Sedative and Behavioral Effects of Intranasal Midazolam in Comparison with Other Administrative Routes in Children Undergoing Dental Treatment – A Systematic Review

Abstract

Aim: The aim of this study was to systematically identify and evaluate the available literature on the effectiveness of intranasal midazolam sedation compared with midazolam administered through other routes in the sedation and behavior management of children during dental treatment. **Materials and Methods:** The search was done using electronic databases such as PubMed Central, Cochrane Database of Systematic Reviews, LILACS, ScienceDirect, and SIGLE. All studies comparing the sedative effect and behavior management effectiveness of intranasal midazolam with midazolam administered through other routes in children were included. **Results:** Electronic database search identified 163 articles, out of which 143 were excluded after reading titles and removing duplication. The remaining 20 studies were evaluated in detail. A final of 13 studies were included based on the inclusion criteria. Among the 13 studies included in the present review, a high risk of bias was noted in all the 13 articles. There was no adequate blinding of personnel and participants in the study, allocation concealment was improper and presence of inadequate blinding of the outcome assessment. . Statistically, no significant difference was observed between intranasal midazolam and other midazolam routes on behavior and sedation level in the studies included in this review. **Conclusion:** Limited studies are available pertaining to the sedative and behavioral effects of intranasal midazolam, and thus, this review recommends need for more research evaluating the sedative effect of intranasal midazolam in comparison with midazolam administered through other routes in the behavior management of children during dental treatment.

Keywords: *Conscious sedation, midazolam, pediatric dentistry, systematic review*

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Introduction

Over the years, pediatric dentists have always been faced with the difficult task of managing dental fear and anxiety which is an obstacle to the successful treatment of children and impeding or even precluding the quality of dental care.[1,2] Dental fear is considered to be a normal emotional reaction to one or more specific threatening stimuli in the dental situation. Dental anxiety denotes a state of apprehension that something dreadful is going to happen in relation to dental treatment and is coupled with the sense of losing control.[3] It has been observed that children are more anxious and uncooperative between 3 and 7 years of age[4] and this anxiety was found to decrease with age.[5] The overall worldwide prevalence of dental anxiety among children ranges from 3% to 43%.[6]

Behavior management serves as the cornerstone factor setting apart pediatric dentistry from all other dental specialties.[7] An important point to be noted is the changing society and population's attitude toward interaction with children that the older methods of physical restraints such as hand-over-mouth exercise or the use of physical restraints have gained less eminence.[8] The guidelines proposed by the American Academy of Pediatric Dentistry has included both pharmacological and nonpharmacological methods for the behavior management of anxious children.[9]

Pharmacological management techniques should be considered in cases where the nonpharmacological or psychological behavior management techniques prove unproductive.[10] Pharmacological behavior management is broadly divided into sedation and general anesthesia. Several factors

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influence the decision on the type of pharmacological behavior management to be provided such as age of the patient, preoperative anxiety, extent of patient's dental needs, risk involved with the pharmacological management, safety, parental expectation, and cost.[11] According to AAPD,[12] the goals of sedation are to (a) guard the welfare and safety of the patient; (b) minimize physical discomfort and pain; (c) control anxiety, minimize psychological trauma, and maximize the potential for amnesia; (d) control behavior and/or movements so as to allow safe completion of procedure; and (e) return the patient to a state in which safe discharge from medical supervision is possible as determined by the recognized criteria.

Sedation was primarily discussed under conscious and deep sedation.[13] However, the modern-day concept modifies the broad term conscious sedation to (i) minimal sedation previously called anxiolysis and (ii) moderate sedation previously called conscious sedation. Conscious sedation is the use of a drug or drugs to produce a depressed state of central nervous system during which the patient remains conscious, retains protective reflexes, maintains a patent airway, and has the ability to understand and respond to verbal commands enabling the treatment to be carried out. Minimal sedation is a drug-induced state wherein the patient can respond normally to verbal commands. Moderate sedation refers to a state of drug-induced depression of consciousness during which patients respond purposefully to verbal commands.[14]

Wide varieties of drugs are available for sedation in pediatric dentistry. The type and the route of administration of the drugs lead to a variability in their efficacy and effectiveness. Among them, midazolam – a newer generation benzodiazepine – has been mentioned as potentially the ideal sedative agent[15] for its wide toxic/therapeutic ratio and safety margin.[10] It can be administered orally, intranasally, sublingually, rectally, or intravenously and has a rapid elimination half-life, produces anterograde amnesia,[16] is a muscle relaxant, and yields no active metabolites.[17] Midazolam when administered intranasally has a faster onset of action as it avoids the hepatic first-pass metabolism and gets absorbed through the cribriform plate into the brain resulting in an increased bioavailability level.[18,19] In the study done by Fukuta *et al*., intranasal midazolam provided a sedative effect to those children who earlier displayed a combative behavior.[20,21] Thus, intranasal sedation by midazolam has gained popularity in the recent years as the other modes of administration such as the oral and rectal administration have a slower onset of sedation[22,23] and parenteral administration leads to anxiety, distress, and trauma in children and it is always better to avoid injections in pediatrics whenever possible.[17] Various studies have been done to study the effectiveness of midazolam administered through various routes and at different concentrations.

However, there is little evidence reviewing the comparative studies of intranasal midazolam and other routes of midazolam. The objective of this study was to systematically identify and evaluate the available literature on the effectiveness of intranasal midazolam sedation compared with midazolam administered through other routes in the sedation and behavior management of children.

Materials and Methods

The review was done according to the guidelines given by the Cochrane Handbook for Systematic Reviews of Interventions.

PICO analysis

- Population: Children below 12 years of age undergoing dental treatment under conscious sedation
- Intervention: Midazolam administered through other routes: Oral, rectal, intravenous, intramuscular, sublingual, submucosal, and buccal
- Comparison: Intranasal midazolam sedation
- Outcome: Sedative effect, effect on anxiety, and behavior.

Inclusion criteria

- Studies involving children receiving dental treatment under sedation
- Studies comparing the sedation level and/or behavior management effectiveness between intranasal midazolam and midazolam administered through other routes: Oral, rectal, intravenous, intramuscular, buccal, sublingual, and submucosal
- Studies published in English language.

Exclusion criteria

- Studies involving adolescents or adults
- Studies involving comparison of midazolam in various routes of administration for any treatment other than routine dental treatment
- Studies involving midazolam as a premedication before general anesthesia or other such procedures
- Studies evaluating only adverse effects, pharmacokinetics, and pharmacodynamics of midazolam.
- Ongoing studies that have not yet been published.

Search strategy

To identify the studies to be included for evaluation in systematic review in detail, the following search strategies were developed for each database searched:

1. The Cochrane Central Register of Clinical Trials (all types of study design published till December 2019)
2. PubMed (all types of study design published till December 2019)
3. LILACS (all types of study design published till December 2019)
4. ScienceDirect (all types of study design published till December 2019)

5. Google Scholar (all types of study design published till December 2019)
6. SIGLE (all types of study design published till December 2019).

PubMed search strategy

Advanced search of PubMed search engine was used using the following keywords:

(Children below 12 years) OR Pediatric dental patients) OR uncooperative children) OR anxious children) OR pediatric dentistry) OR medically compromised patients) OR children with Down's syndrome) OR autistic children) OR children with cerebral palsy) OR children with physical disability) OR mentally challenged children)) AND (oral midazolam sedation) OR oral versed) OR oral midazolam hydrochloride syrup) OR oral mezolam)) OR oral dormicum) OR oral miben) OR oral hypnovoel) OR intramuscular seizalam) OR intramuscular mezolam) OR intramuscular versed) OR intramuscular midazolamum) OR intramuscular dormicum) OR intramuscular miben) OR intramuscular hypnovoel) OR intravenous mezolam) OR intravenous versed) OR intravenous dormicum) OR intravenous midazolamum) OR intravenous miben) OR intravenous hypnovel) OR intramuscular midazolam) OR intravenous midazolam) OR buccal midazolam) OR buccal buccolam) OR buccal versed) OR submucosal midazolam) OR submucosal versed) OR submucosal mezolam) OR submucosal midazolamum) OR submucosal dormicum) OR submucosal miben) OR submucosal hypnovel) OR sublingual midazolam) OR sublingual mezolam) OR sublingual versed) OR sublingual midazolamum) OR sublingual dormicum) OR sublingual miben) OR sublingual hypnovel) AND (intranasal midazolam) OR inhalation midazolam) OR intranasal midacip) OR intranasal mezolam) OR intranasal versed) OR intranasal midazolamum) OR intranasal dormicum) OR intranasal miben) OR intranasal hypnovel) OR intranasal atomized midazolam spray) AND (behaviour management) OR behavior) OR 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 frankl behaviour rating scale) OR FLACC) OR Venham's scale) OR visual analog 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).

The search yielded 84 studies.

Data collection and analysis

Selection of studies

One author (NAP) carried out the search strategy for the individual databases. The total number of titles obtained was scanned and evaluated independently by two authors, NAP and SS, to identify the relevant studies. The studies duplicated in the different databases were excluded. In case of any disagreement between the two authors, the final decision was obtained by discussion between the two authors. Abstracts of the studies were evaluated when complete information regarding the groups and participants included was not mentioned in the title. The abstract evaluation was carried out independently by two authors, NAP and SS, to identify the final studies to be included based on the inclusion and exclusion criteria. Full-text articles were evaluated when the abstracts did not provide adequate information regarding the groups compared. Hand search was done and the reference lists of all the full-text articles were evaluated to identify any other studies which were not included in the electronic search. The PRISMA flowchart describes the number of records identified and screened at different phases of the review process [Figure 1]. All the studies not relevant to the subject were excluded and the reasons for the exclusion were mentioned [Table 1]. The final studies included were further assessed for the quality of studies following the guidelines of the Cochrane Handbook for Systematic Review. This was done by both the authors independently and any discrepancy was resolved by discussion between both the authors.

Data extraction and management

Data for the included studies were evaluated for the characteristics of the study. The following characteristics were included:
- Author and year of study
- Study design
- Sample size and age group
- Route of midazolam administration
- Outcome assessed.

The variables observed were mentioned [Table 2]. A detailed evaluation of the variables observed in the study was noted by their mean values and statistical significance.

Assessment of the quality of included studies

The quality of the included studies was assessed using the guidelines given by the Cochrane Handbook for Systematic Review. The parameters used to evaluate the included studies are as follows:
- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Free of Incomplete outcome data assessment (attrition)
- Free from baseline imbalance (reporting bias)
- Adequate reliability.

Individual parameter was assessed for high risk, low risk, and unclear risk [Table 3]. The final risk of bias of individual study was determined as low risk if all the studies showed low risk for the individual parameters. In case of high risk or unclear risk for one or two parameters, moderate risk was considered for the included study. If
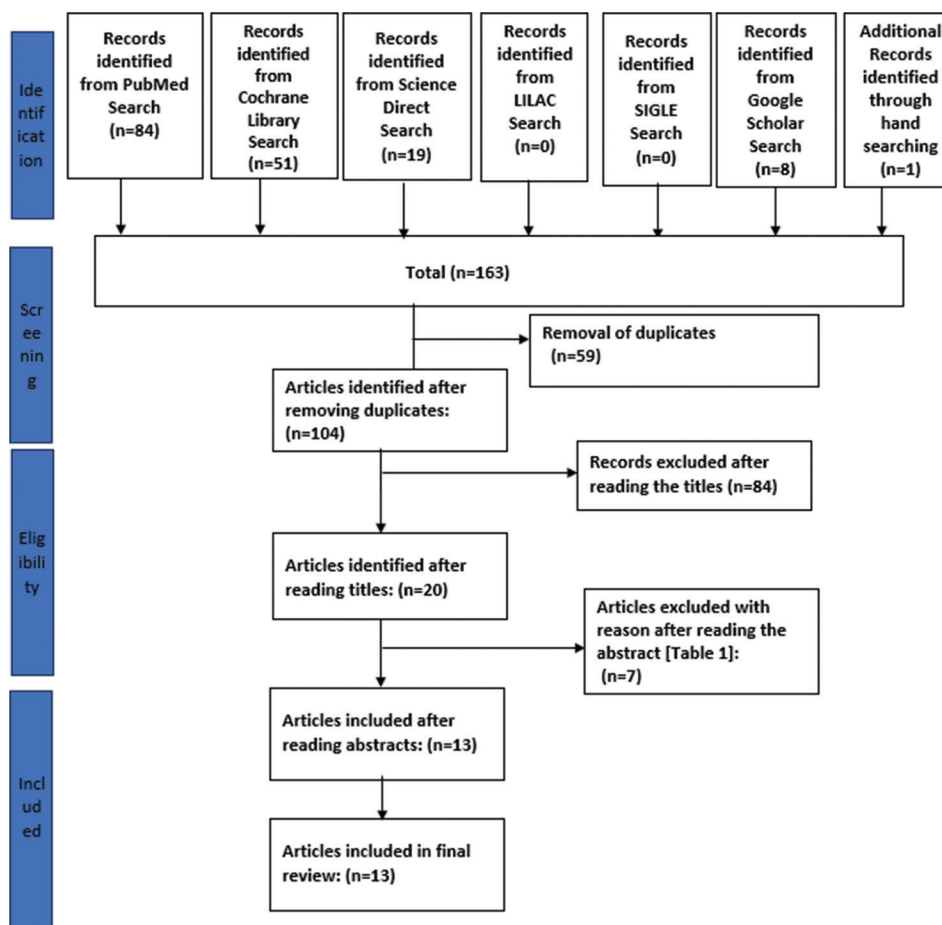
Figure 1: PRISMA flowchart showing included studies

Table 1: Characteristics of excluded studies

Serial number	Study	Reason for exclusion
1	Lam *et al.*, 2005	Compares intramuscular and intranasal midazolam used as premedication before venipuncture and not for procedural sedation for routine dental treatment
2	Gomes HS *et al.*, 2017	It is an ongoing clinical trial and results have not yet been published
3	Klein EJ *et al.*, 2011	Comparison of aerosolized intranasal or buccal midazolam with oral midazolam for laceration repair. This is not for a routine dental procedure
4	Heard C *et al.*, 2010	Four sedative techniques of administration of midazolam are compared. This is not for a routine dental procedure
5	Acworth JP *et al.*, 2001	Evaluates the sedative effect of intranasal and intravenous midazolam in the emergency department and not for routine dental treatment
6	Geldner G *et al.*, 1997	Evaluates the effect of three transmucosal routes of administration as premedication before induction and not for procedural sedation for routine dental treatment
7	Rey E *et al.*, 1991	Assessed only the pharmacokinetics of intranasal and intravenous midazolam and not the behavior or sedative effect

more than 2 parameters showed high risk or unclear risk, the included study showed to have a high risk of bias.

Results

Study selection

The systematic search from the electronic databases of PubMed yielded 84 studies, Cochrane Library yielded 51 studies, Google Scholar yielded 8 studies, and ScienceDirect yielded 19 studies. No studies were obtained from the database of LILACS and SIGLE and 1 study was obtained from hand searching. After removal of duplicate studies and scanning of the titles of the studies, 20 studies were identified and from that 7 studies did not meet the inclusion criteria and were excluded from the systematic review. After scanning of abstracts, 7 articles were eliminated as they did not meet the inclusion and exclusion criteria. Full-text articles for the other

13 studies were evaluated further for better evaluation. The bibliography of these full-text articles was scanned to include studies apart from the electronic databases. A total of 13 studies met the inclusion and exclusion criteria of the present systematic review. The characteristics of the included studies and its results were tabulated and evaluated [Tables 4 and 5]. Based on the study characteristics, risk of bias was assessed for the included studies [Table 6 and Figures 2 and 3].

According to the study results, behavioral management effectiveness was assessed in all the 13 studies.[7,8,24-34] Among these, in only one study,[8] a statistically significant difference in the Houpt's score was found during administration of local anesthesia and after 15 min in favor of intranasal sedation ($P < 0.05$). However, no statistically significant difference was found after 30 min. All other studies showed no statistically significant difference between the groups in the overall behavior rating scores.[7,24-34]

Only two studies comparatively evaluated the sedative effectiveness of intranasal with other midazolam routes.[7,27] The level of sedation was evaluated by Musani and Chandan and Özen et al.[7,27] Musani and Chandan determined sedation level using the Ellis Sedation Scale. Özen et al.

Table 2: Variables of interest

Serial number	Variables of interest	Scale
1	Behavior	Houpt Behavior Rating Scale
		Frankl Behavior Rating Scale
		FLACC
		Venham's Scale
		VAS
		Behavior Profile Rating Scale
		Kirosu Behavior Evaluation Scale
2	Sedation level	Ramsay Sedation Scale
		Richmond Agitation Sedation Scale
		State Behavioral Scale
		Bispectral Index Monitoring
		Comfort Scale

VAS: Visual Analog Scale; FLACC: Face, Legs, Activity, Cry, Consolability scale

Table 3: Criteria for assessment of risk of bias

Serial number	Criteria	Inference
1	Adequate random sequence generation	Yes: Random number table, computer random number generator, stratified or block randomization, low tech - coin toss, shuffling cards, envelopes, throwing dice
		No: Quasi-random - date of birth, day of visit, ID or record number, alternate allocation
		Nonrandom - choice of clinician or participant, availability
		Unclear
2	Allocation concealment	Yes: Central allocation, sequentially numbered, sealed, opaque envelopes, identical containers
		No: Random sequence known to staff in advance, envelope or packing without any safeguard, random predictable sequence
		Unclear
3	Blinding participants and personnel	Yes: Blinding and unlikely that blinding could have been broken, no blinding but outcome cannot be influenced
		No: No blinding, incomplete or broken blinding and outcome likely to be influenced
		Unclear
4	Blinding of outcome assessment	Yes: Blinding and unlikely that blinding could have been broken, no blinding but outcome cannot be influenced
		No: No blinding, incomplete or broken blinding and outcome likely to be influenced
		Unclear
5	Free of incomplete outcome data assessment (attrition and exclusion)	Yes: No missing data. Reason for missing data not related to outcome and missing data balanced across the group
		No: Reason of missing data influencing the outcome
		Unclear
6	Free from baseline imbalance	Yes: Protocol is available, and all the prespecified outcome is reported
		Protocol is not available, but all the outcomes of interest are reported
		No: Outcome is not reported as prespecified or outcome is reported incompletely
		Unclear
7	Adequate reliability	Yes: Study free of any other source of bias
		No: Nonrandomized studies blocked randomization in unblinded trials
		Unclear
8	Risk of bias in the included studies	(A) Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met
		(B) Moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were partially met
		(C) High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met

Table 4: Characteristics of included studies

Author	Design of study	Sample size	Intervention group	Control group	Outcome
Gentz *et al.*, 2017	Retrospective randomized controlled study	650 children (2–6 years)	1.0 mg/kg oral midazolam (172) Midazolam combination (varies around 0.5–2 mg/kg depending on combination) (+meperidine/+hydroxyzine/+meperidine,+promethazine) (168) (nitrous oxide-oxygen was used as adjunct)	0.5 mg/kg intranasal midazolam (234) (nitrous oxide-oxygen was used as adjunct)	Evaluation scale used Behavioral rating± of sedation Overall success of sedation and sedation effectiveness Variables evaluated in study Behavior Sedation success rate
Shanmugaavel *et al*, 2016	Single-blinded randomized controlled trial	40 children (3–7 years)	0.2 mg/kg midazolam via the sublingual route (20)	0.2 mg/kg intranasal midazolam (20)	Evaluation scale used: Venham's Clinical Anxiety Scale Variables evaluated in study Anxiety Acceptance of drug
Fallahinejad Ghajari *et al.*, 2015	Double-blinded randomized controlled crossover trial	23 children (3–6 years)	0.5 mg/kg of oral midazolam with 10 mg/kg of ketamine and 0.25 mg/kg of atropine (23)	Intranasal sedation: (23) First combination: 1 ml of 2% lidocaine hydrochloride Second combination: 0.5 mg/kg intranasal midazolam vial added to 10 mg/kg of ketamine - 5 min after administration of initial drugs	Evaluation scale used Houpt Behavior Rating Scale Variables evaluated in the study Behavior Success rate of drugs Recovery of drugs
Musani and Chandan, 2015	Randomized controlled cross over trial	30 children include (3–6 years)	Oral midazolam 0.2 mg/kg and 30% nitrous oxide and 70% oxygen (30)	Intranasal midazolam 0.1 mg/kg spray and 30% nitrous oxide and 70% oxygen (30)	Evaluation scale used Ellis Sedation Scale Houpt's Behavior Rating Scale Variables evaluated in the study Behavior Sedation level Acceptance of drug Safety of drug Onset of sedative effect
Sunbul *et al.*, 2014	Single-blinded randomized controlled crossover trial	25 children (36–72 months)	0.3 mg/kg atomized midazolam via the buccal route (20)	0.3 mg/kg atomized midazolam via the intranasal route (20)	Evaluation scale used Houpt Behavior Rating Scale Variables evaluated in the study Behavior Acceptability of drug Onset of sedation
Chopra *et al.*, 2013	Single-blinded randomized controlled crossover trial	30 children (2–8 years)	0.25 mg/kg midazolam spray via the buccal route (30)	0.25 mg/kg midazolam spray via the intranasal route (30)	Evaluation scale used Houpt Behavior Rating Scale Variables evaluated in the study Behavior Drug acceptability

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<div style="text-align: center;">**Table 4: Contd...**</div>

Author	Design of study	Sample size	Intervention group	Control group	Outcome
Özen *et al.*, 2012	Randomized controlled trial	240 children (4–6 years)	Group 2 0.75 mg/kg midazolam via the oral route +50%–50% N20/O2 (60) Group 3 0.50 mg/kg midazolam via the oral route +50%–50% N20/O2 (60) Group 4 50%–50% N20/O2 alone (60)	Group 1: 0.20 mg/kg midazolam via the intranasal route (60)	Evaluation scale used Bispectral Index System Modified scale to classify behavior/response to treatment/sedation Modified Vancouver Recovery scale Variables evaluated in the study Sedation level Behavior Success rate
Shanmugaavel *et al.*, 2016b	Single-blinded Randomized controlled trial	20 children (3–7 years)	Sublingual midazolam spray using MAD: 0.2 mg/kg (10)	Intranasal midazolam spray using MAD: 0.2 mg/kg (10)	Evaluation scale used Anxiety scale Variables evaluated in the study: Anxiety Salivary and cortisol level Correlation between anxiety and salivary cortisol level
Johnson *et al*, 2010	Double-blinded randomized controlled crossover trial	31 children (42–84 months)	0.5mg/kg oral midazolam and intranasal saline (placebo) (31)	0.3 mg/kg intranasal midazolam and oral placebo (cherry syrup) (31)	Evaluation scale used Modified Houpt Behavior Rating Scale Variables evaluated in the study Behavior Postoperative complications Physiological parameters
Shashikiran N.D. *et al*, 2006	Randomized controlled trial	40 children (2–5 years)	Intramuscular midazolam 0.2 mg/kg (20)	Intranasal midazolam 0.2 mg/kg (20)	Evaluation scale used Houpt *et al*. Scale for crying, motor movements, and sensory perception Fukuta *et al*. Modified Behavior Rating Scale 5 dichotomous scales for adverse reactions Variables evaluated in the study Behavior Adverse effects
Lee-Kim *et al.*, 2004	Single-blinded randomized controlled trial	40 children (24–72 months)	0.7 mg/kg oral midazolam (20)	0.3 mg/kg oral midazolam (20)	Evaluation scale used Modified Houpt's Behavior Rating Scale Variables evaluated in the study Behavior Sedation duration Onset of sedation
Shanmugaavel *et al.*, 2015	Single-blinded randomized controlled trial	40 children (3–7 years)	Sublingual midazolam 0.3 mg/kg (20)	Intranasal midazolam 0.3 mg/kg (20)	Evaluation scale used Modified Houpt Behavior Rating Scale Variables evaluated in study Behavior Onset of action Physiological effects

Contd...

<div align="center">Table 4: Contd...</div>

Author	Design of study	Sample size	Intervention group	Control group	Outcome
Hartgraves and Primosch, 1994	Randomized controlled trial	100 children (1.5–6 years)	0.3 mg/kg oral midazolam in hydroxyzine pamoate suspension (50)	0.2 mg/kg intranasal midazolam (50)	Evaluation scale used
					Global Behavior Rating Scale
					Variables evaluated in the study
					Behavior
					Success rate of group
					Complications noted in group

Figure 2: Risk of bias summary of all included studies

Figure 3: Risk of bias graph presented as percentage of all the included studies

used the Bispectral Index System to estimate the level of sedation. No statistically significant difference was observed in the level of sedation between intranasal midazolam and oral midazolam in relation to the Ellis Sedation Scale and Bispectral Index Monitoring System, respectively.[7,27]

Discussion

Conscious sedation is considered as an effective alternative in children who are anxious or exhibit uncooperative behavior and in whom the basic behavior management strategies fail to produce the desired effect.[35] It is considered to be an optimal sedation technique if it is accessible and relatively easy to use, has a noted effect, accepted by both children and parents alike, and produces less complications.[36] The onset, depth, and duration of sedation are characterized by critical factors such as the type of drug and its route of administration.[37]

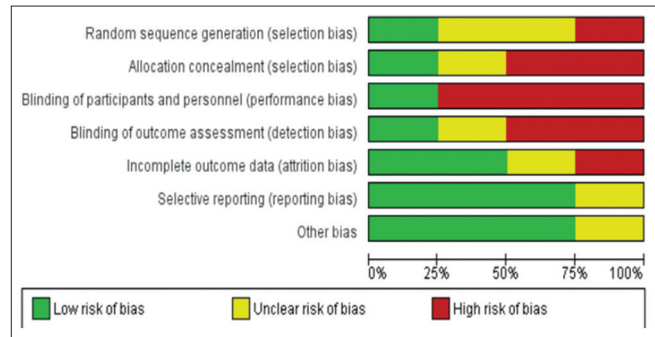Of late, intranasal route of administration has gained popularity in the field of conscious sedation in terms of rapid onset of action which corresponds to the advantage of intravenous and intramuscular sedation.[38] This rapid onset of action can be ascribed to the rich vascular supply of nasal mucosa and rapid achievement of the cerebrospinal fluid level of the drug due to communication with the subarachnoid space through the olfactory nerve.[39] Studies have also reported the increased advantage of inhalation and intranasal route over other sedative routes in that there is a more controlled maintenance of depth and duration of the sedation.[40,41]

Midazolam has been the most common agent evaluated for the sedative effect and behavior management in several studies. Due to the inconsiderable amount of literature being published on the various administrative routes of midazolam for sedation, there is a lack of consensus on the effectiveness of other routes of midazolam administration compared to intranasal midazolam route. There is no existing literature review highlighting the sedative effect and behavior management effectiveness of intranasal midazolam. Hence, the present systematic review compares the intranasal midazolam sedation to provide an insight on its sedative and behavior management effectiveness and compare it with the other routes of midazolam sedation.

The present systematic review includes 13 studies. The outcome for all the studies was assessed using sedation level or behavior rating scale. Venham's Clinical Anxiety Scale was used by two studies to assess the anxiety of the child.[24,25] A particular study used the Global Behavior Rating Scale[26] and another study used a modified scale to classify behavior/response to treatment under sedation.[27] Eight studies used Houpt's/Modified Houpt's Behavior Rating Scale to assess the behavior outcome.[7,8,28-33] One study used

Table 5: Results of included studies

Author	Route of administration of midazolam	Level of sedation	Behavior rating assessment	Success rate assessment
Chopra et al., 2013	0.25 mg/kg midazolam spray via the intranasal route 0.25 mg/kg midazolam spray via the buccal (aerosol mouth spray) route	-	Intranasal midazolam group 60% showed acceptable behavior (score 3–4) Buccal midazolam group 66.7% showed acceptable behavior (score 3–4) No statistically significant difference in the Houpt scores was observed ($P>0.05$, Chi-square test)	Intranasal midazolam group: 17 children out of 30 treatment completed successfully Buccal midazolam group: 20 children out of 30 treatment completed successfully No statistically significant difference in the success of treatment was observed ($P=0.056$, Chi-square test)
Fallahinejad Ghajari et al., 2015	Intranasal sedation: First combination: 1 ml of 2% lidocaine hydrochloride Second combination: 0.5 mg/kg intranasal midazolam vial added to 10 mg/kg of ketamine - 5 min after administration of initial drugs Oral sedation 0.5 mg/kg of oral midazolam with 10 mg/kg of ketamine and 0.25 mg/kg of atropine	-	A statistically significant difference in the Houpt's score was found at LA injection time and after 15 min in favor of intranasal sedation ($P<0.05$). No statistically significant difference was found after 30 min	Intranasal group: 96.6% and 60.9% success rate After 15 and 30 min Oral group 39.1% and 34.7% success rate after 15 and 30 min A statistically significant difference was found in favor of intranasal sedation after 15 and 30 min ($P<0.05$)
Gentz et al., 2017	0.5 mg/kg intranasal midazolam 1.0 mg/kg oral midazolam Midazolam combination (varies around 0.5–2 mg/kg depending on combination) (+meperidine/+hydroxyzine/+meperidine,+promethazine) (168) (nitrous oxide-oxygen was used as an adjunct in both groups)	-	Intranasal midazolam group 45.7% showed negative behavior rating and 54.3% showed positive behavior rating Oral midazolam group 35.7% showed negative behavior rating and 64.3% showed positive behavior rating Oral midazolam combination 43.6% showed negative behavior rating and 54.4% showed positive behavior rating No statistically significant difference between the groups in relation to behavior rating with oral midazolam alone having the most prominent effect and the other two regimens yielding almost equal poor and positive behaviors	Intranasal midazolam group 96.1% treatment completed successfully Oral midazolam 94.1% treatment completed successfully Oral midazolam combination: 85.4% treatment completed successfully No statistically significant difference between the intranasal and oral midazolam groups. Oral midazolam combination group was less likely to have treatment completed than the other two groups with a statistically significant difference ($P=0.0018$)
Hartgraves and Primosch, 1994	0.2 mg/kg intranasal midazolam 0.3 mg/kg oral midazolam in hydroxyzine pamoate suspension	-	Intranasal midazolam group showed 62% satisfactory rate on behavior Oral midazolam group showed 66% satisfactory rate on behavior No statistically significant difference was observed	Intranasal midazolam group: 31 children out of 50 completed treatment successfully Oral midazolam group: 33 children out of 50 completed treatment successfully No statistically significant difference was observed

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Table 5: Contd...

Author	Route of administration of midazolam	Level of sedation	Behavior rating assessment	Success rate assessment
Johnson et al., 2010	0.3 mg/kg intranasal midazolam and 0.5 mg/kg oral midazolam	-	Intranasal midazolam group: Significantly higher scores than the baseline level in the modified Houpt Behavior Rating Scale. Oral midazolam group Significantly higher scores in the Modified Houpt Behavior Rating Scale during the first 15 min of the appointment There was no statistically significant difference in the overall behavior between the groups	Intranasal midazolam group: All 31 children completed treatment successfully. Oral midazolam group: All 31 children completed treatment successfully No statistically significant difference between the groups.
Lee-Kim et al., 2004	Intranasal midazolam 0.3 mg/kg Oral midazolam 0.7 mg/kg	-	Intranasal midazolam group: Children showed more movement and less sleep between 25–20 min; also 30–35 min significant changes toward waking were observed Oral midazolam group Significant change toward waking was noted between 30 and 35 min after administration of sedative There was no statistically significant difference in the overall behavior scores	Intranasal midazolam group All 20 children completed treatment successfully Oral midazolam group: All 20 children completed treatment successfully No statistically significant difference in the success rate of treatment between both the groups
Musani and Chandan, 2015	0.1 mg/kg intranasal midazolam 0.2 mg/kg oral midazolam	Ellis Sedation Scale (Scores) 1:Intranasal group: 23.3% Oral group: 26.67% 2:Intranasal group:60% Oral group:63.3% 3:Intranasal group:16.67% Oral group:10% 4:Intranasal group: 0% Oral group: 0% 5: Intranasal group: 0% Oral group: 0% No statistically significant difference was observed	Intranasal midazolam group: According to the Houpt's Behavior Rating Scale Violent movement and hysterical crying: 0% Continuous movement and persistent crying: 6.67% Controllable movement and mild crying: 46.7% No movement and no crying: 46.7% Oral midazolam group According to the Houpt's Behavior Rating Scale Violent movement and hysterical crying: 0% Continuous movement and persistent crying: 6.67% Controllable movement and mild crying: 40% No movement and no crying: 53.33% No statistically significant difference was observed	Intranasal midazolam group All 30 children completed treatment successfully Oral midazolam group All 30 children completed treatment successfully No statistically significant difference was observed

Contd...

Table 5: Contd...

Author	Route of administration of midazolam	Level of sedation	Behavior rating assessment	Success rate assessment
Özen *et al.*, 2012	Group 1: Intranasal midazolam 0.20 mg/kg Group 2: Oral midazolam 0.75 mg/kg Group 3: Oral midazolam 0.50 mg/kg (along with 50% nitrous oxide and 50% oxygen in all 3 groups above) Group 4: Inhalation sedation with 50%–50% nitrous oxide/oxygen only	Bispectral Index System At 10 min: Group 2 was the only group that had BIS values below 90 From 15 min to end of the procedure All groups had BIS values above 90 BIS values were above 90 at all times for Group 4 At all times except for 30 min, Group 2 was the most sedated of all groups. At 1 and 5 min, there was no statistically significant difference between Groups 1 and 2, but there was a statistically significant difference between Groups 2 and 3 and between Groups 3 and 4	Modified scale to classify behavior/response to treatment/sedation Group 1: Excellent: 72% Adequate: 15% Modified scale to classify behavior/response to treatment/sedation Group 2 Excellent: 70% Adequate: 9% Group 3 Excellent: 48% Adequate: 24% Group 4: Excellent: 23% Adequate: 32% No statistically significant difference between the groups. However, the highest behavior rating was recorded for Group 1	Group 1: Highest success rate (87%) Group 2: Success rate (79%) Group 3: Success rate (72%) Group 4: Success rate (55%) No statistically significant difference between the success rates of Groups 1 and 2 ($P=0.230$) or Groups 2 and 3 ($P=0.399$). Significant difference was found between success rate of Groups 1 and 3 ($P<0.05$) and between Group 4 all the midazolam groups.
Shanmugaavel *et al.*, 2015	Group A: Intranasal midazolam 0.3 mg/kg Group B: Sublingual midazolam 0.3 mg/kg	-	Intranasal midazolam Fair: 5% Good: 10% Excellent: 85% Sublingual midazolam: Fair: 10% Good: 5% Excellent: 85% No statistically significant difference in the sleep, cry, and the overall behavior of the children between the groups at various time periods according to the Modified Houpt's Behavior Rating Scale	-

Table 5: Contd...

Author	Route of administration of midazolam	Level of sedation	Behavior rating assessment	Success rate assessment
Shanmugaavel *et al.*, 2016a	Group A: Intranasal midazolam 0.2 mg/kg Group B: Sublingual midazolam 0.2 mg/kg	-	**Intranasal midazolam** There was a significant decrease in anxiety from baseline to 20 min after drug administration. A statistically significant decrease in anxiety is seen at T1, T2, T3, and T4 time periods also. **Sublingual midazolam** There was a significant decrease in anxiety from baseline after drug administration No statistically significant difference in anxiety was found between the groups according to the Venham's Clinical Anxiety Scale	-
Shanmugaavel *et al.*, 2016b	Group A: Intranasal midazolam 0.2 mg/kg Group B: Sublingual midazolam 0.2 mg/kg	-	**Intranasal midazolam** Significant decrease in anxiety throughout the procedure compared to baseline **Sublingual midazolam** There was no significant decrease in the anxiety level at LA, T2, and T3 compared to baseline There was no significant difference in the anxiety level at various time periods between the intranasal and sublingual groups according to the Venham's Clinical Anxiety Scale. There was a significant increase in anxiety during local anesthetic administration in both intranasal (P=0.002) and sublingual (P<0.001) groups	-
Shashikiran *et al.*, 2006	Group N: Intranasal midazolam 0.2 mg/kg Group M: Intramuscular midazolam 0.2 mg/kg	-	**Intranasal midazolam** Significant difference between presedation and postsedation scores in the 4 major domains: crying, motor movements, sensory perceptions, and overall behavior **Intramuscular midazolam** Significant difference between presedation and postsedation scores in the 4 major domains: crying, motor movements, sensory perceptions, and overall behavior No statistically significant difference in the postsedation outcome and overall improvement in behavior between the two groups according to the Modified Houpt's Behavior Rating Scale and modified version of the scale developed by Fukuta *et al.*	

Table 5: Contd...

Author	Route of administration of midazolam	Level of sedation	Behavior rating assessment	Success rate assessment
Sunbul *et al.*, 2014	Group 1: Intranasal midazolam 0.3 mg/kg Group 2: Buccal midazolam 0.3 mg/kg		Intranasal midazolam Overall behavior rating Excellent - 16% Very good - 52% Good - 20% Fair - 4% Poor - 8% Buccal midazolam: Overall behavior rating Excellent - 12% Very good - 32% Good - 24% Fair - 20% Poor - 12% According to the Houpt's Behavior Rating Scale, there was no statistically significant difference between the two groups in sleep and movement rating scale. There was a statistically significant difference between the two groups in crying rating scale with the buccal group demonstrating increased crying than the intranasal group. In the overall behavior rating scale, there was no statistically significant difference between the two groups	Intranasal midazolam Treatment completed successfully in 96% Buccal midazolam Treatment completed successfully in 88% No statistically significant difference ($P<0.61$) between the buccal and intranasal groups regarding treatment accomplished

Table 6: Quality of assessment of the included studies

Serial number	Study	Adequate random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Free of incomplete outcome data assessment	Free from baseline imbalance	Adequate reliability	Risk of bias
1	Chopra *et al.*, 2013	No	No	No	No	Yes	Yes	Yes	High risk
2	Fallahinejad Ghajari *et al.*, 2015	Unclear	No	Yes	Yes	Yes	Yes	Yes	High risk
3	Gentz *et al.*, 2017	No	No	No	Unclear	Unclear	No	Unclear	High risk
4	Hartgraves and Primosch, 1994	No	No	No	No	Unclear	Unclear	Unclear	High risk
5	Johnson *et al.*, 2010	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	High risk
6	Lee-Kim *et al.*, 2004	Unclear	No	No	Yes	No	Yes	Yes	High risk
7	Musani and Chandan, 2015	Yes	Unclear	No	No	Yes	Yes	Yes	High risk
8	Özen *et al.*, 2012	Unclear	Unclear	No	No	Yes	Yes	Yes	High risk
9	Shanmugaavel *et al.*, 2015	Yes	Unclear	No	Yes	Yes	Yes	Yes	High risk
10	Shanmugaavel *et al.*, 2016a	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	High risk
11	Shanmugaavel *et al.*, 2016b	Yes	Unclear	No	No	Yes	Yes	Yes	High risk
12	Shashikiran *et al.*, 2006	Unclear	Unclear	No	Yes	Yes	Yes	Yes	High risk
13	Sunbul *et al.*, 2014	Yes	Unclear	No	Yes	Yes	Yes	Yes	High risk

a modified version of scale developed by Fukuta *et al.*, in addition to the Modified Houpt's Behavior Rating Scale to assess the behavior of the child.[29]

The level of sedation was assessed by Musani and Chandan and Özen *et al*.[7,27] Musani and Chandan assessed sedation using the Ellis Sedation Scale. Özen *et al*. used the Bispectral Index System to assess the level of sedation.

Seven included studies evaluated behavior scale by comparing oral midazolam with intranasal midazolam.[7,8,26,27,31,32,34] Two included studies compared buccal midazolam with intranasal midazolam to assess behavior outcome.[28,33] Three included studies assessed behavior/anxiety management effectiveness comparing sublingual midazolam with intranasal midazolam.[7,24,25] One study compares intramuscular midazolam route compared to intranasal route for assessing behavior in children.[29]

There was no statistically significant difference in the level of sedation between intranasal midazolam and oral midazolam in relation to the Ellis sedation Scale and Bispectral Index Monitoring System, respectively.[7,27] In the Ellis Sedation Scale, score 1 was observed in 23.3% of the intranasal midazolam group and 26.67% of the oral midazolam group; score 2 was observed in 60% of the intranasal midazolam group and 63.3% in the oral

midazolam group. Score 3 was observed in 16.67% of the intranasal midazolam group and 10% of the oral midazolam group, whereas scores 4 and 5 were not observed in both the groups. However, no statistically significant difference was observed between the groups.[7]

Gentz *et al*.[34] used oral midazolam combination (+me peridine/+hydroxyzine/+meperidine,/+promethazine) in one of the intervention groups. Similarly, Hartgraves and Primosch[26] used oral midazolam in hydroxyzine pamoate suspension in the intervention group. And also, Fallahinejad Ghajari *et al*.[8] evaluated combination sedatives in two different routes of drug administration. The control group was not purely intranasal midazolam but in combination with ketamine, and the intervention group was not just oral midazolam but in combination with atropine and ketamine. These have to be taken into consideration while observing the results of the studies.

The quality of assessment was done based on the Cochrane database with the seven criteria of assessment.[42] The criteria to assess the review were randomized generation of sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, free of incomplete data outcome, free from baseline imbalance, and adequate reliability. In the present review, a high risk was observed as blinding of the participants as well as the

personnel was not adequate.[7,24,26-31,33,34] Hence, there is a need for more studies in the future free from any bias.

Another limitation is the less number of sample size evaluated in ten of the included[7,8,24,25,28-33] studies. There were no studies available comparing intravenous and rectal midazolam with intranasal midazolam for sedation during routine dental treatment for children. Thus, more studies are required with a larger sample size.

The present systematic review recommends more research in the field of sedation as it will assist in managing the child in the dental operatory. Furthermore, there is a need for more studies comparing the different modes of administration and types of administration devices used to evaluate the sedative and behavior management effectiveness.

Conclusion

This systematic review concludes that there is no statistically significant difference between intranasal midazolam and other midazolam routes on the outcome of behavior and sedation level. It is recommended to conduct substantial research in the field of sedation to devise a better and safer clinical protocol for the administration of any sedative agent to a child, thereby assisting pediatric dentists in the successful management of child behavior in the dental operatory.

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Conflicts of interest

There are no conflicts of interest.

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