REVIEW ARTICLE

# Comparing the Sedative Effect of Oral and Intranasal Midazolam and their Effect on Behavior in Pediatric Dental Patients

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## Abstract

**Aim:** To systematically identify and evaluate the available literature based on the sedative effect of oral midazolam compared with midazolam administered intranasally and also compare their effect on behavior of pediatric dental patients.

**Objective:** This systematic review compares the sedative effect and the effect on behavior with oral midazolam and intranasal midazolam.

**Methods:** A search was undertaken through PubMed Central, Cochrane Database of Systematic Reviews, LILACS, Science Direct and SIGLE. All the studies included the comparison of the sedative effect of oral and intranasal midazolam. Database search identified 178 articles. 165 articles were excluded based on titles and duplication. Abstract and complete text of 13 articles were thoroughly evaluated. Four articles were included based on the inclusion criteria to meet the criteria. The selected studies analyzed the children's behavior or anxiety by oral midazolam in comparison to intranasal midazolam administration.

**Results:** Among the four studies included in the present review, risk of bias was high in all the articles. The high risk was obtained due to inadequate blinding of personnel and participants in the study, improper allocation concealment and inadequacy in blinding of the outcome assessment. Also, difference observed between oral and intranasal midazolam routes on behavior and sedation level in the studies included in this review was not statistically significant.

**Conclusion:** Studies comparing the effect on behavior of oral and intranasal midazolam in children are limited. More number of high-quality clinical trials evaluating the sedative effect and effect on behavior of oral and intranasal midazolam in pediatric dental patients is required.

**Keywords:** Midazolam, Pediatric dentistry, Sedation, Systematic review.

*International Journal of Clinical Pediatric Dentistry* (2022): 10.5005/jp-journals-10005-2117

## Introduction

Anxiety and fear play a major role in influencing a child's approach toward dental treatment. There are many techniques involved in managing the behavior of a child. Behavior management is crucial in the care of children in pediatric dentistry. Procedural sedation is a treatment modality used to manage an anxious child in recent times.[1] This has led to a decrease in need of general anesthesia in both medical as well as dental practices.[2]

Conscious sedation is indicated in children lacking cooperation or those with fear and anxiety toward dental treatment. This treatment modality not only enhances the comfort level of the patient but also aids in controlling the anxiety and behavior of a child for successful completion of the procedure.

The goals of sedation for diagnostic and therapeutic procedures are to:

- Guard the welfare and safety of the patient
- Minimize physical discomfort and pain
- Control anxiety, minimize psychological trauma, and maximize the potential for amnesia.
- Control behavior and/or movements so as to allow safe completion of procedure
- Return the patient to a state in which safe discharge from medical supervision is possible as determined by the recognized criteria[3]

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**How to cite this article:** Kotian N, Subramanian EMG, Jeevanandan G. Comparing the Sedative Effect of Oral and Intranasal Midazolam and their Effect on Behavior in Pediatric Dental Patients. Int J Clin Pediatr Dent 2022;15(1):128–134.

**Source of support:** Nil

**Conflict of interest**: None

A variety of sedatives and various routes of administration are being used for procedural sedation in dental operatories, each of them having their own pros and cons.[4] Owing to its pharmacological profile, midazolam, which is a short-acting water-soluble benzodiazepine, serves as an ideal sedative and is administered through various routes such as oral, intramuscular, intravenous, rectal, and intranasal.

The oral administration of sedatives is one of the most commonly used method in pediatric dental patients. Despite having advantages like ease in administration and patient acceptance it has ceratin disadvantages like delayed absorption rate, lack of titration capacity, and delayed onset time.[5]

Intranasal sedation is also used by the pediatric dentists for dental sedation. Although it has been proven to be highly technique sensitive, it is well tolerated by children as it is effective and fast acting ensuring rapid absorption into systemic circulation. Intranasal administration may be less suitable than oral administration because of risk of harmful long term effects on the nasal epithelium.

To overcome the limitations of both the drug routes, intranasal technique is used in combination with oral medication.

Thus the present systematic review was done with the aim of evaluating the available literature on the sedative and behavioral effectiveness of oral and intranasal midazolam in children undergoing routine dental treatment .

## Materials and Methods

This review was done following the guidelines of Cochrane Handbook of Systematic Review.

### Inclusion Criteria

Studies were selected using the following inclusion criteria.

- Randomized controlled trials involving pediatric dental patients undergoing midazolam sedation.
- Studies comparing the sedative and/or the behavior effect of oral and intranasal midazolam.
- Studies published in no other language except English.

### Exclusion Criteria

Studies were excluded based on the following exclusion criteria.

- Studies involving children above 12 years of age.
- Studies involving administration of midazolam other than oral and intranasal route.
- Studies involving midazolam as a premedication before general anaesthesia.
- Studies evaluating any other effects of midazolam other than sedation and behavior.
- Ongoing studies in which results have not yet been published.

### Search Strategy:

*PUBMED Search Strategy*

The following keywords were used for Pubmed search engine:

((((((((((((((Children below 12 years) OR Pediatric dental patients) OR uncooperative children) OR anxious children) OR pediatric dentistry) OR uncooperative child) OR anxious child) OR fearful child) OR children undergoing procedural sedation) OR children undergoing conscious sedation) OR children undergoing mild sedation)) AND ((((((((((((((((((((((((((((((((((((((((((((((((((oral midazolam sedation) OR oral midazolam) OR oral midazolam hydrochloride syrup) OR oral mezolam) OR oral midazolamum) OR oral dormicum) OR oral miben) OR oral hypnovoel)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 ((((((((((((((((((((((behavior 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 houpt behavior rating scale) OR frankl behavior rating scale) OR FLACC) OR Venham's scale) OR visual analog scale) OR VAS) OR behavior profile rating scale) OR kirosu behavior evaluation scale) OR Ramsay sedation scale) OR Richmond agitation sedation scale) OR state behavior rating scale) OR bispectral index monitoring).

The search yielded 60 studies.

*COCHRANE Search Strategy*

The following keywords were used for Cochrane search engine:

((((((((((((Children below 12 years) OR Pediatric dental patients) OR uncooperative children) OR anxious children) OR pediatric dentistry) OR uncooperative child) OR anxious child) OR fearful child) OR children undergoing procedural sedation) OR children undergoing conscious sedation) OR children undergoing mild sedation)) AND ((((((((((((((((((((((((((((((((((((((((((((((((((oral midazolam sedation) OR oral midazolam) OR oral midazolam hydrochloride syrup) OR oral mezolam) OR oral midazolamum) OR oral dormicum) OR oral miben) OR oral hypnovoel)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 ((((((((((((((((((((((behavior 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 houpt behavior rating scale) OR frankl behavior rating scale) OR FLACC) OR Venham's scale) OR visual analog scale) OR VAS) OR behavior profile rating scale) OR kirosu behavior evaluation scale) OR Ramsay sedation scale) OR Richmond agitation sedation scale) OR state behavior rating scale) OR bispectral index monitoring).

The search yielded 84 studies.

*Science Direct search strategy:*

The following keywords were used for Science Direct search engine:

(Children OR paediatric dental patients) AND (oral midazolam) AND (intranasal midazolam) AND (behavior management OR sedation level OR anxiety)

The search yielded 32 studies.

*Sigle:*

The following keyword were used for Sigle search engine:

Comparison of effects on level of sedation and behavior by oral midazolam and intranasal midazolam in paediatric dental patients.

No relevant studies were obtained

*LILACS:*

The following keyword were used for LILACS search engine:

children OR pediatric dental patients OR uncooperative children OR anxious children OR pediatric dentistry [Words] AND (Oral midazolam) AND (intranasal midazolam OR inhalation midazolam) [Words] and behavior management OR behavior OR management OR managing OR sedative effect OR sedation level OR procedural sedation [Words].

No relevant studies were obtained.

*Google Scholar:*

Google Scholar database was searched using the following keywords:

Midazolam, sedation, oral and intranasal[words]

The search yielded 1 study.

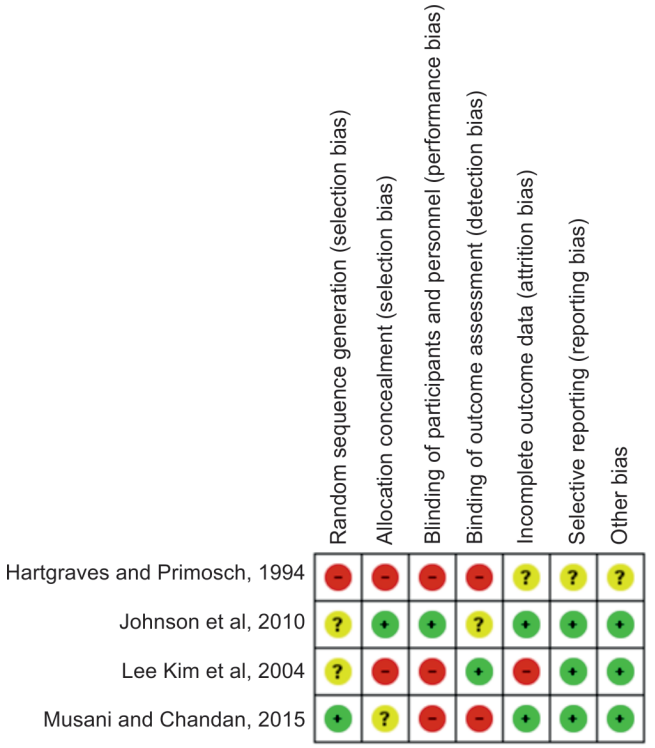


**Fig. 1:** Prisma flowchart showing included studies

**Table 1:** Characteristics of excluded studies

| *Sr. no.* | *Study* | *Reason for exclusion* |
|---|---|---|
| **1.** | Yildirim et al. (2006) | Oral midazolam and nasal midazolam was used as a premedication and not for routine dental procedure. |
| **2.** | Klein EJ et al. (2011) | Comparison of aerosolized intranasal or buccal midazolam with oral midazolam for laceration repair and not for routine dental treatment. |
| **3.** | Heard C et al. (2010) | Four sedative techniques of midazolam are compared for dental surgery and not for routine dental procedures. |
| **4.** | Tschirch et al. (2007) | Not evaluated for routine dental procedure. |
| **5.** | Kogan et al. (2002) | Oral midazolam and nasal midazolam was used as a premedication and not for routine dental procedure. |
| **6.** | Malinovsky et al. (1992) | Oral midazolam and nasal midazolam was used as a premedication and not for routine dental procedure. |
| **7.** | Tolksdorf et al. (1991) | Oral midazolam and nasal midazolam was used as a premedication and not for routine dental procedure. |
| **8.** | Connors et al. (1994) | Comparison of oral midazolam and nasal midazolam for laceration repair and not for routine dental procedure. |
| **9.** | Manoj et al. (2017) | Oral midazolam and nasal midazolam was used as a premedication and not for routine dental procedure. |

## Data Collection and Analysis

Figure 1: depicts the PRISMA flow diagram for the included studies. The studies not following the inclusion criteria were excluded [Table 1]. The selected articles were evaluated for the quality of studies following the guidelines given by Cochrane Handbook of systematic review which was done independently by both the authors and any discrepancy was resolved by discussion between both the authors.

## Results

### Study Selection

After removal of duplicates and title scan, 13 studies were identified and from that 9 studies did not meet the inclusion criteria and were excluded from the systematic review. Full text articles for the other 4 studies were evaluated in detail. A total of four studies met the inclusion and exclusion criteria of the intended research.

### Study Characteristics

Characteristics of the included studies were mentioned and the Outcome of these studies were assessed using sedation scale and/or behavior assessment scale (Tables 2 and 3). Hartgraves and Primosch,1994 compared 0.2 mg/kg of intranasal midazolam with 0.3 mg/kg of Oral midazolam in hydroxyzine paomate suspension (along with 40% Nitrous oxide and 60% oxygen) and observed no statistically significant difference in the Global behavior rating scale scores.

Lee-Kim et al. (2004) compared 0.3 mg/kg of intranasal midazolam with 0.7 mg/kg of Oral midazolam (45% nitrous oxide and papoose board provided for all patients). There was no statistically significant difference in the overall behavior scores in the Houpt behavior scale between the two groups.

Johnson et al. (2010) compared 0.3 mg/kg of intranasal midazolam with 0.5 mg/kg of Oral midazolam in children and observed no statistically significant difference in the overall behavior scores in the modified Houpt behavior scale between the groups.

Musani and Chandan, 2015 assessed the sedative level using Ellis sedation scale and the behavioral outcome using Houpt behavior rating scale between 0.1 mg/kg of Intranasal midazolam and 0.2mg/kg of Oral midazolam. No statistically significant difference in Ellis sedation score was observed between the groups. Also,there was no statistically significant difference in the overall behavior scores in the Houpt behavior scale between the groups.

Based on these, assessment of risk of bias was done for the included studies (Figs 2 and 3).

## Discussion

Behavior management in young pediatric patients is challenging both for the child and the dentist.[7,8] In a scenario where a child is not cooperating for the dental procedure it is advisable to perform the treatment under general anesthesia or conscious sedation to avoid providing substandard treatment.

Since general anesthesia requires a minimal hospital setup and an experienced operator, conscious sedation is proven to be a more convenient and feasible choice of treatment.[9–11]

The clinical outcome of the sedation varies from one child to another, depending on the child's response to the sedative.

Therapeutic index and wide margin of safety are reasons for considering Midazolam as the most extensively used sedative agent.[11-17]

**Table 2:** Characteristics of included studies

| *Sr. No.* | *Author and Year* | *Study design* | *Sample size and Age-group* | *Sedative agent used* | | *Outcome assessment* | |
|---|---|---|---|---|---|---|---|
| | | | | *Intervention* | *Control* | *Criteria used* | *Variables evaluated* |
| **1.** | **Hartgraves and Primosch (1994)** | Randomized controlled trial | 100 children in the age-group of 1.5 to 6 years. | Oral midazolam 0.3 mg/kg in hydroxyzine paomate suspension (50) (along with 40% nitrous oxide and 60% oxygen) | Intranasal midazolam 0.2 mg/kg(50) (along with 40% Nitrous oxide and 60% Oxygen) | i) Global behavior rating scale<br>ii) Success level by group<br>iii) Distribution of complications by group | i) Behavior<br>ii) Success rate<br>iii) Complications |
| **2.** | **Lee-Kim et al. (2004)** | Single-blinded randomized controlled trial | 40 children in the age-group of 24 to 72 months | Oral midazolam 0.7 mg/kg(20) | Intranasal midazolam 0.3 mg/kg(20) | i) Onset of sedation<br>ii) Maximum working time<br>ii) Modified Houpt's behavior rating scale | i) Behavior<br>ii) Sedation onset<br>iii) Duration of sedation |
| **3.** | **Johnson et al. (2010)** | Double-blinded randomized controlled crossover trial | 31 children in the age-group of 42 to 84 months | Oral midazolam 0.5 mg/kg (cherry syrup) and intranasal saline placebo (31) | Intranasal midazolam 0.3 mg/kg and oral placebo (cherry syrup) (31) | i) Modified Houpt behavior rating scale<br>ii) Physiological parameters<br>iii) Adverse effects<br>iv) Postoperative survey | i) Behavior<br>ii) Physiological effects<br>iii) adverse effects<br>iv) Postoperative complications / sideeffects |
| **4.** | **Musani and Chandan (2015)** | Randomized controlled crossover trial | 30 children in the age-group of 3-6 years | 0.2 mg/kg of oral midazolam in syrup form and 30% nitrous oxide 70% oxygen(30) | 0.1 mg/kg of intranasal midazolam spray and 30% nitrous oxide 70% oxygen (30) | i) Patient's acceptability of drug<br>ii) level of co-operation during acceptance of nasal mask<br>iii) Ellis sedation score<br>iv) Houpt's behavior rating scale<br>v) Safety scale<br>vi) Time of sedation onset | i) Behavior and alertness<br>ii) Onset of sedation<br>iii) Safety<br>iv) Acceptability of drug<br>v) Level of sedation |

The most common route for administration of midazolam is the oral route, although the other routes of administration like intranasal, intra muscular, transmucosal and intravenous have also been defined.[18-23]

Though, intranasal route of administering midazolam tends to cause mucosal irritation in young patients, it has gained popularity due to its rapid onset of action.[24-26]

There is no existing literature review comparing the sedative effect of oral and intranasal midazolam as well as its effect on the behavior of a child undergoing dental treatment. Hence, the present systematic review was carried out to compare the effectiveness of oral midazolam with intranasal midazolam.

The present systematic review includes 4 studies based on the pre-determined inclusion and exclusion criteria. The outcome for all the studies was assessed using behavior rating scale and/or level of sedation. One study used Global behavior rating scale[27] while the other three studies used Houpt's or Modified Houpt's behavior rating scale to assess behavior outcome.[28-30]

All the studies included in the present systematic review showed no significant difference in behavior scores between oral and intranasal midazolam.

Ellis sedation scale was used to assess the level of sedation in one of the studies,[28] while the other three studies did not use any scale for measurement of sedation.

Musani and Chandan (2015)[28] found no statistically significant difference in the level of sedation between oral midazolam and intranasal midazolam with Ellis sedation Scale. In the Ellis sedation scale, score 1 (No uninvited limb movement. Total cooperation-no restlessness) was observed in 23.3% of intranasal and 26.67% of oral midazolam group; score 2 (Small amount of uninvited limb movement. Still total cooperation and no restlessness) was observed in 60% of intranasal midazolam group and 63.3% in the oral midazolam group. Score 3 (More uninvited limb movement. Small degree of restlessness and anxiety. Patient less cooperative. Still able to perform all dental procedures) was observed in 16.67% of intranasal and 10% of oral midazolam group whereas score 4 (Considerable degree of limb movement. Unhelpful head movements. Poor cooperation. Patient quite restless and anxious. Able to perform only basic dentistry. Advanced delicate work not possible) and 5 (Restless, anxious and limb movements severe. Impossible to perform any dentistry. Not determined=t oo uncooperative) was not observed in both the groups. However, no statistically significant differences were observed between the groups indicating that be it oral or intranasal route of administering midazolam has no effect on the level of sedation.[28]

The quality of assessment was done based on Cochrane database with the seven criteria of assessment for a standardized method.[31] The criteria assessed were random sequence generation,

**Table 3:** General information on the results of included studies

| S.No. | Author and year | Type and route of administration of sedative agent | Sedation level | Behavior rating | | Overall success rate | |
|---|---|---|---|---|---|---|---|
| 1. | Hartgraves and Primosch (1994) | Intranasal midazolam (0.2 mg/kg) Oral midazolam (0.3 mg/kg) in hydroxyzine paomate suspension (along with 40% Nitrous oxide and 60% oxygen) | NA | Intranasal midazolam:62% showed a satisfactory behavioral effect on sedation | Oral midazolam:66% showed a satisfactory behavioral effect on sedation | Intranasal midazolam:31/50 treatment completed successfully | Oral midazolam:33/50 treatment completed successfully |
| | | | | No statistically significant difference in the Global behavior rating scale scores was observed | | No statistically significant difference in the success of treatment was observed. | |
| 2. | Lee-Kim et al. (2004) | (0.3 mg/kg) intranasal midazolam 0.7 mg/kg Oral midazolam (45% nitrous oxide and papoose board provided for all patients) | NA | Intranasal midazolam: Between 25 and 30 minutes subject showed more movement and less sleep and between 30 and 35 minutes significant changes toward waking after administration of sedation. | Oral midazolam: Significant change toward waking was seen between 30 to 35 minute after administration of sedation. | Intranasal midazolam: 20/20 treatment was completed successfully. | Oral midazolam: 20/20 treatment was completed successfully. |
| | | | | There was no statistically significant difference in the overall behavior scores in the Houpt behavior scale between the groups analyzed using multivariate ANOVA. | | No statistically significant difference in the success of treatment between the groups. | |
| 3. | Johnson et al. (2010) | Intranasal midazolam (0.3 mg/kg) Oral midazolam(0.5 mg/kg) | | Intranasal midazolam:There was no statistically significant difference in the overall behavior scores in the Houpt behavior scale between the groups analyzed using multivariate ANOVA. | Oral midazolam: there was significantly higher scores in the modified Houpt behavior rating scale only for first 15 minutes of appointment. | Intranasal midazolam:31/31 treatment completed successfully | Oral midazolam:31/31 treatment completed successfully |
| | | | | There was no statistically significant difference in the overall behavior scores in the Modified Houpt behavior scale between the groups. | | No statistically significant difference in the success of treatment between the groups. | |
| 4. | **Musani and Chandan (2015)** | Intranasal midazolam 0.1 mg/kg Oral midazolam 0.2 mg/kg (along with 30% Nitrous oxide and 70% oxygen) | Ellis sedation score: Score 1:Intranasal: 23.3% Oral:26.67% Score 2:Intranasal:60% Oral:63.3% Score 3:Intranasal:16.67% Oral:10% Score 4:Intranasal and oral:0% Score 5: Intranasal and oral:0% | Intranasal midazolam: According to 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: According to 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% | Intranasal midazolam: 30/30 treatment was completed successfully. | Oral midazolam: 30/30 treatment was completed successfully. |
| | | | No statistically significant difference in Ellis sedation score of treatment between the groups. | There was no statistically significant difference in the overall behavior scores in the Houpt behavior scale between the groups. | | No statistically significant difference in the success of treatment between the groups. | |

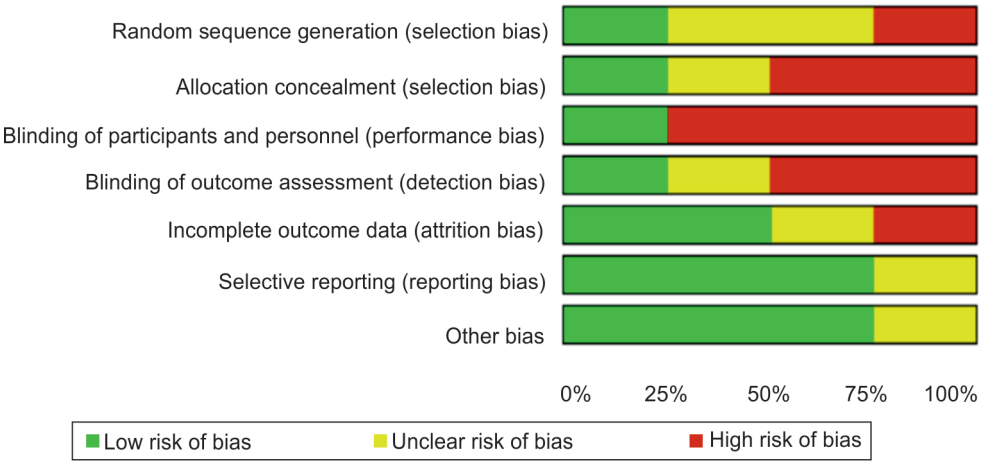


**Fig. 2:** Risk of bias Graph: judgement about each risk of bias item presented as percentage among included studies

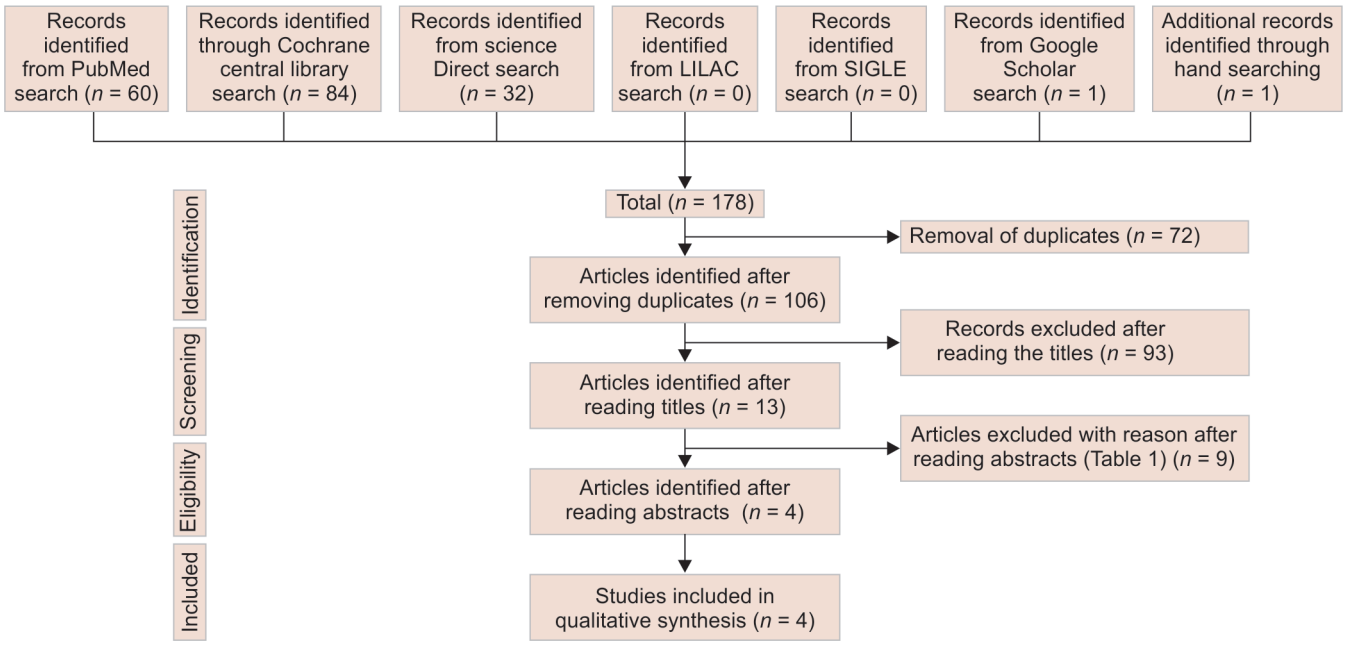


**Fig. 3:** Risk of bias summary: Judgement about each risk of bias item for each included study

allocation concealment, blinding of participants and personnel, blinding of outcome assessment, free of incomplete data outcome, free from baseline imbalance and adequate reliability. All the four included studies showed high risk of bias. The high risk was obtained due to inadequate blinding of personnel and participants in three of the studies[27-29] and due to inadequate blinding of outcome assessment in two studies. This shows a need for high quality studies which are free from any source of bias for better assessment of oral and intranasal midazolam.

According to the present systematic review there are limited studies comparing intranasal midazolam with oral midazolam routes. This systematic review advocates more number of research to be conducted in the field for better clinical outcome in behavior management. Hence, there is a need for more high quality research to evaluate the sedative and behavior management effectiveness of intranasal midazolam and oral medicine as well as updating the current existing literature for a better understanding and clinical judgement of the same.

## Conclusion

There is no statistically significant difference between oral midazolam and intranasal midazolam routes on the outcome of behavior and sedation level. It also advocates the need for high quality studies using oral as well as intranasal midazolam to obtain a better protocol and to draw into conclusion. This research also advises to update the existing literature on oral and intranasal midazolam sedation to devise a better clinical protocol and a more effective and safe technique for sedation in paediatric dental patients compared to the other administrative routes of midazolam available.

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