Original Article

A Comparative Study of Intranasal Midazolam Spray and Oral Midazolam Syrup as Premedication in Pediatric Patients

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Abstract

Background: Preoperative preparation of children to alleviate the stress and anxiety related to surgery is an important aspect of balanced anesthesia care, it can not only affect the smoothness of induction and emergence from anesthesia but also the emotional and psychological make-up of the child, considering the pharmacological profile, midazolam is widely considered to be the ideal premedicant. The purpose of our prospective randomized observer-blinded study is to compare the effect of midazolam through oral and intranasal routes and determine the safer, more effective, and acceptable route by children. **Subjects and Methods:** Sixty patients aged 2–8 years, belonging to the American Society of Anesthesiologist I and II undergoing various surgeries were randomized into two groups of 30 each. Group O received 0.5 mg/kg of oral midazolam syrup, and Group N received 0.2 mg/kg of midazolam intranasal spray. Hemodynamic variables, sedation scores, ease of parental separation, and mask acceptance at the time of induction were studied. **Results:** Onset of sedation was shorter and the sedation scores were higher in intranasal group, separation from parents and acceptance to mask were satisfactory but statistically insignificant in both the groups. There was no statistical difference in hemodynamic parameters, and no major adverse effects were seen in either group. **Conclusion:** Both oral and intranasal midazolam are safe and effective as sedative premedication in children.

Key words: Intranasal spray, midazolam, oral, syrup

Introduction

The fear of experiencing pain, the physical environment of the hospital, unfamiliar personnel, parental separation, and several other stressors contribute to psychological distress and preoperative anxiety in children undergoing surgical interventions. The homeostatic disturbance secondary to sympathetic activation and neuroendocrine stress response does not only affect the smoothness of induction and emergence from anesthesia but also it is associated with several adverse postoperative outcomes. Maladaptive behavioural problems such as enuresis, eating disorders, and general anxiety are some of the consequences of preoperative anxiety,[1] negative behavioral changes, and psychological problems have presented days after surgery.[2]

Owing to its pharmacological profile, midazolam, a short-acting water-soluble benzodiazepine, serves as an ideal premedicant with its anxiolytic, sedative, hypnotic anterograde amnesic, and antiemetic effects.[3,4] Midazolam, being the most commonly used premedicant,[5] is administered through various routes such as oral, intramuscular, intravenous, rectal, and intranasal.

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The purpose of this study is to compare the alternative routes of administration and study the effects of midazolam through intranasal and oral routes, determine the safer, more effective, and acceptable route by children.

Subjects and Methods

After obtaining the Institutional ethical committee clearance, 60 pediatric patients aged between 2 and 8 years with American Society of Anesthesiologist (ASA) physical status I and II, undergoing various elective surgical procedures were included in our prospective, randomized, observer-blinded study.

The sample size was determined with a power of study at 80% and confidence interval at 95% to detect 25% difference in

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sedation scores between the two groups. Though the sample size of 27 was obtained, we selected 30 patients in each group to compensate for possible dropouts in our study.

Patients with respiratory and cardiac diseases, active respiratory tract infections, patients taking other sedative medications, and patients allergic to study drug were excluded from the study.

Thorough preoperative assessment was done on the previous day of surgery, study plan was explained to the parents/guardian, and informed consent was obtained. Patients were kept adequately nil per oral and no sedative premedicants were given before our study.

The next day, all patients were accompanied by their parent/guardian to the preoperative holding area of operation theater complex and were randomly allocated into two groups using a computer generated table.

- Group O received midazolam 0.5 mg/kg oral syrup
- Group N received intranasal midazolam 0.2 mg/kg.

Commercial preparation of oral midazolam syrup available at 2 mg/ml was administered orally at the dose of 0.5 mg/kg while patients were sitting on parents lap. Intranasal midazolam spray, commercially available as 0.5 mg/spray was administered at a dose of 0.2 mg/kg in supine position on parent's lap, where the total dose was divided equally into the half, for each nostril.

After obtaining baseline values, the study drug was prepared and administered by an independent anesthesiologist, not involved in the observation or administration of anesthesia and the attending anesthesiologist who was blinded to the route of administration observed and recorded the variables. Hemodynamic variables which included the heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), respiratory rate (RR), and peripheral capillary oxygen saturation (SpO_2) were observed every 5 min until 30 min after the administration of the study drug.

The degree of sedation was assessed every 5 min for 30 min using a five-point sedation scale.[6]

1. Agitated – Patient clinging to parent and/or crying
2. Alert – Patient is aware but not clinging to parent, may whimper but not cry
3. Calm – Sitting or lying comfortably with spontaneous eye opening
4. Drowsy – Sitting or lying comfortably with eyes closed, responding stimulation
5. Asleep – Eyes closed arousable but not responding to minor stimulation.

Where scores more than 3 were considered satisfactory sedation scores.

At 30 min patients were separated from their parent/guardian and parental separation was assessed using a four-point scale.[7]

1. Excellent – Happily separated
2. Good – Separated without crying
3. Fair – Separated with crying
4. Poor – Need for restraint.

Scores 1 and 2 were considered satisfactory parental separation.

And response to mask placement was studied at the time of induction using a five-point scale.[6]

1. Agitated and/or refuses mask
2. Alert and/or accepts mask on persuasion
3. Calm and accepts mask
4. Drowsy and accepts mask
5. Asleep.

A score of more than 3 was considered satisfactory mask placement.

Patients were induced with inhalation induction technique using facemask. Intravenous line was started after induction. After surgery, neuromuscular reversal and emergence from anesthesia, patients were monitored in the postanesthesia care unit for adverse effects.

Settings and design

Prospective, randomized, observer-blinded, comparative study.

Duration of study

July 2015 to August 2015.

Statistical analysis used

Results on continuous measurements are presented on mean ± SD (minimum to maximum), and results on categorical measurements are presented in *n* (%). Significance is assessed at 5% level of significance. Student's *t*-test (two-tailed, independent) to find the significance of study parameters on a continuous scale, intergroup analysis on metric parameters. Chi-square/Fisher Exact test for categorical scale between two groups.

$P < 0.05$ was suggestive of significance ($0.05 < P < 0.10$) and $P \leq 0.01$ as strongly significant.

Statistical softwares namely, SPSS 15.0, STATA 10.1, MedCalc 9.0.1 and R environment 2.11.1 were used for statistical analysis of the data. Microsoft word and excel have been used to generate graphs and tables. Manufacturers details: SPSS 15.0- IBM, MedCalc 9.0.1- Microsoft, Stata 10.1-StataCorp.

Results

The study was implemented on sixty pediatric patients aged between 2 and 8 years, who were randomly divided into two groups of thirty each. Group N received 0.2 mg/kg of intranasal midazolam spray, and Group O received 0.5 mg/kg oral midazolam syrup.

No statistical significance was observed in demographic data and ASA physical status distribution [Tables 1 and 2]. Vital and hemodynamic variables included SBP, DBP, RR, and SpO2 in both the groups were comparable and statistically not significant [Figures 1-3].

Sedation score analysis revealed a very high, statistically significant difference of $P = 0.00076$ at 5 min interval, further significant change in sedation score was observed until 10 min ($P = 0.030$), indicating a shorter onset of sedation in Group N. Comparable sedation scores at 15, 20, 25, and 30 min were observed in both the groups which were satisfactory but statistically insignificant [Figure 4].

86% of children in group N and 83% in Group O achieved satisfactory parental separation [Table 3] at 30 min, response to mask placement [Table 4] at the time of induction was also satisfactory but, did not reveal any significant difference ($P = 0.764$) between the two groups.

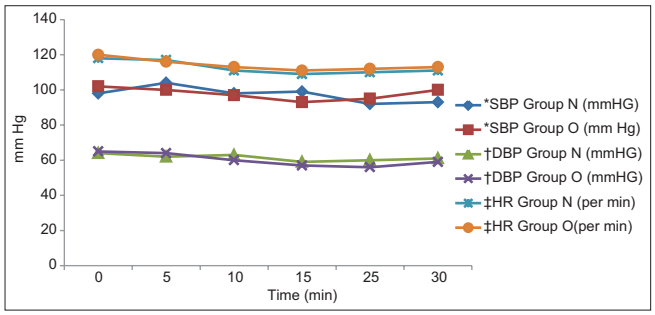

Figure 1: Distribution of hemodynamic variables between the two groups. *SBP: Systolic blood pressure, †DBP: Diastolic blood pressure, ‡HR: Heart rate, Group N: Intranasal midazolam, Group O: Oral midazolam

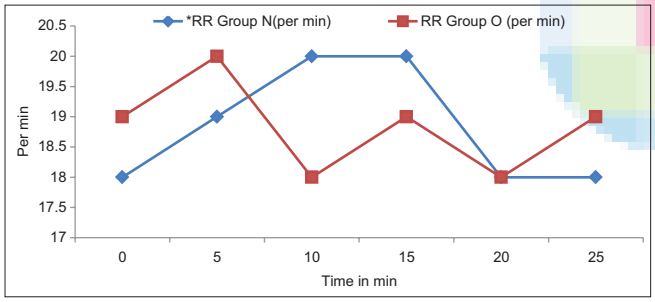

Figure 2: Distribution of respiratory rate between the two groups. *RR: Respiratory rate, Group N: Intranasal midazolam, Group O: Oral midazolam

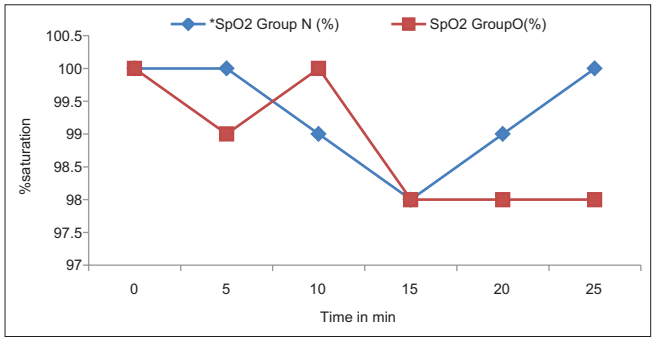

Figure 3: Distribution of SpO_2 between the two groups. *SpO_2: Peripheral arterial oxygen saturation, Group N: Intranasal midazolam, Group O: Oral midazolam

Discussion

Having the characteristics of an ideal premedicant, midazolam has time and again proven to be a safe and effective drug in alleviating preoperative anxiety, providing smooth transition from anesthesia, and preventing adverse postoperative outcomes.

Oral midazolam is the most commonly used premedicant in most parts of the world. Results from follow-up national

Table 1: Distribution of demographic data

	Mean±SD		*P*	*T*
	Group N*	Group O*		
Age (years)	3.03±0.92	3.36±1.25	0.259	1.138
Weight (kg)	13.13±2.71	13.9±3.33	0.327	0.987
Duration of surgery (min)	48.369.3	47.9±9.01	0.846	0.194
ASA grade† (I/II)	23/7	28/2	0.071	0.161
Gender (male/female)	21/9	17/13	0.284	0.617

*N: Intranasal midazolam, O: Oral midazolam, $P<0.05$ is significant. †ASA: American Society of Anesthesiologist, SD: Standard deviation

Table 2: Distribution of gender and American Society of Anesthesiologist physical status classification

	Group N*	Group O*	*P*	Chi-square statistic
ASA grade† (I/II)	23/7	28/2	0.071	0.161
Gender (male/female)	21/9	17/13	0.284	0.617

*N: Intranasal midazolam, O: Oral midazolam, †ASA: American Society of Anesthesiologist, $P<0.05$ is significant

Table 3: Response to parental separation

	Group N*		Group O*	
Score	Number of patients	Percentage	Number of patients	Percentage
Excellent	14	46.66	12	36.66
Good	12	40	14	46.6
Fair	3	10	5	16.6
Poor	1	3.33	0	0

*N: Intranasal midazolam, O: Oral midazolam, 86% Group N and in 83% Group O had satisfactory separation (scores 1 and 2). $P=0.616$ (not significant), $\chi^2=1.791$

Table 4: Response to mask placement

	Group N*		Group O*	
Score	Number of patients	Percentage	Number of patients	Percentage
1	1	3.33	0	0
2	4	13.33	5	16.66
3	9	30	11	36.66
4	13	43.33	10	33.33
5	3	10	4	13.33

*N: Intranasal midazolam, O: Oral midazolam, 83% in Group N and 82% in Group O with satisfactory mask acceptance (scores 3 and above). $P=0.764$ (not significant). $\chi^2=1.845$

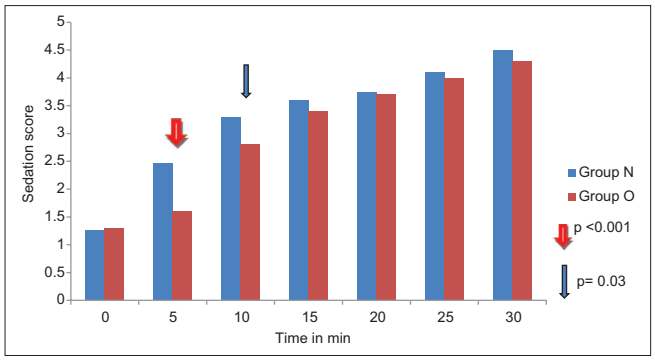

Figure 4: Distribution of sedation score between the two groups. Group N: Intranasal midazolam, Group O: Oral midazolam. $P < 0.001$ at 5 min interval (highly significant), $P = 0.030$ at 10 min interval (statistically significant)

survey evaluating trends in practice and use of preoperative sedation by McCann and Kain,[1] Kain *et al*.[5] indicate oral midazolam to be the most commonly used premedicant in pediatric age group.

Various studies suggest the dose of oral midazolam 0.5 mg/kg to be optimal for preesthetic sedation, effectively reducing the anxiety associated with parental separation and mask application.[8-10] Randomized, double-blind study conducted by McMillan *et al*.[11] on eighty pediatric patients where, different doses of midazolam 0.5, 0.75, and 1.0 mg/kg were compared to placebo, concluded 0.5 mg/kg to be effective in providing satisfactory sedation and anxiolysis scores, whereas doses of 0.75 and 1 mg/kg provided no additional benefit. In a similar study conducted by Feld *et al*.[10] evaluated the level of sedation, quality of separation from parents and used picture recall to assess amnesic effect on 124 children, who received three different doses oral midazolam, 0.25, 0.50, and 0.75 mg/kg also reported 0.5 mg/kg midazolam to be optimal and effective dose for pediatric outpatients. Hence, we used a dose of 0.5 mg/kg oral midazolam in our study.

Intranasal midazolam has emerged as an excellent alternative to intravenous, intramuscular, rectal, and other invasive routes in children, a dose of 0.2 mg/kg of intranasal midazolam was used in this study as various clinical trials have demonstrated the efficacy of intranasal dose of 0.2 mg/kg in providing optimal sedation and anxiolysis, without any adverse events.[6,12]

Studies comparing oral midazolam with other premedicants such as oral clonidine,[8] dexmedetomidine,[13] ketamine,[14] fentanyl,[15] and butorphanol[16] have inconclusive results and failed to be an effective alternative to midazolam. Furthermore, studies evaluating intranasal route of administration[17] also conclude midazolam to be safe and effective premedicant. Abrams *et al*.[18] in their randomized, double-blinded study comparing intranasal ketamine 3 mg/kg, sufentanil 1.5 or 1.0 mcg/kg, or midazolam 0.4 mg/kg - to evaluate sedation and ease of administration in 30 children aged of 17 and 62 months of age undergoing short dental procedures concluded intranasal midazolam to be an effective and acceptable premedicant, similar results were obtained in studies comparing intranasal midazolam with ketamine[19] and dexmedetomidine.[20]

The significant finding in our prospective, randomized, observer-blinded, clinical study was the rapid onset of sedation with intranasal group, satisfactory sedation scores (sedation scale score of more than 3) were observed at 10 min interval, where as a delayed onset of sedation was seen in the oral midazolam group which was in concordance with other studies.[21,22] This rapid onset of intranasal midazolam can be attributed to pharmacokinetic properties of midazolam where it is rapidly absorbed from highly vascular nasal mucosa into the systemic circulation, first pass hepatic metabolism is bypassed and therapeutic plasma and cerebrospinal fluid (CSF) concentrations are achieved rapidly. Animal studies show evidence of transfer of midazolam into the CSF from the olfactory mucosa, where the drug is absorbed through olfactory nerve cells as well as perineurial space around the olfactory cells.[23,24] Pharmacodynamic studies of intranasal midazolam administration in humans indicate a similar phenomenon;[25] however, further research is needed.

Our observations at 15, 20, 25, and 30 min intervals did not yield any significant differences, and both the groups were equally effective in providing satisfactory sedation. Parental separation which was assessed at 30 min and was satisfactory in both the groups with 86% in the intranasal group and 83% in oral group showed satisfactory parental separation and acceptance to mask placement at the time of induction (34 ± 2.75 min) was satisfactory in both the groups, which was comparable to many studies.[12,26,27]

Three patients in the intranasal group had bouts of sneezing and complained of nasal irritation immediately after administration of the drug, which subsided promptly without causing much discomfort and no major adverse events were observed in both the groups.

Assessment of hemodynamic variables included the HR, SBP DBP, and RR did not reveal any significant difference. Adverse events such as hypoxemia, hypotension, and apnoea were not observed in our study, postoperative periods were uneventful.

We feel our study was confounded by various nonpharmacological interventions such as the presence of parent/guardian facilitating drug administration, preparation visits, and demeanor of anesthesiologist may have influenced sedation and anxiety scores. A small sample size was also a limitation of our study.

Conclusion

To conclude, 0.2 mg/kg intranasal midazolam provides satisfactory and rapid onset of sedation compared to the oral route. And it is a safe and effective alternative to oral midazolam administration.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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