



Original Research Article

Intranasal midazolam versus intranasal ketamine as premedication in paediatric patients: A comparative study

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ABSTRACT

Aim: This study aims to compare the efficacy of intranasal midazolam and ketamine as premedication before anaesthesia in paediatric patients.

Materials and Methods: Sixty pediatric patients scheduled for surgery between the age group of 2-8 years and belonging to the American Society of Anesthesiologists (ASA) grade I and II were selected for the study. Group A received midazolam (0.2 mg/kg) and Group B received ketamine (5 mg/kg), intranasally 30 minutes before surgery with monitored anesthesia care. Sedation score, parenteral separation reaction, intravenous cannula acceptance, mask acceptance, and hemodynamic parameters were measured.

Results: Patients of both the groups were calm and tranquil, but sedation scores were higher in the ketamine group (3.37±0.67) in comparison to midazolam group (2.60±0.67) at 30 minutes. Parenteral separation was easier in ketamine group compared to midazolam group with a significantly higher separation reaction scores (p<0.05). Venous cannulation and face mask acceptance was also better in the ketamine group with a significantly higher percentage of patients with satisfactory venous cannulation and face mask acceptance (p<0.05). Non-invasive blood pressure, oxygen saturation, and respiratory rate were maintained in both the groups throughout the study period, however tachycardia was observed in the ketamine group.

Conclusion: Administration of the drug through the nasal route is an effective way for paediatric premedication. Both midazolam and ketamine gave a good level of sedation, however, level of sedation, venipuncture acceptance, and face mask acceptance were significantly better in the ketamine group. No adverse effects of the premedication drugs were observed in any of the groups.

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1. Introduction

Preoperative period is a stressful event for paediatric patients undergoing surgery. Young children are not able to fully comprehend the necessity of the surgery, so unlike grown-up patients, psychological preparation is not feasible in this age group. The fear of operation room, injections, and separation from parents before anesthesia produces traumatic experiences in the immature minds of the young patients and instigate the fear of physicians, nightmares, and post-operative behavioral changes.¹ In addition to the behavioral manifestations, preoperative anxiety activates the human stress response, leading to increased serum cortisol,

epinephrine, and natural killer cell activity.²

The only way to have a calm child before surgery is through the use of a proper preoperative medication.³ However, premedication in the pediatric age group also presents a challenging situation as the anxiety, experienced by child as well as the parent, is dual. The ideal premedication in children therefore should act rapidly with adequate sedation and analgesia, with less respiratory depression, no post-operative sickness, and should reduce the separation anxiety. Likewise, the ideal route of drug administration should be non-traumatic, less unpleasant, and should require little co-operation so that the parents are less apprehensive.^{2,3}

The commonly used premedicants in children are benzodiazepines like midazolam, opioids like fentanyl and

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sufentanil, phencyclidine derivative like ketamine, and short-acting barbiturates like pentobarbital, and alpha 2 adrenoreceptor agonist like clonidine, each having its own specific advantages and disadvantages. These premedicants can be delivered through oral, intramuscular (IM), rectal, and nasal routes.⁴ The intranasal route is a practical, relatively easy, and non-traumatic way to deliver a premedicant in paediatric patients. It provides a rapid onset of action due to rich blood supply of nasal mucosa and bypasses the first pass hepatic metabolism, which increases the bio-availability of the drug.^{5,6}

Midazolam is a water-soluble benzodiazepine with rapid onset, short duration of action, and it produces amnesia and allays anxiety.⁷ Ketamine is a phencyclidine derivative that antagonizes the N-methyl D-aspartate (NMDA) receptor which produces sedation with a trance-like state, analgesia, and preserves upper airway muscle tone and respiratory drive.⁸

The aim of our study was to evaluate and compare the efficacy of intranasal midazolam and intranasal ketamine as premedication in paediatric patients. To this aim, we compared the sedative effects of using intranasal midazolam and ketamine in young patients. We evaluated the intravenous cannula insertion, face mask acceptance, and parental separation reaction. We also assessed any adverse reactions to the drugs used in premedication.

2. Materials and Methods

The study was designed as a prospective, randomized, comparative, double blind study. After obtaining prior approval of Institutional Ethics Committee (Regn.No.ECR/306/Inst/WB/20B) 60 paediatric patients of age group 2-8 years belonging to the American Society of Anesthesiologists (ASA) grade I and II undergoing orthopaedic, ENT, or paediatric surgeries under general anaesthesia were selected for the study and were enrolled in the study after a thorough pre-operative examination and after obtaining written informed consent from the parents.

Children with a known drug allergy or hypersensitivity reaction to the drugs used for the study, children with mental retardation, nasal pathology, running nose, or those whose parents refused to participate in the study were excluded.

Patients were divided into two groups of 30 each using a randomization chart. Group A (n=30) patients received intranasal midazolam 0.2 mg/kg (injectable preparation in the concentration 5 mg/ml) and Group B (n=30) patients received intranasal ketamine 5 mg/kg (injectable preparation in the concentration of 50 mg/ml) 30 minutes before surgery.

An anaesthesiologist who was otherwise not participating in the study prepared the drugs into a ready to use form in identical syringes. The anaesthesiologist who administered the drug, examined the patients, and collected the data, as well as, the statistician who analyzed the data

were all unaware of the group allocation to exclude the possibility of subjective bias.

The medication was administered in both the nostrils using a 2 ml syringe from which the needle was removed and a lectro-cath was attached, which was shortened in length by cutting the tip. The children were made to lie in their parents' lap and the drug was administered very slowly to avoid the anterior and posterior spillage. After administration of the drug patients were kept supine. All the resuscitation and monitoring equipments were kept ready before administration of pre-medication and baseline heart rate (HR), respiratory rate (RR), oxygen saturation (SpO₂), non invasive blood pressure (NIBP) were recorded with a multichannel monitor.

After administration of the drug the degree of sedation was noted at 15 minutes and 30 minutes. HR, RR, SpO₂, NIBP were noted every 10th minute for 30 minutes. After 30 minutes children were separated from the parents and shifted to the operation theatre, reaction to separation from parents was assessed, IV canula was inserted and reaction to venous cannulation was recorded. After attaching the appropriate monitor lines (precordial stethoscope, electrocardiogram, NIBP, pulse oximeter) injection glycopyrrolate 0.01 mg/kg was given and general anaesthesia was induced using sevoflurane 8% along with 100% oxygen. Simultaneously, the response to mask placement was assessed and recorded. Intubation was facilitated by atracurium besylate 0.4 mg/kg, fentanyl 2 mcg/kg was used for analgesia and maintenance was done with N₂O:O₂ (40:60) and sevoflurane. At the conclusion of surgery, reversal was done with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and extubation was done.

The parameters measured were:

1. Sedation score - recorded using a six point scale (Ramsay Sedation scale)
 - 1- Anxious, restless or both, 2- Co-operative, oriented and tranquil, 3- Response to commands, 4- Brisk response to stimulus, 5- Sluggish response to stimulus, 6- No response to stimulus.
2. Parental separation reaction – assessed using a four point scale
 - 1- Crying and difficult to separate, 2- Crying, but not clinging to parent, 3- Whimpers, easily reassured, 4- Co-operative or asleep, easy separation.
3. Intravenous cannulation acceptance - assessed using a four point scale
 - 1- Terrified or crying, 2- Fear of needle and not reassured, 3- Slight fear, easily reassured, 4- Accepts intravenous cannula readily. Scores of 1 or 2 were considered unsatisfactory, while the scores of 3 or 4 were considered as satisfactory acceptance.
4. Face mask acceptance - assessed using a four point scale
 - 1- Struggling and crying, 2- Crying but not struggling,

3- Whimpers, reassured easily, 4- Calm, accepts face mask readily. Scores of 1 or 2 were considered unsatisfactory, while the scores of 3 or 4 were considered as satisfactory acceptance.

5. Haemodynamic parameters including, HR, NIBP, RR and SpO₂.
6. Adverse effects, if any.

2.1. Statistical analysis

Statistical analysis was performed with help of Epi Info which is a trademark of the Centers for Disease Control and Prevention (CDC). Corrected Chi square test was used in case of any one of the cell frequency less than 5 in the bivariate frequency distribution. Test of proportion (Z-test) was used to test the significant difference between two proportions. Student t-test was used to test the significant difference between means. $p\text{-value} \leq 0.05$ was considered statistically significant.

3. Results

The administration of medication was successful in all the children even though a mild resistance was observed in younger patients. Older children complained of a bitter taste but none of them vomited. The demographic variables including age, weight, and gender distribution were comparable in both the groups (Table 1).

The baseline heart rate of the two groups was comparable. However, the mean heart rate of patients of group who received ketamine was significantly higher than those of the group who received midazolam at 10, 20 and 30 minutes ($p < 0.01$) (Table 2). There was no significant difference in the systolic blood pressure and respiratory rate between the two groups (Table 2). There were no significant changes in the oxygen saturation of patients of both the groups throughout the study period (Table 2).

Most of the children were co-operative, oriented, tranquil, and responded to verbal commands at 15 minutes in both the groups, with comparable Ramsay sedation scores of 1.93 ± 0.83 in midazolam group and 2.33 ± 0.80 in ketamine group. The sedation scores were however significantly higher in the ketamine group at the end of 30 minutes ($p < 0.001$) (Table 3). The parental separation of the group of patients who received ketamine was easier. The mean parental separation score of patients receiving ketamine (2.67 ± 0.74) as premedication was significantly higher than the patients who received midazolam (1.53 ± 0.51) ($p < 0.002$) (Table 4).

Acceptance to intravenous cannulation was satisfactory in only 13.3% patients in midazolam group, while it was satisfactory in 49.3% patients in ketamine group and the difference was significant ($p < 0.05$). None of the patients in the study groups had poor acceptance to mask. Satisfactory face mask acceptance was observed in 30% patients in the

midazolam group while in the ketamine group face mask acceptance was good in 63.30% patients and the difference was significant ($p < 0.05$) (Table 5).

4. Discussion

Without proper premedication, children are difficult to separate from parents before surgery. They are fearful of needle pricks and object to inhalational induction. Children of 2-8 years are especially vulnerable as their understanding is limited.^{1,2} Various drugs have been used through various routes as premedication for paediatric patients, each with its own set of advantages and disadvantages.^{4,9}

Although it is challenging to consider a single drug as an ideal premedicant, however, midazolam and ketamine have been very commonly tried for paediatric premedication through various routes.^{4,10} Midazolam has been used for premedication quite frequently through oral administration.^{11,12} Gutstein et al. used ketamine 3 mg/kg and 6 mg/kg for oral premedication. They found this route smooth, predictable, and satisfactory without significant side-effects.¹³ However, oral premedicants are frequently rejected by children even when palatable, and the drug has to undergo first pass metabolism, which decreases bioavailability and causes the late onset of desired action.¹⁰ Notably, the bioavailability of ketamine is reported to be only 16%, while for midazolam it is 27% when administered through oral route.^{7,8}

The intramuscular route involves an injection, and per rectal route involves an insertion of a tube, both of which are painful and traumatic interventions. The nasal route has an advantage of rapid absorption of the drug directly into the systemic circulation from an area rich in blood supply without the disadvantage of passing through the portal circulation. The onset of the desired drug action is rapid and reliable, and the procedure convenient and non-traumatic.^{9,10} Rawat et al. have studied the effect of intranasal midazolam in children between 3-5 years of age and found it to be very useful and safe.¹⁴ Weksler and Ovadia have also demonstrated the feasibility of intranasal ketamine for preoperative sedation.¹⁵

In the present study, 60 children were recruited, which were scheduled for various surgeries under general anaesthesia. The demographic parameters of the children in this study were comparable. Both groups belonged to a homogenous population keeping the demographic confounding factors to be minimal. In our study, the baseline mean pulse rate of the two groups was comparable, but the mean heart rate of the ketamine group was significantly higher at 15 minutes, which was persistent at 30 minutes. This effect is consistent with the results of Narendra et al., and is due to the known cardiovascular effect of ketamine owing to its sympathomimetic properties.^{16,17} No significant difference was observed in the non-invasive blood pressure between the two groups (Tables 3, 4 and 5).

Table 1: Comparison of demographic parameters of the patients of the study groups. Data is expressed as mean \pm standard deviation

Parameter	Group-A (n=30)	Group-B (n=30)	Test Statistic	p-value
Age (years)	4.97 \pm 2.09	5.53 \pm 2.15	$t_{58}=1.036$	0.31
Male	21(70%)	17(56.7%)		0.284
Female	9(30%)	13(43.3%)		
Weight (Kg)	15.17 \pm 3.71	14.77 \pm 4.02		0.691

Table 2: Oxygen saturation and hemodynamic changes in the study groups. Data is expressed as mean \pm standard deviation. * Significant (p<0.05)

	Group A (n=30)	Group B (n=30)
Oxygen Saturation (%) SpO ₂		
Baseline	98.03 \pm 0.85	98.13 \pm 0.86
10 minutes	97.03 \pm 0.81	97.33 \pm 0.76
20 minutes	98.03 \pm 0.81	98.07 \pm 0.78
30 minutes	98.03 \pm 0.65	98.15 \pm 0.76
Systolic Blood Pressure (mmHg)		
Baseline	97.51 \pm 4.53	97.34 \pm 3.57
10 minutes	97.19 \pm 4.36	97.43 \pm 3.81
20 minutes	94.46 \pm 2.25	95.34 \pm 3.59
30 minutes	90.25 \pm 2.17	92.74 \pm 3.09
Heart Rate (beats/min)		
Baseline	112.23 \pm 6.51	111.30 \pm 6.39
10 minutes	104.13 \pm 6.65	115.27 \pm 6.78*
20 minutes	108.00 \pm 6.71	117.17 \pm 6.63*
30 minutes	102.23 \pm 6.51	114.30 \pm 6.18*
Respiratory rate (Rate/min)		
Baseline	22.07 \pm 0.87	22.20 \pm 0.85
10 minutes	19.93 \pm 0.74	18.60 \pm 1.92
20 minutes	18.57 \pm 0.50	16.80 \pm 1.75
30 minutes	18.93 \pm 1.73	17.80 \pm 1.75

Table 3: Comparison of sedation score at different time of the study groups. Data is expressed as mean \pm standard deviation.

*Significant (p<0.05)

Sedation score	Group-A (n=30)	Group-B (n=30)	Test Statistic(t_{58})	p-value
At 0 minute	1.40 \pm 0.50	1.43 \pm 0.50	0.258	0.798 NS
After 15 Minutes	1.93 \pm 0.83	2.33 \pm 0.80	1.901	0.062 NS
After 30 Minutes	2.60 \pm 0.67	3.37 \pm 0.67	4.421	<0.001 *

Table 4: Comparison of parental separation score at 30 minutes of the study groups. Data is expressed as mean \pm standard deviation.* significant (p<0.05)

	Group-A (n=30)	Group-B (n=30)	Test Statistic(t_{58})	p-value
Parental separation score	1.53 \pm 0.51	2.67 \pm 0.74	3.257	0.002*

Table 5: Satisfactory intravenous cannulation and face mask acceptance in the study groups. Data is expressed as percentage. * significant (p<0.05)

	Group-A (n=30) (%)	Group-B (n=30) (%)	P value
Intravenous cannulation	13.30	49.30	0.021*
Face mask acceptance	30	63.3	0.037*

Our findings are consistent with the results previously reported by Narendra et al. and Audenaert et al.^{16,18}

None of the drugs produced any significant change in the respiration and oxygen saturation after premedication and throughout the observation duration. With lower doses used for premedication or sedation, significant respiratory depression does not occur. These findings are consistent with those of García-Velasco et al.¹⁹ and Wilton et al.⁶ One patient in the midazolam (2%) group showed a decrease in oxygen saturation to 90% after administration, which was reversed by oxygen supplementation through the face mask. Midazolam is known to depress both chemoreceptor response to hypoxia and ventilatory response to CO₂.

There was no significant difference in mean sedation score at 0 min. At 15 min, most of the patients were calm and tranquil, and the level of sedation between the two groups was not significantly different. However, the mean sedation score of the patients of ketamine group was significantly higher than that of the patients of midazolam after 30 minutes ($p < 0.01$). In their comparison, García-Velasco et al. found that with both the drugs significant sedation occurred in 10 min. However, the mean onset time is not mentioned in their study.¹⁹ Similarly, Wilton et al. concluded that intranasal midazolam in doses of 0.2 mg/kg and 0.3 mg/kg produced sedation, which was comparable and better than placebo.⁶ Rawat et al. have demonstrated satisfactory sedation with 0.2 mg/kg intranasal midazolam compared to the placebo at 5 minutes of administration.¹⁴ Khatavker et al. reported that intranasal midazolam 0.2 mg/kg produced onset of sedation at 10.27 ± 3.35 minutes, which lasted for 20 minutes.²⁰ Although we have not measured the time of onset but our patients were calm and tranquil at 15 min. At 30 min the level of sedation in midazolam group was 2.60 ± 0.67 , which was more than at 15 min. A prolonged action of both drugs in our study might be due to accidental swallowing of the drug while being administered through nasal route. In the study by Narendra et al., children were asked to put their tongue out after administration of the nasal drug to prevent involuntary swallowing action but no such measure was taken in our study. Level of sedation was significantly higher in the ketamine group at 30 min. This variation may be due to the site and mechanism of action of the two drugs. The site of action of midazolam is locus coeruleus, where it induces electroencephalograph activity similar to natural sleep, but ketamine is a phencyclidine derivative that creates a trance-like dissociative state characterized by sedation, amnesia, analgesia, and catalepsy.^{7,8}

In line with previous findings, parental separation scores were significantly higher in the ketamine group. Diaz et al. had compared the outcome of intranasal ketamine premedication with placebo in paediatric outpatients and observed that ketamine premedication allows a pleasant and rapid separation of children from their parents, a ready acceptance of monitoring and mask inhalation induction.²¹

Gharde et al. in their study of efficacy of intranasal midazolam, ketamine and their mixture as premedication in children undergoing TOF repair, also reported ketamine to fare better, either alone or in mixture.²² Khatavkar et al. found the combination of ketamine and midazolam to be better than midazolam considering sedation, comfort, and venous cannula acceptance.²⁰

Response to venipuncture was significantly satisfactory in the ketamine group compared to the midazolam group. This observation can be attributed to the excellent analgesic properties of ketamine.²³ The absence of analgesia in midazolam group led to pain during insertion even in patients who were calm and tranquil, and hence the acceptance was not good. These findings correlate with the findings of Narendra et al., Gharde et al., and Mostafa et al.^{16,22,24} Face mask acceptance was significantly better in the ketamine group. The ability of ketamine to produce a trance-like dissociative state may be the reason for patients to be lesser aware of the mask on their faces. These observations are in contrast to the findings of Narendra et al. and García-Velasco et al. who did not observe any difference between the two groups regarding face mask acceptance.^{16,19} Another limitation associated with the use of ketamine is excessive salivation; however, in the present study, we did not observe salivation, which needed suction in any of the patients. All patients were given injection glycopyrrolate 0.1 mg/kg before induction. Weskler et al. and Agrawal N. et al. did not detect emergence reaction in any of the children receiving low dose intranasal ketamine.^{15,25} We have not observed the postoperative recovery and the emergence reaction in this study, which could be one of the limitations of this study.

5. Conclusion

Intranasal route is convenient and safe for premedication in children. Premedication with both intranasal ketamine and midazolam is effective for the purpose of sedation. Intranasal ketamine achieved better quality of sedation, enabling easier parental separation along with a better acceptance of venous cannulation and face mask induction.

6. Conflicts of Interest

There are no conflicts of interest.

7. Source of Funding

Nil.

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