Original Article

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Anaesthesia Section

Comparison between Oral Midazolam and Intranasal Midazolam for Sedative Premedication in Paediatric Patients: A Randomised Clinical Study

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ABSTRACT

Introduction: Preoperative anxiety in paediatric patients can complicate anaesthetic induction and recovery. Midazolam is a commonly used sedative, administered either orally or intranasally.

Aim: This study aimed to compare oral midazolam solution and intranasal midazolam spray for sedative premedication in paediatric patients.

Materials and Methods: The present randomised clinical study was conducted on 100 children undergoing elective surgeries. Participants were divided into two groups: Group O (n=50) received oral midazolam (0.5 mg/kg), and Group I (n=50) received intranasal midazolam spray (0.2 mg/kg). Sedation levels were measured at 5, 10, 15, and 20 minutes using a Five-Point Sedation Score. Additional parameters included drug acceptance, ease of parental separation, mask acceptance, venepuncture response, and postoperative recovery using the Modified Aldrete Score. Data was analysed with Statistical Package for Social Sciences (SPSS) v21 with quantitative variables by mean, median, standard deviation, and range .Qualitative variables by frequency and percentage; comparisons between groups were performed using two-tailed Student's t-tests for continuous data and Chi-square tests for categorical data, with a significance threshold of $p<0.05$.

Results: Baseline demographics were similar between groups ($p>0.05$). group I had a mean age of 2.9±2.54 years, and group O had 1.28±1.1 years. Gender distribution was nearly identical. group I showed significantly higher drug acceptance (50% good vs. 10% in group O; $p<0.001$), faster sedation onset, and superior sedation scores at 5, 10, and 15 minutes ($p<0.001$). Parental separation was smoother in group I (72% excellent vs. 40% in group O; $p=0.005$), as was mask acceptance (52% excellent vs. 40%; $p=0.016$). group I also demonstrated more favourable venepuncture responses (88% satisfactory vs. 68%; $p=0.016$). Postoperative recovery was faster and better in group I at all assessed intervals ($p<0.05$). Vital signs remained stable across both groups, with minimal adverse effects; only 6% in group I experienced mild nasal irritation.

Conclusion: Intranasal midazolam spray is superior to oral midazolam for paediatric preoperative sedation, providing quicker and deeper sedation, better cooperation during procedures, smoother recovery, and higher overall acceptance, with minimal side-effects. Larger studies with extended follow-up are recommended to further evaluate long-term safety and behavioural outcomes.

Keywords: Benzodiazepine, Paediatric anaesthesia, Preoperative anxiety, Sedation depth

INTRODUCTION

Preoperative anxiety in paediatric patients remains a significant concern, often leading to distress, poor cooperation, and difficulties during anaesthesia induction. Sedative premedication is essential to ease anxiety, facilitate smooth parental separation, and improve the overall anaesthesia experience. Midazolam, a commonly used sedative in children, offers anxiolytic, sedative, and amnestic effects. While the oral route has been traditionally preferred, the intranasal route is gaining popularity due to its rapid onset, ease of administration, and non-invasiveness. However, the optimal route for midazolam administration in children remains a topic of debate.

Some studies by Verma RK et al., and Nainegali SR et al., reported better acceptance with oral midazolam [1,2]. Others studies by Mayel M et al., and Shah MI et al., noted higher acceptance with intranasal midazolam [3,4]. Some studies by Shah MI et al., Mehdi I et al., Bhakta P et al., showed intranasal midazolam often had a faster onset and better sedation scores, but a few like Yildirim SV et al., found no significant difference [4-7]. Different studies used varying doses and delivery methods (spray, atomizer, syrup) which affects drug absorption and outcomes [1-3,5]. This variability creates ambiguity warranting further comparison. Few studies assessed all relevant parameters- drug acceptance, sedation quality, parental separation, venepuncture response, mask acceptance, recovery profile, and side-effects in a single, unified trial [8,9]. This motivated the authors to conduct the present study to provide clearer clinical guidance for paediatric premedication.

Preoperative anxiety affects up to 65% of paediatric patients and can lead to emotional distress, complicate smoothness of anaesthetic induction, emergence from anaesthesia affecting psychological and postoperative outcomes [1]. Maladaptive behavioural responses such as general anxiety, night time crying, enuresis, separation anxiety occur in up to 44% of children two weeks after surgery. Twenty percent of these children will continue to demonstrate negative behaviour even six months after surgery [10-12]. The management of preoperative anxiety in children has thus become a crucial component of paediatric perioperative care, with pharmacological premedication emerging as a widely adopted strategy [13]. Being a short acting benzodiazepine, midazolam's rapid onset, short duration of action, sedative, anxiolytic, and amnestic properties have contributed to its widespread adoption for sedative paediatric premedication [14]. While oral midazolam is easy to administer and is commonly used, its bitter taste despite flavouring agents and reduced bioavailability due to first-pass metabolism limit its effectiveness [15]. Intranasal midazolam offers a

promising alternative, with faster absorption due to nasal mucosa's rich vascular plexus and ease of administration. Furthermore, the absence of first pass metabolism potentially allows for lower doses to achieve therapeutic effects and greater bioavailability [16]. This study compared oral and intranasal midazolam in paediatric surgical patients to determine the optimal route for premedication, focusing primarily on depth of sedation and ease of parental separation. Secondary outcome measures include acceptance of drug, response to venepuncture, ease of face mask induction and postoperative recovery.

MATERIALS AND METHODS

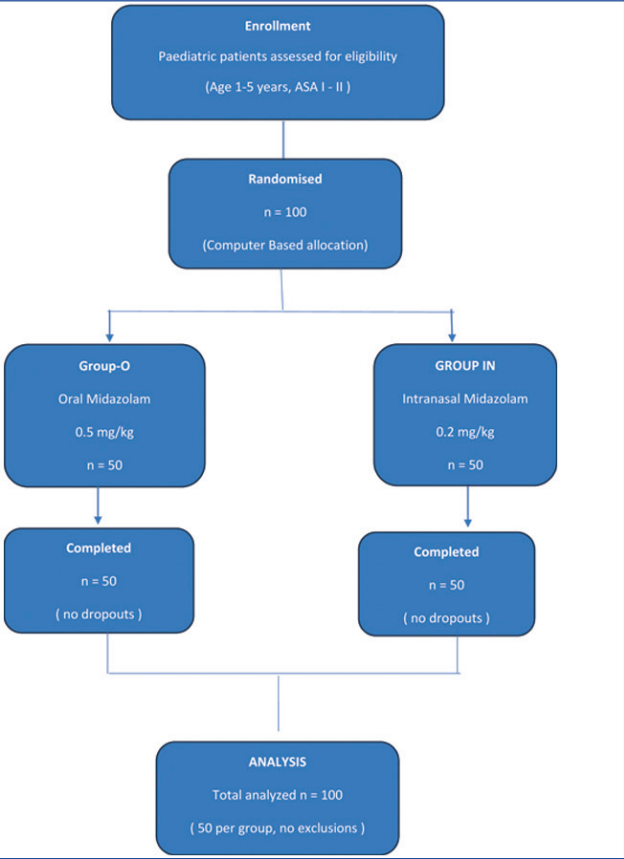
The present randomised clinical study was conducted from July 2024 to February 2025 at Dr DY Patil Hospital, Pune, Maharashtra, India. The study received ethical approval from the Institutional Ethical and Scientific Committee (Approval No. IESC/PGS/2023/144) and was registered with the Clinical Trials Registry of India (CTRI/2024/07/071230).

Sample size calculation: In a study conducted by Deshmukh PV et al, considering the mean SD of recovery score at 20 minutes of oral and intranasal midazolam as 0.6 and 0.8, mean difference as 0.4 with power of 80%, significance level at 5%, minimum sample size calculated to be 100 (50 for oral midazolam and 50 for intranasal midazolam) with the help of software WINPEPI 11.3 [8].

A total of 100 patients were randomly allocated to two equal groups. The allocation sequence was generated using a computer-based randomisation method, managed by an investigator not involved in clinical management or data collection to minimise the bias.

Group-O (Oral Midazolam group): recieved Midazolam orally in solution form in the dose 0.5 mg/kg from a 5 mg/mL ampoule.

Group-I (Intranasal Midazolam group): recieved Midazolam intransally in spray form in the dose 0.2 mg /kg from a 5 mg/mL atomiser spray with half the dose administered in each nostril (each spray delivering 0.1 mL or 0.5 mg) Similar dosages were used in other studies [8,9] [Table/Fig-1].



[Table/Fig-1]: Consort flow diagram.

Inclusion and Exclusion criteria: Patients aged 1-5 years of either sex undergoing routine paediatric surgeries under ASA grade I or II were enrolled. Informed written consent was taken from respective guardians. Eligible patients were haemodynamically stable with all routine investigations within normal limits Those patients, who had known allergy to study drugs, had ASA grade III or higher, had any nasal or gastrointestinal tract pathology, had history of cardiorespiratory disease, had preoperative heart rate <45 beats per minute or had renal and liver impairment and whose guardians were unwilling to participate and give consent, were excluded from the study.

Study Procedure

In the preoperative room, standard monitoring with pulse oximeter, 3-lead Electrocardiography (ECG) and non-invasive blood pressure monitoring was established. Baseline heart rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation were recorded.

For both groups, children were positioned sitting on their parent's lap facing forward. Parents gently restrained the child's arms with one hand while using the other hand to tilt the forehead back 15°. Group-O received prepared solution via 2 millilitre syringe orally, while group I received the medication through an atomised nasal spray by the attending anaesthesiologist. Drug acceptance was scored on a three-point scale[Table/Fig-2] [8].

Patient acceptance		Scores
Poor	Refused to accept medication	Score 1
Moderate	Accepted medication with difficulty	Score 2
Good	Accepted medication without complaint	Score 3

[Table/Fig-2]: Drug acceptance [8].

Patients were observed for any adverse effects like watering of eyes, nasal irritation, sneezing, nausea, vomiting and dizziness. Following drug administration heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, SpO_2 and degree of sedation was also assessed using a Five Point Sedation Score for 20 minutes at 5-minute intervals[Table/Fig-3] [9].

Sedation level	Criteria	Score
Agitated	Patient clinging to parents and/or crying	1
Alert	Patient is aware but not clinging to parent but not crying	2
Calm	Sitting or lying comfortably with spontaneous eye opening	3
Drowsy	Sitting or lying comfortably with eyes closed but respond to stimulation	4
Asleep	Eyes closed, arousable but does not respond to minor stimulation	5

[Table/Fig-3]: Five point sedation score [9].

After 20 minutes of drug administration, the child was separated from the parent to the operation theatre and ease of separation was noted under Parental Separation Score [Table/Fig-4] [8,9].

Behaviour of the Child	Criteria	Score
Excellent	Patient unafraid, cooperative or Asleep	1
Good	Slight fear/crying, quiet with reassurance	2
Fair	Moderate fear and crying, not quiet with reassurance	3
Poor	Crying, need for restraint	4

[Table/Fig-4]: Parental Separation Score [8,9].

In the operating room, standard monitors were attached and i.v. cannulation was attempted. Response to venepuncture during i.v. cannulation was then assessed as either satisfactory (score 2) or unsatisfactory (score 1) [Table/Fig-5] [9].

Reaction to venepuncture	Criteria
If the child showed no response or winced or whimpered	Satisfactory demeanour
If the child cried or behaved in a violent manner	Unsatisfactory demeanour

[Table/Fig-5]: Reaction to venepuncture [9].

Inhalational induction was started uniformly with oxygen and sevoflurane. Meanwhile mask acceptance was assessed using a three-point criteria [Table/Fig-6] [8].

Quality of anaesthetic induction	Score	
Excellent	1	Satisfactory
Good	2	
Poor	3	Unsatisfactory

[Table/Fig-6]: Acceptance to mask [9].

Post-extubation vital signs were monitored and recovery until full awakening was assessed using the Modified Aldrete Score at 10-minute intervals for 30 minutes in the postoperative recovery room. Patients with a recovery score of 8 or higher were transferred to ward [Table/Fig-7] [9].

Parameter	Criteria	Score
Circulation	Bp±50mm Hg pre op	0
	Bp±20-50mm Hg pre op	1
	Bp±20 mm Hg	2
O2 saturation	Saturation, 90% even with supplemental O2	0
	Needs O2 inhalation to maintain O2 saturation >90%	1
	Maintain >92% on room air	2
Respiration	ApnoeicDyspnoea	0
	Shallow breathing	1
	Able to take deep breaths and cough	2
Consciousness	Non-responding	0
	Arousable on Calling	1
	Fully Awake	2
Activity	Able to move no extremities voluntarily or on command	0
	Able to move 2 extremities voluntarily or on command	1
	Able to move 4 extremities voluntarily or on command	2

[Table/Fig-7]: The Modified Alderte Score [9].

STATISTICAL ANALYSIS

Statistical analysis was conducted to assess the differences between group O (oral midazolam) and group I (intranasal midazolam) across various parameters. Data was entered in Microsoft Excel spread sheet and analysed using SPSS version 21. Results were presented in tabular and graphical forms mean, median, standard deviation and ranges were calculated for quantitative data. Qualitative data were expressed in terms of frequency and percentages. Student t-test (Two Tailed) was used to test the significance of mean and p-value <0.05 was considered statistically significant. Categorical variables like gender and ASA classification were compared using the Chi-square test, also with significance set at a p-value of less than 0.05.

RESULTS

Age: Age Groups and Gender Comparison in Study Groups: [Table/Fig-8] shows that the mean age of children in group I (intranasal midazolam) was 2.9 years with a standard deviation of 2.54, while in group O (oral midazolam) it was 1.28 years with a standard deviation of 1.1. The p-value was 'non-significant' between the groups since it was >0.05 with p=0.79.

The age distribution in both groups, with 66% of children in group I and 74% in group O falling within the 1-3 years age range, while 34% in group I and 26% in group O were in the 4-5 years range,

Variables	Group I (n=50)	Group O (n=50)	p-value
Age			
Mean age	2.9	1.28	0.79
Standard deviation	2.54	1.1	
Age groups (in years)			
1-3	33 (66%)	37 (74%)	0.38
4-5	17 (34%)	13 (26%)	
Gender			
Female	27 (54%)	24 (48%)	0.54
Male	23 (46%)	26 (52%)	

[Table/Fig-8]: Comparison of two groups according to age, age groups and gender.

The p-value was 'non-significant' between the groups since it was more than 0.05 with p=0.38.

Gender distribution was identical in both groups, with 54% female and 46% male patients in group I and 48% males and 52% females in group O (p=0.54). The p-value was 'non-significant' between the groups since it was more than 0.05 with p=0.54.

Baseline Vitals: [Table/Fig-9] demonstrates baseline heart rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation.

Baseline (Mean+SD)	Group I (n=50)	Group O (n=50)
Heart rate	114.7±5.1	114.3±5.1
Systolic blood pressure	98.9±4.4	97.9±4.5
Diastolic blood pressure	65.4±2.9	64.6±3.1
Respiratory rate	24.7±2.3	24.8±2.2
Oxygen saturation	24.7±2.3	24.8±2.2

[Table/Fig-9]: Baseline vitals.

Comparison of Groups According to Acceptance of Drug: [Table/Fig-10] demonstrates acceptance of drug between groups. Group-I shows better overall acceptance (50% good, 38% moderate, 12% poor) compared to group O (10% good, 30% moderate, 60% poor). Both differences were statistically significant (p<0.001).

Acceptance of drug	Group I (n=50)	Group O (n=50)	p-value
Poor	6 (12%)	30 (60%)	<0.001
Moderate	19 (38%)	15 (30%)	
Good	25 (50%)	5 (10%)	

[Table/Fig-10]: Comparison of groups according to acceptance of drug.

Heart rate, systolic BP, diastolic BP and oxygen saturation comparison in study groups: [Table/Fig-11] shows that heart rate distribution in the two groups and was comparable between both groups at baseline and throughout the 20-minute monitoring period at five minute intervals. The p-value was 'non-significant' between the two groups since all p-values >0.05, with no statistically significant differences at any point of time.

Systolic blood pressure was similar between groups at baseline and through the first 15 minutes, but at 20 minutes, group O had slightly higher readings compared to group I with a p-value 0.09. However, the p-value was 'non-significant' between the two groups since all p-values >0.05.

Diastolic blood pressure readings were comparable between both groups throughout all time points from baseline to 20 minutes at five minute intervals, with no statistically significant differences. The p-value was 'non-significant' between the groups since all p-values >0.05.

Oxygen saturation (SpO_2) levels were comparable between groups at most time points, but at 10 minutes, group O had statistically significant more levels (97.6±0.92) than group I (97±0.85). The p-value was 'significant' at 10 minutes between the groups since it was less than 0.05, with p=0.001.

Parameters	Group I (n=50)	Group O (n=50)	p-value
Heart rate (mean±SD)			
5 minutes	110.2±4.6	110.3±5.2	0.96
10 minutes	106.1±4.7	105.9±5.2	0.85
15 minutes	103.1±4.5	102.9±5.2	0.87
20 minutes	100.1±4.5	99.9±5.2	0.87
Systolic BP (mean±SD)			
5 minutes	96.7±3.6	96.7±3.7	0.95
10 minutes	94.3±3.7	94.22±4.1	0.91
15 minutes	92.3±3.6	92.4±3.9	0.93
20 minutes	91.4±3.5	92.9±5.2	0.09
Diastolic BP (mean±SD)			
5 minutes	63.02±3.04	62.2±2.8	0.17
10 minutes	62.4±3.01	61.5±3.1	0.12
15 minutes	61.5±2.8	60.6±2.5	0.08
20 minutes	60±3.1	59.5±3.1	0.43
SPO_2 (mean±SD)			
5 minutes	97.8±0.62	98.1±0.8	0.07
10 minutes	97±0.85	97.6±0.92	0.001
15 minutes	97.5±1.1	97.8±0.87	0.07
20 minutes	97.5±1.1	97.4±1.1	0.78
Respiratory rate (mean±SD)			
5 minutes	26.4±2.4	25.4±1.9	0.02
10 minutes	23.8±2.3	23.8±1.9	0.96
15 minutes	23.02±2.2	22.5±2.2	0.29
20 minutes	22.16±2	21.6±1.7	0.15

[Table/Fig-11]: Comparison of heart rate, systolic BP, diastolic BP and oxygen saturation between the two groups.

Respiratory rates groups from baseline to 20 minutes at five minute intervals which were similar between the two groups except at the 5-minute mark, where group I had a significantly higher rate (26.4±2.4) compared to group O (25.4±1.9). The p-value was 'significant' at five minutes between the groups since it was less than 0.05 with p=0.02.

Comparison of Sedation Scores between Groups: [Table/Fig-12] demonstrates the five point sedation score at 20 minutes after administration. The comparison showed a highly significant difference in sedation scores at five minutes, 10 minutes and 15 minutes between the two groups (p<0.001). However, the two groups were comparable at 20 minutes with respect to sedation scores (p>0.05) with more number of children being drowsy and asleep (21 and 13 in group I) unlike only (5 and no children in group O), respectively.

Comparison of Parental Separation Scores between Groups: [Table/Fig-13] shows that parental separation scores between groups.

Group-I demonstrates scores with 72% excellent and 26% good compared to group O which had 40% excellent, 44% good, 8% fair and 8% poor. These differences were statistically highly significant (p=0.005).

Parental separation scores	Group I (n=50)	Group O (n=50)	p-value
Excellent	36 (72%)	20 (40%)	0.005
Good	13 (26%)	22 (44%)	
Fair	1 (2%)	4 (8%)	
Poor	0	4 (8%)	

[Table/Fig-13]: Comparison of parental separation scores between groups.

Comparison of Acceptance of Mask Between Groups: [Table/Fig-14] shows mask acceptance between groups. It was significantly better in group I with 52% excellent and 44% good acceptance, while group O had 40% excellent, 36% good, and 24% poor mask acceptance. These differences were statistically significant (p=0.016).

Acceptance of mask	Group I (n=50)	Group O (n=50)	p-value
Excellent	26 (52%)	20 (40%)	0.016
Good	22 (44%)	18 (36%)	
Poor	2 (4%)	12 (24%)	

[Table/Fig-14]: Comparison of acceptance of mask between groups.

Comparison of Reaction to Venepuncture between Groups: [Table/Fig-15] demonstrates reaction to venepuncture between groups. Group-I shows a more favourable reaction with 88% satisfactory reactions compared to only 68% in group O. Both differences were statistically significant (p=0.016).

Reaction to venepuncture	Group I (n=50)	Group O (n=50)	p-value
Unsatisfactory	6 (12%)	16 (32%)	0.016
Satisfactory	44 (88%)	34 (68%)	

[Table/Fig-15]: Comparison of reaction to venepuncture between groups.

Comparison of Modified Alderte Score between Groups: [Table/Fig-16] shows Modified Aldrete recovery scores between groups. The recovery scores were significantly better in group I at all-time intervals. These differences were statistically significant at all time intervals as p=<0.001 at 0 minutes, p=<0.001 at 10 minutes, p=0.033 at 20 minutes and p=<0.001 at 30 minutes.

Modified Alderte score	0 min		10 min		20 min		30 min	
	I	O	I	O	I	O	I	O
7	31 (62%)	40 (80)%	6 (12%)	26 (52%)	0	0	0	0
8	19 (38%)	10 (20%)	30 (60%)	24 (48%)	8 (16%)	20 (40%)	00	2 (4%)
9	0	0	14 (28%)	0	24 (48%)	18 (36%)	2 (4%)	22 (44%)
10	0	0	0	0	18 (36%)	0	48 (96%)	26 (52%)
p-value	<0.001		<0.001		0.033		<0.001	

[Table/Fig-16]: Comparison of Modified Alderte Score between the two groups. All 100 patients were transferred to ward. group I were transferred earlier as they achieved a higher postoperative recovery score faster than those in group O

Comparison of Side-Effects among the Two Groups: [Table/Fig-17] reveals that side-effects were comparable between groups (p>0.05).

Sedation Scores	Basal		5 min		10 min		15 min		20 min	
	I	O	I	O	I	O	I	O	I	O
Agitated	36 (72%)	38 (76%)	0	31 (62%)	0	24 (48%)	0	16 (32%)	0	13 (26%)
Alert	14 (28%)	12 (24%)	15 (30%)	19 (38%)	3 (6%)	16 (32%)	0	11 (22%)	0	12 (24%)
Calm	0	0	34 (68%)	0	30 (60%)	10 (20%)	24 (48%)	18 (36%)	16 (32%)	20 (40%)
Drowsy	0	0	1 (2%)	0	15 (30%)	0	21 (42%)	5 (10%)	21 (42%)	5 (10%)
Asleep	0	0	0	0	2 (4%)	0	5 (10%)	0	13 (26%)	0
p-value	0.99		<0.001		<0.001		<0.001		0.293	

[Table/Fig-12]: Comparison of sedation scores between groups.

Side-effects	Group I (n=50)	Group O (n=50)	p-value
Nausea	0	1(2%)	0.671
Vomiting	0	0	
Hypotension	0	0	
Bradycardia	0	0	
Hypoxia	0	0	
Nasal irritation	3 (6%)	0	
Absent	47 (94%)	49 (98%)	

[Table/Fig-17]: Comparison of side-effects among the two groups.

DISSCUSION

Effective premedication strategy in paediatric patients is crucial to facilitate smooth perioperative transitions. An ideal premedicant should have rapid onset, predictable duration and rapid recovery. Midazolam is one such potent benzodiazepine [17,18]. The present study aimed to compare the efficacy of oral and intranasal midazolam as sedative premedication in paediatric patients. The results provide valuable insights into the onset of sedation, patient acceptance, perioperative behaviour, and recovery outcomes associated with both routes. By analysing these parameters, we can better understand the practical implications of each method in clinical practice and determine the more effective and child-friendly approach to preoperative anxiolysis.

The demographic characteristics of both groups were comparable in terms of age, gender distribution, and weight, indicating effective randomisation and minimising potential confounding factors. The mean age of children in group I was 2.9±2.54 years compared to 1.28±1.1 years in group O (p=0.79), with the majority of children in both groups falling within the 1-3 years age range (66% in group I and 74% in group O). Gender distribution was identical in both groups with 54% female and 46% male patients in group I while 48% were females and 52% males in group O.

Intranasal midazolam spray demonstrated significantly better acceptance compared to oral midazolam solution. Oral liquid formulations have different flavours and sweeteners added to enhance their taste, making them more appealing to children. This variation in taste may influence their acceptance. However, since an oral liquid formulation of midazolam was not available in the pharmaceutical market, we had to use the injectable form for oral sedation.

Mehdi I compared intranasal midazolam spray with oral midazolam and found significantly better acceptance with the intranasal route (89.8% in group I versus 36.9% in group O, p<0.001) [5]. When using atomised spray devices that distribute the medication more effectively across the nasal mucosa, potentially reducing local irritation. The better acceptance of intranasal midazolam in our study may be attributed to several factors. First, the use of a spray formulation rather than drops may have resulted in more consistent and less irritating administration. Second, the unpleasant bitter taste of oral midazolam, likely contributed to poor acceptance despite attempts at flavour masking. Third, the volume of medication required for oral administration (typically larger than intranasal) may have presented additional challenges for young children.

The overall haemodynamic stability observed with both routes of midazolam administration in this study supports the safety profile of this agent for paediatric premedication.

The intranasal route demonstrated significantly faster onset of sedation compared to the oral route. At 5, 10 and 15 minutes after premedication, sedation scores were significantly higher in the intranasal group compared to oral group. However the two groups were comparable at 20 minutes with more number of children in group I being drowsy and asleep. Intranasal administration allows midazolam to be absorbed directly through the highly vascularised nasal mucosa, bypassing first-pass hepatic metabolism and resulting in more rapid and predictable onset of action. Oral midazolam, conversely, must undergo absorption through the gastrointestinal tract and first-pass metabolism, leading to variable bioavailability and delayed onset. Verma RK et al., reported similar findings in their comparative study, demonstrating that intranasal midazolam resulted in more effective sedation compared to oral administration, with peak sedation occurring approximately 10 minutes after intranasal delivery compared to 20-30 minutes after oral administration [1]. After five minutes of premedication, in intranasal group 15/30 children (50%) had score ≥3 and in oral midazolam group no children have sedation score ≥3.After 10 minutes of premedication, in intranasal group 28/30 children (93.4%) and in oral group 9/30 children (30%) had desirable sedation level (score ≥3). The intranasal group were sedated early (p<0.001) at 15 minutes but at 30 mins of premedication both groups were sedated (p >0.05). Mean sedation score at 5, 10, 15 min was more in intranasal midazolam group. But afterwards it was comparable in both groups. Similarly, Nainegali SR et al., found that the intranasal group was sedated significantly earlier (p<0.001) at 15 minutes, but at 30 minutes of premedication, both groups were comparably sedated (p>0.05) [2]. Patel MG documented that while both routes eventually produced satisfactory sedation by 20 minutes [19]. The earlier onset with intranasal administration represented a clinically important advantage, allowing for more predictable timing of parent-child separation and transfer to the operating room. Mehdi I et al., reported similar findings in their study of 66 patients, noting that the time to onset of sedation was 11 minutes with intranasal midazolam compared to 19 minutes with oral midazolam [5]. They found that sedation scores were significantly better with intranasal midazolam than oral midazolam at 10 minutes (p<0.001), 15 minutes (p<0.01) and 20 minutes (p<0.001). Similarly, Mayel M et al., reported that both routes provided effective sedation, but the onset was significantly faster with intranasal administration (p≤0.001) [3].

Group-I demonstrated a more favourable parental separation than group O (72% excellent vs 40% excellent). Our findings align with several previous studies. Nainegali SR et al., emphasised that the quality of separation was notably better in the intranasal group, with 72% achieving “excellent” separation versus only 40% in the oral group, suggesting a deeper level of anxiolysis with the intranasal route [2]. Deshmukh PV et al., observed that the quality of separation was better in the intranasal group, with a higher proportion of children showing excellent than merely good separation compared to the oral group [8]. Mehdi I et al., reported that parental separation scores were significantly better in the intranasal group compared to the oral group [5]. In the study conducted by Shah MI et al., only 9% of children in the intranasal group required restraint during separation compared to 26% in the oral group [4].

Similarly, mask acceptance was significantly better in group I. The findings of the study are consistent with studies conducted by Deshmukh PV et al., Kapdi M et al., and Patel MG et al., wherein the authors concluded better quality of mask acceptance with intranasal premedication [8,9,19]. The predictable anxiolysis achieved with intranasal midazolam appears to effectively mitigate separation anxiety and fear of mask application, two critical stress points in the paediatric perioperative experience.

The response to venepuncture serves as an objective measure of the anxiolytic and analgesic effects of premedication. The improved reaction to venepuncture in the intranasal group in our study likely reflects effective anxiolysis and potentially better amnestic effects due to more reliable plasma concentrations from intranasal midazolam. Ljungman G et al., reported similar findings, noting that children who received intranasal midazolam demonstrated significantly less distress during venous cannulation compared to those who received oral midazolam [20]. This finding has important implications for paediatric perioperative management, as venous access represents a significant source of distress for many children and can negatively impact the overall perioperative experience.

Significantly better Modified Aldrete scores were attained faster in the intranasal midazolam group in our study. More children attained a score more than 8 at 10 minutes and 20 minutes as compare to group O. A total of 96% in the group I attained a modified alderete score of 10 whereas only 52% attained a score of 10 at 30 minutes and was highly significant. This difference in recovery profile is somewhat counterintuitive, as the higher bioavailability and potentially higher peak plasma concentrations with intranasal administration might be expected to result in more prolonged sedative effects. However, the better recovery profile in the intranasal group could potentially be explained by several factors. First, the more effective preoperative anxiolysis achieved with intranasal midazolam may have reduced the stress response to surgery, potentially resulting in lower anaesthetic requirements and consequently faster emergence. Second, the differential timing of peak plasma concentrations between the two routes (approximately 10-15 minutes for intranasal versus 20-30 minutes for oral) might have resulted in different midazolam concentrations at the time of emergence from anaesthesia. Third, the variability in absorption and bioavailability with oral administration might have led to more erratic recovery profiles in some children. Verma RK similarly reported more favourable recovery profiles with intranasal compared to oral midazolam, with shorter time to full alertness and discharge readiness [1]. In the study, conducted by Mehdi I et al., the level of recovery of Group N (median 3.00; mean: 2.73±0.45) was found to be higher as compared to group O (median: 2.00; mean: 1.97±0.47), and the difference in level of recovery between group O and Group N was found to be statistically highly significant ($p<0.001$) [5]. Both onset and recovery times were found to be significantly lower in intranasal as compared to intraoral group. The improved recovery profile with intranasal midazolam in this study represents an additional advantage of this route of administration, potentially facilitating earlier discharge and improving patient output in paediatric surgical settings.

The side-effect profiles observed in the present study suggest that both routes of midazolam administration are generally well-tolerated, with route-specific adverse effects that are generally mild and self-limiting. The lower overall incidence of side-effects with intranasal administration represents an additional advantage of this route in the paediatric population. The higher incidence of reported nasal discomfort with intranasal midazolam noted in our study is consistent with previous studies. In studies of Bhakta P et al., nasal irritation was observed in 20/31, nasal discomfort in 17/38 patients, respectively [6]. The study conducted by Deshmukh PV et al., reported that 40% patients had nasal irritation [8]. Patel MG et al., reported a transient nasal irritation in the form of rubbing of the nose, watering, sneezing and lacrimation was observed in 03/30 (10%) patients of Group N [19]. Kapdi MS et al., reported in INM group nasal irritation/congestion was observed in 2/30 (6.6%), sneezing in 1/30(3.3%) and watering of eye in 1/30(3.3%) of patients [9] while nausea and vomiting observed in 3/30(10%) of group OM patients. Only 2% patients in group O experienced nausea in our study. No other side-effects were observed. More serious adverse effects such as respiratory depression, excessive sedation, bradycardia and vomiting which have been occasionally reported with midazolam administration were notably absent in our study.

The intranasal midazolam atomised spray produced faster sedation, anxiolytic and separation scores as compared to oral syrup, leading to more cooperation of the children facilitating smooth induction. Hence, intranasal midazolam atomiser spray can be preferred over oral midazolam syrup. However, its use may be limited by nasal discomfort which can be attributed to acidic pH (3.34). A more concentrated intranasal midazolam spray with lipophilic vehicle and neutral pH would improve its acceptability. Therefore nasal irritation can be minimised if a more concentrated form of midazolam in a lipophilic vehicle with a neutral pH became available, unlike the current formulation, which is in a hydrophilic vehicle with an acidic pH.

Limitation(s)

This study has several limitations. The narrow age range (1-5 years) restricts broader applicability, and the lack of pharmacokinetic data or long-term follow-up limits understanding of drug behaviour and post-discharge outcomes. Partial blinding may have introduced observer bias, and standardised dosing may not reflect optimal route-specific effects. Finally, factors such as parental anxiety, patient/parent satisfaction, alternative premedication strategies, and cost-effectiveness were not assessed, which could have provided a more comprehensive evaluation.

CONCLUSION(S)

Based on the findings of our study, we conclude that intranasal midazolam spray provides superior efficacy as a sedative premedication in paediatric patients when administered intranasally offering better drug acceptance, faster onset, deeper sedation, smoother parental separation, improved mask acceptance, more favourable response to venepuncture and a better recovery profile compared to the oral route. These benefits are particularly relevant in the clinical setting, where minimising procedural anxiety and facilitating smooth anaesthetic induction are primary goals of paediatric premedication. The technical simplicity of intranasal midazolam administration, combined with its predictable onset, haemodynamic stability and minimal side-effects, supports the overall safety profile and positions it as an excellent alternative for routine premedication in paediatric anaesthesia practice.

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