_2O group - 5 children vomited. Midaz group - 4 participants showed sneezing/coughing/hiccups iv) Onset of sedation: The lesser time required for the onset of sedation in midaz group ($p=0.000$)*	Intranasal midaz is as effective as N_2O in providing safe and satisfactory sedation. It also shows a faster onset of action than N_2O.

*Statistically Significant; Midaz = Midazolam; N_2O = Nitrous-oxide; RCCT = Randomised, Cross-Over Clinical Trial; HBRS = Houpt Behaviour Rating Scale; FLACC = Face, Legs, Activity, Cry, Consolability.

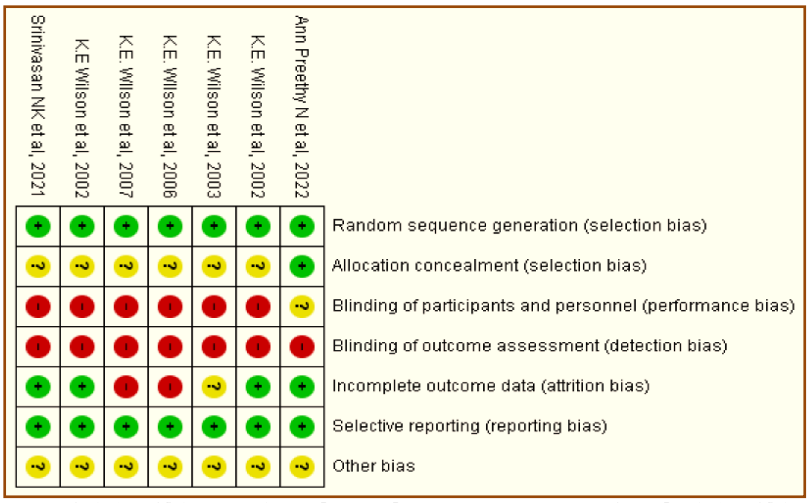

Figure 3. Summary of risk of bias: review the author's assessment of each risk of bias item for every included study.

Discussion

Midazolam and nitrous oxide are regularly used as sedative agents in the dental office. This is the only systematic evaluation to examine the effectiveness and safety of these two agents when used individually for pediatric dental treatment. Considering the heterogeneity in methodology and assessment of studies, a meta-analysis could not be carried out.

Based on the method of induction, the included studies compared the conventional method of nitrous oxide with the oral [18-20], intravenous [8], transmucosal [21], and intranasal [22,23] routes of midazolam administration. Regardless of the dose, oral midazolam induced a significantly more profound level of sedation than nitrous oxide inhalation [18-20]. However, intravenous and transmucosal administration of midazolam induced similar levels of sedation as nitrous oxide inhalation [8,21]. Another method of administering midazolam that has gained favour in recent years is the intranasal route; a mucosal atomization device is used to produce a fine 30 µm particle spray, which increases bioavailability to 55% leading to the rapid absorption of the drug into the systemic circulation [24].

Regarding behaviour, the only study which showed some disparities in the scores given by Houpt behaviour rate scaling was the one where Wilson et al. [20] compared 0.3mg/kg midazolam to 30% nitrous oxide. The route of administration justifies this disparity, as the intravenous route involves the placement of a cannula, which can be painful for children. Unlike our findings, Tyagi et al. [25] found that overall behaviour with intravenous midazolam was significantly better than with oral midazolam.

Physiological aspects must be considered to assess the efficacy of the sedative approach under investigation thoroughly. Since respiratory depression is the most prevalent side effect of benzodiazepines [13], measuring arterial oxygen saturation is required to monitor both respiratory and cardiovascular function. An oxygen saturation of at least 90%, if not higher, should always be maintained in sedated patients [26]. In all studies, the lowest arterial oxygen saturation observed throughout the session with the midazolam group was 97%. All other vitals were within acceptable clinical limits for both agents.

Adverse effects, including nausea, vomiting, and drowsiness, were found in both groups. Sneezing and hiccups were also seen in the intranasal groups. Midazolam-induced anterograde amnesia [27] may be advantageous during painful procedures such as extractions, and the children under midazolam sedation were more forgetful of the therapy when compared to the nitrous oxide group [18-20].

The assessment of the risk of bias was computed using the Cochrane database and the seven assessment factors for a standardised process. All the included studies showed a high risk of bias as blinding of outcome assessments was not achieved. Moreover, the studies by Wilson et al. [20] in 2006 and 2007 [21] were at high risk of attrition bias due to incomplete outcome data on the participants who dropped out.

A limitation of this review is that the included studies have been carried out only in the UK and India, thereby restricting the external validity and generalisability of the findings. Moreover, high heterogeneity in doses of midazolam, routes of administration, and tools used for assessment was seen.

Conclusion

Midazolam and nitrous oxide can be used effectively and safely in children undergoing dental treatment. Both agents are equally effective for sedation and behaviour modification while maintaining vital levels. A significant difference is seen in the sedation depth and level of amnesia between midazolam when administered orally and nitrous-oxide inhalation. This review advocates the need for global studies to assess the efficacy and safety of midazolam and nitrous oxide in children of all ethnicities.

Authors' Contributions

PJ	https://orcid.org/0000-0002-4957-3083	Conceptualization, Methodology, Software, Resources, Data Curation, Writing - Original Draft and Visualization.
DG	https://orcid.org/0000-0002-6014-946X	Conceptualization, Methodology, Data Curation, Writing - Review and Editing and Supervision.

All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

Financial Support

None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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