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Original Research Paper

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A COMPARATIVE STUDY OF ORAL MIDAZOLAM SYRUP AND INTRANASAL MIDAZOLAM SPRAY FOR SEDATIVE PREMEDICATION IN PEDIATRIC SURGERIES

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ABSTRACT

Background: Paediatric patients often exhibit significant anxiety prior to surgery, necessitating effective premedication to ease induction. Midazolam, a short-acting benzodiazepine, is widely used through various routes. **Objective:** To compare the efficacy of oral midazolam syrup and intranasal midazolam spray as sedative premedication in children aged 2–8 years undergoing elective surgeries. **Methods:** Sixty ASA I/II children scheduled for elective surgery were randomized into two groups: Group O received oral midazolam syrup (0.5 mg/kg), and Group N received intranasal midazolam spray (0.2 mg/kg). Sedation and anxiolysis were assessed at 10, 20, and 30 minutes post-administration. Parental separation, response to venepuncture, and mask acceptance were also evaluated. **Results Summary:** Intranasal midazolam demonstrated a significantly faster onset of sedation (8.43 ± 2.08 min) compared to oral midazolam (15.63 ± 2.82 min, $p<0.001$). Sedation and anxiolysis scores were consistently higher in the intranasal group across all time intervals. Though oral midazolam was slightly better accepted during parental separation and mask application, overall sedation efficacy favoured the intranasal route. **Conclusion:** Both oral and intranasal midazolam are safe and effective for paediatric premedication. However, intranasal midazolam provides faster onset and superior sedation scores, making it an ideal choice when rapid effect is desired.

KEYWORDS : Midazolam, intranasal, oral, paediatric sedation, premedication, anxiolysis, anaesthesia induction

INTRODUCTION:

Surgical procedures in paediatric populations often provoke significant anxiety, both in children and their parents. This preoperative stress can result in behavioural disturbances, increased anesthetic requirements, delayed recovery, and adverse postoperative outcomes. Children may exhibit fear of separation from caregivers, unfamiliar environments, or anticipated pain, all of which contribute to heightened psychological stress.

Anxiety before surgery is common among paediatric patients and can manifest in both physiological and psychological disturbances. Studies have shown that about 60% of children undergoing surgical procedures exhibit significant levels of preoperative anxiety, which can lead to adverse outcomes such as delayed recovery, increased analgesic requirements, and postoperative behavioural changes.[1,2]

Pharmacologic premedication plays a pivotal role in alleviating this anxiety, facilitating smoother anesthetic induction, and improving perioperative cooperation. Benzodiazepines, particularly midazolam, have been a cornerstone in paediatric premedication due to their anxiolytic, amnestic, and sedative properties. Midazolam's short half-life, rapid onset of action, and favourable safety profile make it particularly suitable for paediatric use.

Its effectiveness and safety profile have been well established.[3,4] Oral midazolam has been a traditional route of administration due to its ease of use, although it has a delayed onset of action and variable bioavailability owing to first-pass metabolism.[5]

Intranasal administration, in contrast, provides a non-invasive alternative with rapid systemic absorption through the nasal mucosa. This route bypasses first-pass metabolism and has been associated with a faster onset and more predictable sedation effects.[6,7] Despite some concerns about nasal irritation, intranasal midazolam is increasingly being used in paediatric anesthesia practice.

Recent advancements in intranasal drug delivery, such as atomized sprays, have enhanced the clinical utility of this route. These devices ensure better drug dispersion, higher bioavailability, and reduced discomfort compared to conventional droplet-based methods.

Despite its advantages, the intranasal route may cause transient nasal irritation, and some children may resist administration. Therefore, it remains important to weigh the benefits of rapid sedation against ease of administration and patient acceptability.

This study was undertaken to compare the efficacy of oral midazolam syrup and intranasal midazolam spray as sedative premedication in paediatric patients undergoing elective surgical procedures. It aimed to evaluate not only the onset and depth of sedation but also associated anxiolytic effects and procedural ease, including responses to parental separation, venepuncture, and mask application.

METHODS:

This prospective, randomized observational study was conducted over a period of two years at the Department of Anaesthesiology, D.Y. Patil University School of Medicine, Navi Mumbai, after obtaining ethical clearance from the institutional ethics committee. A total of 60 paediatric patients, aged 2–8 years, of ASA physical status I and II, scheduled for elective minor surgeries, were enrolled after obtaining informed consent from parents. Patients with history of hypersensitivity to benzodiazepines, neurological disorders and patients with upper respiratory tract infection or nasal pathology were excluded from the study

Randomization and Group Allocation: Patients were randomly divided into two groups using a computer-generated randomization table:

- **Group O:** Received oral midazolam syrup at a dose of 0.5

mg/kg. The bitter taste of the drug was masked with apple juice for better palatability.

- **Group N:** Received intranasal midazolam spray at a dose of 0.2 mg/kg using a metered-dose Insed Atomiser, with half the dose administered in each nostril for optimal mucosal absorption.

Sedation and anxiolysis scores were recorded at 10, 20, and 30 minutes post-administration. Cooperation during parental separation, venepuncture, and mask application was scored. Data were analysed using t-tests and chi-square tests, with $p<0.05$ considered significant.

Premedication Protocol: Children were kept nil per oral for at least 4 hours prior to the procedure. Written informed consent was obtained from parents. Baseline vitals were recorded. Premedication was administered 30 minutes before surgery. In Group O, the oral dose was administered in sitting position. In Group N, the dose was split equally between both nostrils with the child held in a slightly reclined head-down position for 2 minutes post-administration to facilitate absorption.

Monitoring And Observations: Children were continuously monitored for heart rate, oxygen saturation, and respiratory rate. Sedation and anxiolysis levels were assessed using standardized scoring systems at 10, 20, and 30 minutes post-premedication. Ease of parental separation, response to venepuncture, and mask acceptance were also evaluated.

Scoring Systems Used:

Score Type	Score 1	Score 2	Score 3	Score 4
Sedation Score	Alert/agitated	Alert/calm	Drowsy/responds to voice	Drowsy/easily arousable
Anxiolysis Score	Poor	Fair	Good	Excellent
Parental Separation Score	Strong refusal	Moderate resistance	Slight hesitation	Accepts readily
Venepuncture Response Score	Poor	Fair	Good	Excellent
Mask Acceptance Score	Poor	Fair	Good	Excellent

Statistical Analysis: Data were compiled and analysed using SPSS software. Continuous variables were expressed as mean ± standard deviation and compared using independent Student's t-test. Categorical data were analysed using Chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS:

The demographic characteristics of the two study groups, including age and weight, were statistically comparable. Group O had a mean age of 3.89 ± 1.44 years, while Group N had a mean age of 3.43 ± 1.41 years ($p = 0.213$). Similarly, the average weight was 12.10 ± 2.56 kg in Group O and 11.57 ± 2.34 kg in Group N ($p = 0.404$).

This homogeneity indicates that both groups were well-matched for baseline characteristics, minimizing potential confounders.

The time of onset of sedation (figure 1) was significantly faster in the intranasal group (Group N), averaging 8.43 ± 2.08 minutes, compared to 15.63 ± 2.82 minutes in the oral group (Group O), with a highly significant p-value of <0.001. This demonstrates the superior pharmacokinetics of intranasal midazolam, likely due to its faster systemic absorption and bypassing of first-pass hepatic metabolism.

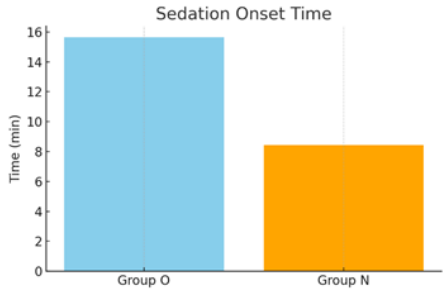

Figure 1 Time Of Onset Of Sedation

Sedation scores (figure 2) at all measured intervals—10, 20, and 30 minutes—were consistently higher in Group N. At 10 minutes, the sedation score was 2.57 ± 0.57 in Group N compared to 1.17 ± 0.38 in Group O ($p < 0.001$), indicating that the intranasal group achieved meaningful sedation much earlier. At 20 minutes, Group N maintained significantly deeper sedation (3.23 ± 0.43) versus Group O (2.40 ± 0.81; $p < 0.001$). Even at 30 minutes, sedation remained superior in the intranasal group (3.77 ± 0.43) compared to the oral group (3.37 ± 0.56; $p = 0.003$).

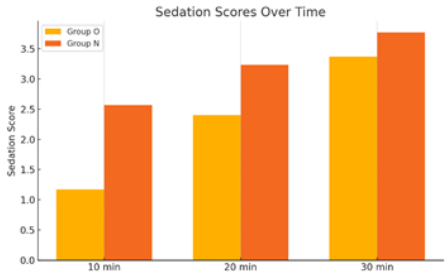

Figure2 Sedation score

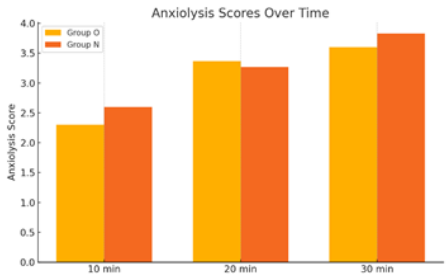

Figure 3 Anxiolysis Score

Anxiolysis scores (figure3) also showed a marginal but statistically significant advantage for the intranasal route at 30 minutes post-administration, with Group N scoring 3.83 ± 0.38 and Group O scoring 3.60 ± 0.50 ($p = 0.046$). This reflects a slightly enhanced anxiolytic effect with intranasal midazolam.

Regarding parental separation, the average score was 3.43 ± 0.50 in Group O and 3.17 ± 0.53 in Group N, with a p-value of 0.051. Although not statistically significant, this suggests slightly better cooperation in the oral group during separation from parents. Similarly, for venepuncture response, Group N had a marginally higher score (3.53 ± 0.51) compared to Group O (3.33 ± 0.61), with a p-value of 0.171, which is not significant. Finally, mask application scores were comparable between groups (3.80 ± 0.41 for Group O and 3.67 ± 0.48 for Group N; $p = 0.250$), indicating that both routes facilitated satisfactory cooperation during anaesthetic induction.

These findings collectively highlight the faster onset and greater depth of sedation with intranasal midazolam, without compromising safety or cooperation during key perioperative steps.

Table 1 Summary of Mean ± standard deviation with p-value of observed parameters

Observational Parameter	Group O (Oral)	Group N (Intranasal)	p-value
Age (years)	3.89 ± 1.44	3.43 ± 1.41	0.213
Weight (kg)	12.10 ± 2.56	11.57 ± 2.34	0.404
Time of Sedation (min)	15.63 ± 2.82	8.43 ± 2.08	<0.001
Sedation Score at 10 min	1.17 ± 0.38	2.57 ± 0.57	<0.001
Sedation Score at 20 min	2.40 ± 0.81	3.23 ± 0.43	<0.001
Sedation Score at 30 min	3.37 ± 0.56	3.77 ± 0.43	0.003
Anxiolysis Score at 30 min	3.60 ± 0.50	3.83 ± 0.38	0.046
Parental Separation Score	3.43 ± 0.50	3.17 ± 0.53	0.051
Venepuncture Response Score	3.33 ± 0.61	3.53 ± 0.51	0.171
Mask Application Score	3.80 ± 0.41	3.67 ± 0.48	0.250

DISCUSSION:

Preoperative anxiety in paediatric patients contributes significantly to perioperative stress, negatively affecting cooperation, increasing anesthetic requirements, and potentially leading to adverse psychological outcomes. Effective premedication ensures smoother induction and postoperative recovery.

This study establishes intranasal midazolam as a superior route in terms of pharmacodynamic efficacy. It produced a significantly faster onset of sedation and higher sedation scores at all evaluated intervals. This rapid onset can be attributed to the nasal route's avoidance of hepatic first-pass metabolism and its rich vascular plexus, facilitating faster systemic absorption.

Although intranasal midazolam showed superior clinical outcomes in sedation and anxiolysis, oral midazolam demonstrated marginally better patient cooperation during parental separation and mask application. This may be due to the ease of oral administration and lack of local irritation, making it more acceptable to children despite its slower onset. The findings of this study are consistent with previous literature demonstrating the clinical advantages of intranasal midazolam in paediatric anesthesia. Children undergoing surgery are particularly vulnerable to perioperative stress due to fear of separation, unfamiliar environments, and anticipation of pain, as described by Eckenhoff et al., who emphasized that preoperative anxiety is significantly associated with adverse postoperative behaviors.[1]

Midazolam, a short-acting benzodiazepine with high lipid solubility, is frequently utilized for its anxiolytic, sedative, and amnestic properties. The intranasal route facilitates rapid absorption through the richly vascular nasal mucosa, bypassing first-pass hepatic metabolism. Our findings align with those of Malinovsky et al., who demonstrated a faster rise in plasma concentrations and earlier peak effects with intranasal midazolam compared to oral or rectal routes.[3]

The significantly faster onset and higher sedation scores observed in Group N are corroborated by studies like those of Kogan et al. and Singh et al., which reported superior sedation outcomes with intranasal midazolam in paediatric populations.[5,6] Alex et al. similarly found that intranasal midazolam led to quicker onset of sedation than oral midazolam, with comparable safety profiles.[7]

The marginal advantage in anxiolysis scores at 30 minutes, though statistically significant, suggests that both routes are effective in reducing perioperative anxiety. This supports the findings by Shashikiran et al., who reported effective anxiolysis and sedation via both intramuscular and intranasal routes, with faster pharmacodynamic effects intranasally.[8]

Parental separation and cooperation during venepuncture and mask application were not significantly different between the two groups, echoing the findings by Alex et al. and Pradipta Bhakta et al., who noted that while intranasal midazolam acts faster, both administration routes yield similar behavioural cooperation during anesthesia induction.[4,7]

The mild nasal irritation noted with intranasal administration, although not formally quantified in our study, is a recognized limitation of this route and has been mentioned in earlier literature, such as in studies by Nainegali et al. and Verma et al. Improvements in formulation, including buffering and use of lipophilic vehicles, may further enhance the acceptability of intranasal midazolam.[9,10]

Clinical application of these findings suggests that intranasal midazolam is more suitable for situations requiring rapid sedation or when IV access is challenging. However, in settings where time permits, or when patient comfort and compliance are paramount, oral midazolam may be preferred.

In summary, the results of this study reaffirm that intranasal midazolam is an effective and well-tolerated alternative to oral midazolam for preoperative sedation in paediatric patients. Its rapid onset, satisfactory sedation and anxiolysis, and comparable cooperation during procedural steps make it a viable choice, particularly in situations demanding quicker premedication effects.

Limitations This study is limited by its small sample size and single-centre design, which may restrict generalizability. Nasal irritation in the intranasal group was not objectively scored. Subjective assessment tools for sedation and anxiolysis may introduce observer bias. Additionally, lack of pharmacokinetic data limits correlation between clinical effects and serum levels.

Conclusion Intranasal midazolam spray is a more effective option for rapid sedation in paediatric patients undergoing elective surgery compared to oral syrup. Both routes are safe and practical, with intranasal offering superior onset and depth of sedation.

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