



# Nebulized vs. oral midazolam as a sedative premedication in pediatric anesthesia: A randomized controlled double-blinded study

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## ABSTRACT

**Objective:** This study was carried out to compare different routes of midazolam administration (nebulized vs. oral) to achieve a satisfactory level of sedation, RAMSAY Sedation Score (RSS) of 4, within 30 minutes of midazolam administration in pediatric operative patients.

**Methods:** After approval of the ethical committee in Kasr Al-ainy university hospital and obtaining written consent from parents/legal guardians; Seventy-two pediatric patients scheduled for general and urological surgical operations under general anesthesia were included in this randomized double-blinded study. Patients were randomly assigned into one of the two equal groups. Group N: 36 children received nebulized midazolam 0.2 mg/kg in 3 ml normal saline plus 5 ml clear juice 30 min before undergoing general anesthesia (GA). Group O: 36 children received oral midazolam 0.5 mg/kg in 5 ml clear juice plus nebulizer of 3 ml normal saline 30 min before undergoing general anesthesia.

**Results:** We found no statistical difference between nebulized and oral midazolam regarding drug acceptance, peri-operative (sedation scores, hemodynamics, and side effects); P-value >0.05 for all values.

**Conclusion:** Nebulized midazolam is a good alternative to oral midazolam as a sedative premedication in pediatrics.

## ARTICLE HISTORY

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## KEYWORDS

Nebulized; midazolam;  
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## 1. Introduction

Fear and anxiety are common responses in children during hospitalization. Anxiety in children may lead to immediate adverse postoperative reactions such as nightmares, separation anxiety, eating disturbances and, new-onset enuresis. Anxiety may also activate a stress response, resulting in catabolism, delayed wound healing and postoperative immune suppression [1]. The treatment approach for preoperative anxiety in children should be multimodal. Several techniques are available, such as psychological and behavioral intervention and a pharmacological strategy [2]. Although variety of pre-induction techniques exist, the most popular technique involves administering a sedative premedication, such as midazolam. Preoperative administration of midazolam, alone or combined with other pharmacological agents, is the most effective technique to reduce anxiety in the child and parents [3].

Many studies compared different routes of midazolam administration in adults and pediatrics including oral, intranasal, buccal, and nebulized routes [4–7]. These studies compared levels of sedation, ease of administration, and possible complications.

In this study, we hypothesized that, nebulized midazolam premedication, being directly deposited into the

respiratory system and rapidly absorbed at high concentrations, would be more effective than commonly used oral midazolam in children. The primary outcome of this study was to detect the time required to reach a satisfactory level of sedation, RAMSAY sedation score 4 (RSS of 4) in both groups. Secondary outcomes included patient acceptance of the method of administration of midazolam, ease of separation from parents using (ease of separation and ease of induction scoring system), face mask acceptance during induction, changes in hemodynamics and oxygen saturation till the end of surgery and recovery time to baseline sedation score.

## 2. Materials and methods

This randomized controlled double-blinded study is a single institutional, prospective, clinical trial carried out in Abu El-Reesh Children's Hospital, Cairo University, from March 2021 to August 2021 after obtaining institutional ethics committee approval (N-35-2018) and registering at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04760041). All procedures were conducted in accordance with the Helsinki Declaration-2013. Written informed consent was obtained from the parents or legal guardians before patient's enrollment.

We included American society of anesthesiologist I and II children aged 2–6 years scheduled for elective non-cardiac surgery under general anesthesia.

Patients with renal or hepatic dysfunction, pre-existing neurologic disease, history of allergy to midazolam, patients with atopy or history of asthma and patients undergoing prolonged procedure (> 2 hr) were excluded.

Randomization was done using a computer-generated randomization table, using EXCEL 2010 (Microsoft corp. U.S.A.), and group allocation was placed in sealed, concealed, opaque, and sequentially numbered envelopes. A researcher was responsible for envelopes opening and drug preparation without any further involvement in the study.

### 2.1. Drug preparation

**In Group N**, the nebulization solution was midazolam 0.2 mg kg<sup>-1</sup> in 3 ml normal saline, and the oral solution was 5 ml clear juice.

**In Group O**, the nebulization solution was 3 ml normal saline, and the oral solution was midazolam 0.5 mg kg<sup>-1</sup> in 5 ml clear juice.

Patients in both study groups were allowed to eat solid and semi-solid food till 6 hours before surgery, and drink clear fluids till 2 hours pre-operatively. In the pre-anesthesia room with the presence of a parent or guardian; routine monitoring was applied (pulse oximetry, non-invasive blood pressure, and electrocardiogram), and children from both groups received nebulizer and juice 30 minutes before the surgery. Nebulization was administered by a standard hospital jet nebulizer via a mouthpiece, with a continuous flow of 100% oxygen at 6 L.min<sup>-1</sup>. A supervising nurse made sure that the nebulizer was properly applied all through until all the contained solution was administered.

Level of sedation was evaluated using Ramsay sedation score (RSS) [8] the score was as follows; 1: Anxious and agitated patient, 2: Cooperative patient, 3: Sleeping patient, brisk response to loud voice, 4: Sleeping patient, sluggish response to loud voice, 5: No response to loud voice, 6: No response to pain. The RSS was assessed every 5 min until achieving RSS of 4.

A blinded observer evaluated patient acceptance of the medication as excellent (accept medication without complaint), good (complaint, will briefly tearful or unhappy, but then accept medication), fair (complaint, initially uncooperative but eventually accept medication), or poor (refuse medication) [9].

After 30 min, if the child was not adequately sedated (RSS less than 4), IM ketamine 3 mg kg<sup>-1</sup> would be administered as an alternative to midazolam, and this case would be discarded from the study. After reaching RSS of 4 and before transfer to operating room, reaction to separation from the parents was assessed after

sedation by the ease of separation and ease of induction score system (1: Excellent patient unafraid, cooperative, or asleep, 2: Good slight fear and/or crying, quiet with reassurance, 3: Fair moderate fear and crying, not quiet with reassurance, 4: Poor crying, need for restraint) [9].

Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR) and peripheral oxygen saturation (SpO<sub>2</sub>) were recorded at baseline and every 15 minutes preoperatively.

In the operating room, facemask acceptance was graded as poor (terrified, crying, and combative), fair (moderate fear of mask not calmed with reassurance), good (slight fear of mask, easily reassured), or excellent (unafraid, cooperative, and accepts mask readily) [9].

General anesthesia was induced with sevoflurane in oxygen via a facemask. When venous access was secured, intravenous fentanyl 1.5 µg.kg<sup>-1</sup> and atracurium 0.5 mg.kg<sup>-1</sup> were administered to facilitate endotracheal intubation. Intravenous ketorolac 0.5 mg kg<sup>-1</sup> was given for intraoperative analgesia. Anesthesia was maintained by 1.2% isoflurane in oxygen and incremental doses of atracurium

The HR, MAP, and SpO<sub>2</sub> were continuously monitored and recorded intraoperatively every 15 min until the end of the operation in all patients.

At the end of the surgery, residual neuromuscular block was antagonized with intravenous neostigmine 0.05 mg.kg<sup>-1</sup> and atropine 0.02 mg.kg<sup>-1</sup>. The duration of anesthesia was recorded in minutes.

By the end of the surgery, recovery was assessed by an anesthesiologist, blinded to the treatment groups. Recovery time from discontinuation of anesthesia until regaining baseline sedation score was recorded in minutes. Sedation scores, HR, MAP, RR, and SpO<sub>2</sub> were assessed in PACU every 15 min until discharge criteria were fulfilled.

Any perioperative adverse effects (vomiting, bradycardia, and hypotension) were recorded.

Primary outcome was time to achieve adequate sedation, defined as the time from completing the intervention until achieving RSS of 4 or more.

Secondary outcomes included tolerance to intervention, ease of separation, face-mask tolerance, recovery time, and incidence of complications as well as perioperative HR, MAP, SpO<sub>2</sub> and RR.

### 2.2. Sample size

Based on a previous study by Majidinejad S, et al. [10] that compared oral midazolam vs. oral midazolam and ketamine for sedation in 66 children. Time to achieve adequate sedation in oral midazolam group was 33.8 (±7.5) min by assuming 20% difference between two groups with a type I error of 0.05 and a power of 0.95, a sample size of 33 patients/group was required, rolled up to 36 patients per group to compensate for possible

dropouts. Statistical power calculations were performed using the computer program G\*Power 3 for Windows (Franz Faul, Universität Kiel, Germany).

### 2.3. Statistical analysis

Continuous data are expressed as mean  $\pm$  standard deviation or median (quartiles) according to the normality test. The Student t-test or Mann-Whitney was used for analyzing unpaired continuous data as appropriate. Categorical data were expressed as frequency and were analyzed using the chi-square test. Analysis of repeated measured data was done using repeated-measures analysis of variance followed by Bonferroni test if significant results were recorded. Statistical Package for Social Science (SPSS) computer program (version 26 windows) was used for data analysis. P-value 0.05 or less is considered significant.

### 3. Results

Seventy-six children were screened for eligibility, four children were excluded for not fulfilling the inclusion criteria. Seventy-two children were included and were randomized at 1:1 ratio into the study's groups (36 children in each group), all the included children

received the intervention and were available for the final analysis. (Figure 1)

Demographic data and baseline clinical characteristics were comparable between the two groups. (Table 1)

Time to achieve adequate sedation was comparable between the two groups. None of the included patients required supplemental ketamine for sedation. Furthermore, tolerance to intervention, ease of separation, and face-mask tolerance were comparable between the two groups. (Table 2) The recovery time and incidence of complication were also comparable between the two groups. None of the included patients developed perioperative hypoxia or hypotension. (Table 2)

Perioperative MAP, HR, RR, and SpO<sub>2</sub> were generally comparable between the two groups. (Figures 2–5). All these parameters decreased in relation to the baseline 15-min after drug administration in each group. The MAP was maintained in relation to the intra- and postoperatively in each group (Figure 2). The HR was generally maintained intraoperatively but it decreased in relation to the baseline toward the end of the surgery, at 60 min, and postoperatively. (Figure 3) The RR was generally decreased in relation to the baseline in each group 15 min after drug administration and postoperatively. (Figure 4)

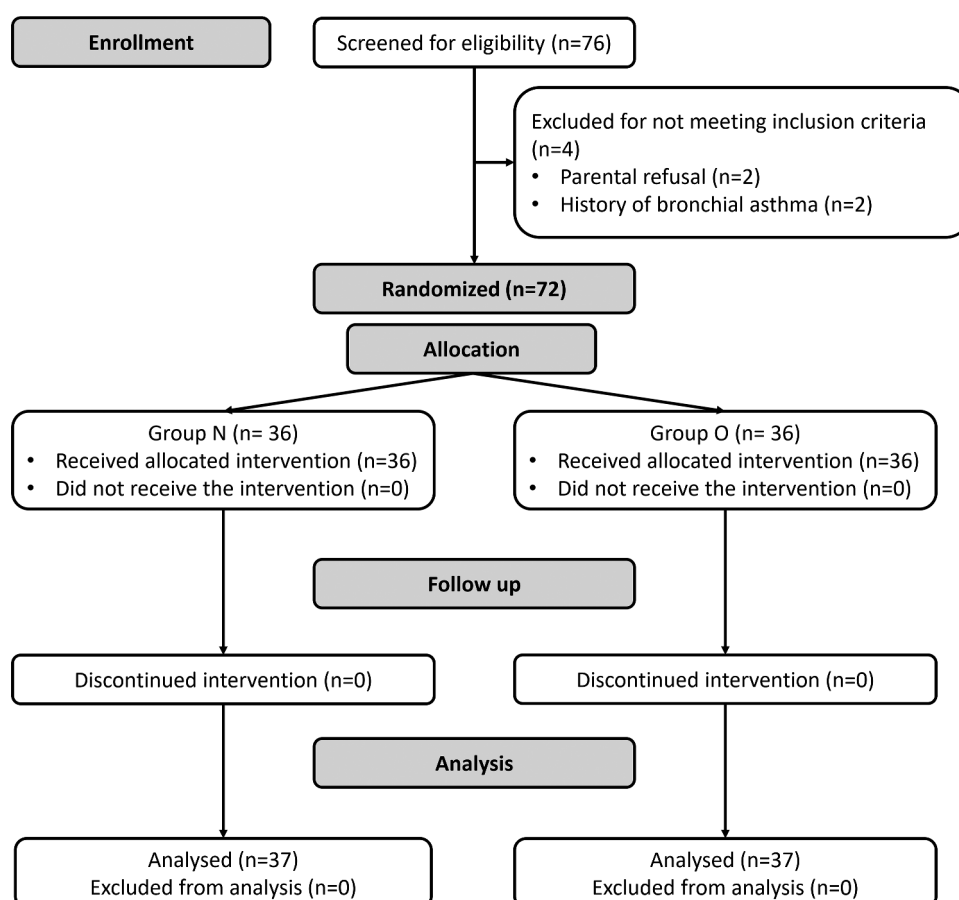


Figure 1. CONSORT's flowchart.

**Table 1.** Demographic data, clinical and surgical characteristics. Data presented as mean  $\pm$  standard deviation, median (quartiles), and frequency (%).

	Group N (n = 36)	Group O (n = 36)	P-value
Age (years)	3.0 (2.1, 5.6)	3.7 (2.0, 5.0)	0.735
Male sex	34 (94%)	31 (86%)	0.233
Weight (kg)	16 (13, 19)	16 (13, 19)	0.504
ASA-PS			0.239
I	33 (92%)	36 (100%)	0.239
II	3 (8%)	0 (0%)	0.239
Baseline heart rate (bpm)	133 $\pm$ 15	134 $\pm$ 15	0.721
Baseline mean arterial pressure (mmHg)	63 $\pm$ 6	64 $\pm$ 9	0.523
Baseline RR (breath per minute)	25 $\pm$ 5	24 $\pm$ 5	0.317
Baseline SpO <sub>2</sub> (%)	99 (99, 100)	99 (98, 100)	
Type of surgery			0.214
Hernia	18 (50%)	16 (44%)	
Circumcision	8 (22%)	10 (28%)	
Urological procedure	6 (17%)	2 (6%)	
Testicular surgery	3 (8%)	3 (8%)	
Dermoid cyst/thyroglossal cyst	0 (0%)	4 (11%)	
Perianal fistula	1 (3%)	0 (0%)	
Release finger	0 (0%)	1 (3%)	
Duration of surgery (min)	60 (60, 60)	60 (60, 60)	0.970

ASA-PS: American society of anesthesiologists-physical status, RR: respiratory rate, SpO<sub>2</sub>: peripheral oxygen saturation.

**Table 2.** Perioperative data. Data presented as median (quartiles), and frequency (%).

	Group N (n = 36)	Group O (n = 36)	P-value
Time to adequate sedation (min)	25 (16, 30)	20 (16, 30)	0.621
Tolerance to intervention			0.699
Excellent	24 (67%)	27 (75%)	
Good	2 (6%)	2 (6%)	
Fair	9 (25%)	7 (19%)	
Poor	1 (3%)	0 (0%)	
Ease of separation			0.556
Excellent	24 (67%)	20 (56%)	
Good	10 (28%)	11 (31%)	
Fair	2 (6%)	4 (11%)	
Poor	0 (0%)	1 (3%)	
Face-mask tolerance			0.438
Excellent	23 (64%)	17 (47%)	
Good	4 (11%)	4 (11%)	
Fair	7 (19%)	10 (28%)	
Poor	2 (6%)	5 (14%)	
Recovery time (min)	5 (3, 10)	5 (3, 8)	0.388
Complication			
Nausea and vomiting	1 (3%)	0 (0%)	1.000
Bradycardia	1 (3%)	0 (0%)	1.000
Laryngo-/bronchospasm	2 (6%)	1 (3%)	1.000
Hypotension	0	0	
Hypoxia	0	0	

#### 4. Discussion

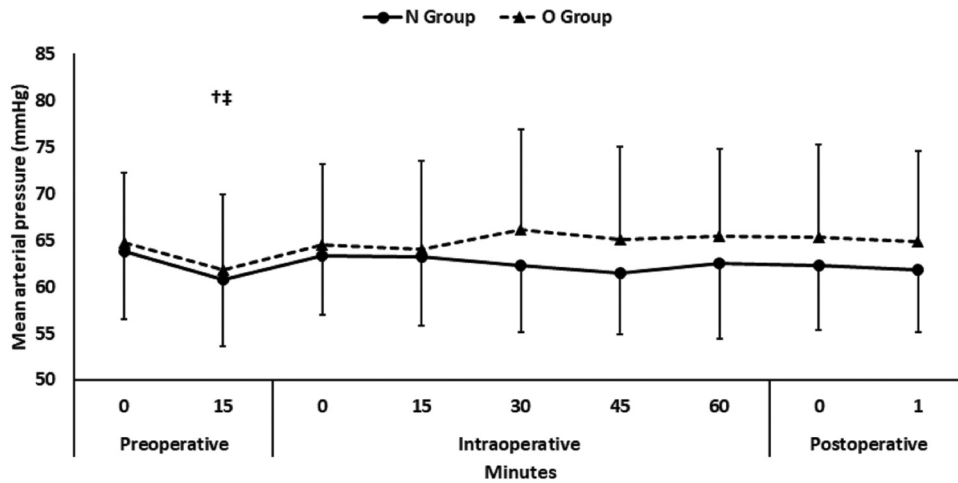
For pediatrics undergoing surgery, the preoperative period is full of anxiety and distress, fearing the unknown and parental separation [11]. This anxiety is likely to predispose to uncooperativeness and long-term behavioral alters like enuresis, nightmares, eating problems, and extreme fear of medical personnel and hospitals [12]. Because of its anxiolytic and amnesic properties, midazolam has been the most frequently used drug as a preoperative sedative in pediatric patients [13].

In a search for the easiest, most acceptable, and effective way to give midazolam to a child, the route of administration remained a great challenge for any anesthesiologist. Our study compared nebulized to oral midazolam as a painless and needleless route of drug administration for pre-anesthetic

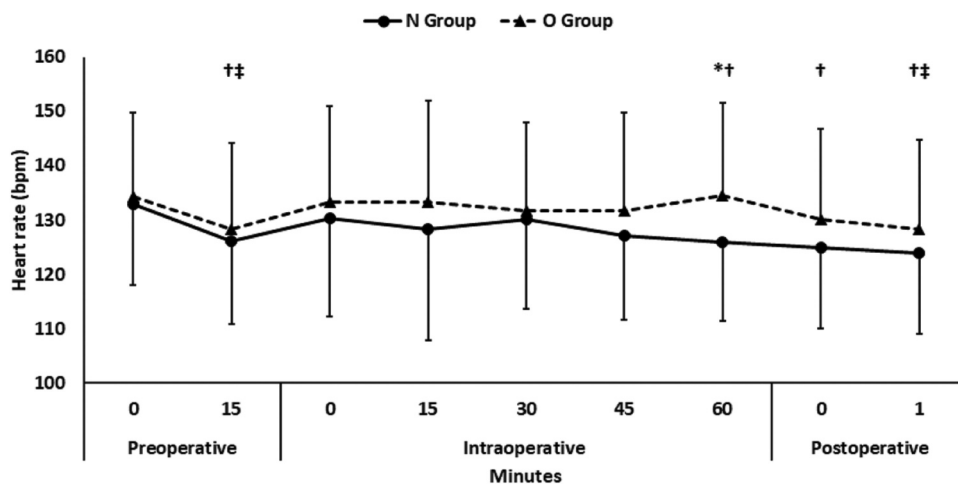
sedation in 72 ASA I, II children aged 2–6 years, undergoing general and urological surgical operations. In our study, we found no statistical difference between the two routes of administration which declares the nebulized midazolam as a good and accepted alternative preoperative route of sedation to oral midazolam.

Anisha D et al. [4] compared intranasal midazolam spray with placebo (normal saline) in 60 pediatric surgical patients. Like our study, they reached the target sedation score (RSS) in equivalent mean duration values, with no statistical difference. Mounika M et al. [5] compared sedation scores after nebulized and intravenous midazolam in 86 children and they also observed no statistical differences regarding the RSS.

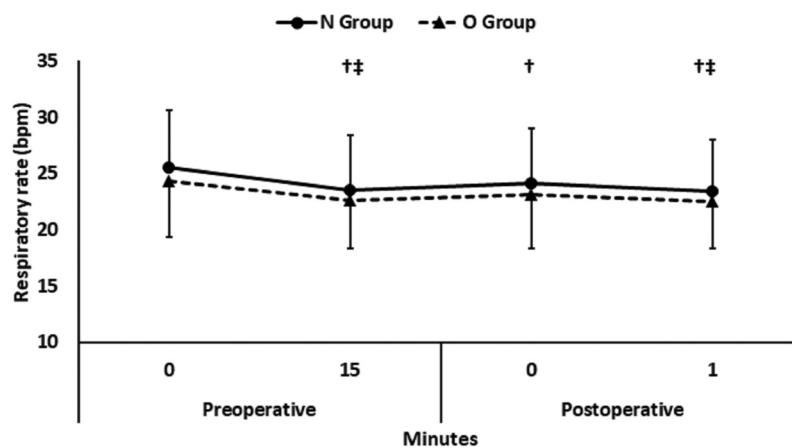
Deshmukh PV et al. [14] observed better acceptance in the oral group when comparing 60 pediatric



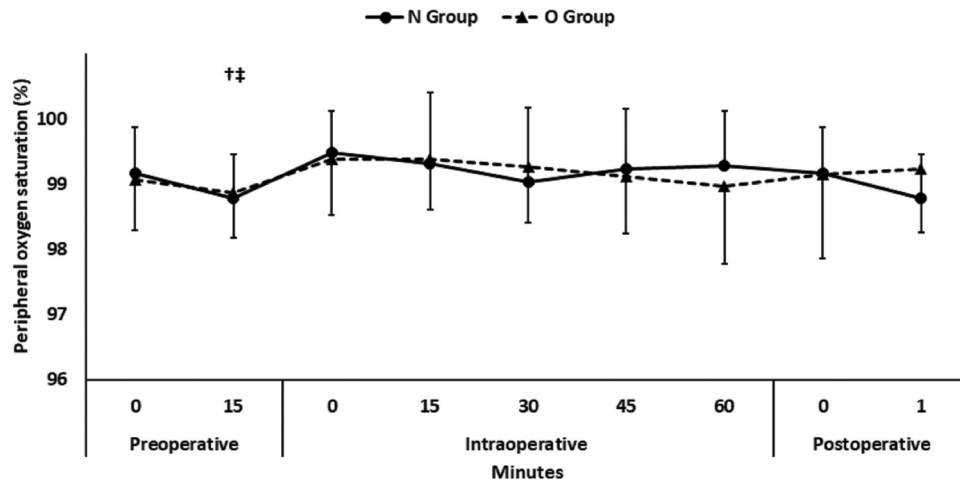
**Figure 2.** Perioperative mean arterial pressure. Markers are the means and error bars are the standard deviation. † denotes statistical significance compared to the baseline reading within the N group, ‡ denotes statistical significance compared to the baseline reading within the O group.



**Figure 3.** Perioperative heart rate. Markers are the means and error bars are the standard deviation. \*denotes significance between the two groups, † denotes statistical significance compared to the baseline reading within the N group, ‡ denotes statistical significance compared to the baseline reading within the O group.



**Figure 4.** Perioperative respiratory rate. Markers are the means and error bars are the standard deviation. † denotes statistical significance compared to the baseline reading within the N group, ‡ denotes statistical significance compared to the baseline reading within the O group.



**Figure 5.** Perioperative peripheral oxygen saturation. Markers are the means and error bars are the standard deviation. † denotes statistical significance compared to the baseline reading within the N group, ‡ denotes statistical significance compared to the baseline reading within the O group.

patients receiving oral and nasal midazolam as pre-anesthetic sedation. Similarly, Verma RK et al. [6] used the nasal spray midazolam as an alternative to oral midazolam in 60 children and found it less tolerable being more irritant and distressing when applying into the nasal cavity. In our study, we found the nebulized route to be as equally accepted as the oral one without any statistical difference, setting nebulized midazolam as a good alternative route to oral midazolam in pediatrics.

One of the most important criteria of a satisfactory preoperative sedative is its ability to facilitate the separation of the pediatric patient from his parent. We observed that nebulized midazolam as a route achieved effective sedation enough to facilitate smooth parental separation same as the oral route without any difference. Deshmukh PV et al. [14] noted the same when compared nasal to oral midazolam.

In our study, we evaluated MAP, HR, RR, and  $SPO_2$  at 15 minutes intervals preoperatively. There was a significant decrease in mean values in MAP, HR and RR from baseline in both groups, but this decrease showed no significant difference between the two groups. Mounika M et al. [5] found the same in their study when comparing MAP and Özmert S et al. [15] stated a similar outcome when evaluated the sedative effect of midazolam administered via three different routes (oral, nasal, and rectal) during cytometry in 124 children. Deshmukh PV et al. [14] as well discovered the same result when comparing HR. On the other hand, McCormick AS et al. [7] observed higher diastolic and systolic pressure when studied plasma concentrations and sedation scores after applying nebulized and intranasal midazolam in 10 adult cases. These findings were attributed to the discomfort caused by the nasal route of administration.

Tavassoli-Hojjati S et al. [16] compared Oral and Buccal Midazolam for Pediatric Dental Sedation for its efficacy, acceptance, and safety. Although they studied different routes of midazolam administration than ours, identically, no significant differences were found in oxygen saturation between the two methods.

Deshmukh PV et al. [14] demonstrated, similar to our results, no statistical difference between oral midazolam and intranasal midazolam group regarding perioperative complications recorded as (nausea, vomiting, hypertension, and hypoxia). But on the contrary, they found significant nasal irritative symptoms in the intranasal midazolam group. Such a complication was not found in our study, giving the nebulized midazolam a privilege over the oral and nasal route of administration. The nebulized route for premedication in pediatric patients is not enough adopted by anesthesiologists and more drug combinations and dose adjustment studies are needed.

Our study has multiple strength points being a double-blinded randomized comparative research that was conducted on a considerable number of patients. It was done in a highly specialized well-equipped institute with properly trained staff to perform the research design, procedures, and deal with any raised complications.

Being executed on pediatric patients ASA I–II, excluding ASA III–IV and overweight children was considered a point of weakness. Furthermore, the intraoperative analgesia given might interfere with our postoperative measurements and assessment.

The nebulized route for premedication in pediatric patients is not enough adopted by anesthesiologists, more drug combinations and dose adjustment studies are required. Wider range of pediatric patients with different co-morbidities can be included in further research work.



## 5. Conclusion

We found that there was no statistical difference between nebulized and oral midazolam regarding time to reach adequate level of sedation, drug acceptance, peri-operative (hemodynamics, and side effects). We concluded that nebulized midazolam is an acceptable alternative to oral midazolam as a sedative premedication in pediatrics.

## Disclosure statement

No potential conflict of interest relevant to this article was reported.

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