Original Research Article

Comparative Study between Intranasal Midazolam and Ketamine as a Premedication in Pediatric Surgical Patients

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Abstract

Background: The preoperative period is a stressful event, especially in the pediatric patients. The goals of preanesthetic medication for children include allaying patient anxiety and facilitating the smooth induction of anaesthesia. For providing premedication to pediatric surgical patients, various drugs and many routes have been studied. Midazolam, a GABA receptor inhibitor, is the most commonly used sedative drug for premedication in children. It provides effective sedation, anxiolysis, and varying degrees of anterograde amnesia. 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. Intranasal route is one of the preferred route because of the ease of administration.

Aims & objectives: In this study, we compared the effects of intranasal midazolam and ketamine on preoperative sedation, parenteral separation, response to intravenous cannulation and mask acceptance in paediatric patients. **Materials & Methods:** Sixty children classified as ASA physical status I & II, aged between 2- 10 years, who were scheduled to undergo an elective surgeries, were enrolled for a prospective, randomized, and double-blind controlled trial. All of the children received intranasal premedication approximately 30 min before the induction of anaesthesia. Group M (n = 30) received 0.2 mg/kg of intranasal midazolam, and Group K (n = 30) received intranasal ketamine 5mg/kg. All of the patients were anesthetized with nitrous oxide, oxygen, and sevoflurane, administered via a face mask. **Results:** No significant differences were observed in demographic, hemodynamic, and respiratory parameters, however significant tachycardia was observed in the ketamine group. Intranasal ketamine results in more successful parental separation and yields a higher sedation score (3.87± 0.66) compared to midazolam group (2.62± 0.69) at 30 minutes, with negligible side effects. 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 ($p<0.05$). **Conclusion:** Intranasal ketamine is superior in decreasing anxiety upon separation from parents and providing satisfactory conditions during mask induction and venous cannulation. No adverse effects of the premedication drugs were observed in any of the groups.

Key words: premedication, anxiety, midazolam, ketamine and intranasal

Introduction

The perioperative period is a stressful event for the majority of individuals undergoing surgery and this is especially true in paediatric patients, owing to their limited understanding of nature of procedure and need of surgery. Anxiety during perioperative period in children can produce aggressive reactions, increased distress, tachycardia, hypertension, may prolong induction of anaesthesia, increased postoperative pain, postoperative behavioural changes, and postoperative agitation due to increased catecholamine levels.[1] Hence premedication facilitates by overcoming these difficulties.

The commonly used premedicants in children are benzodiazepines like midazolam, opioids like fentanyl and sufentanil, phencyclidine derivative like ketamine, short-acting barbiturates like pentobarbital, and α- 2 adrenoreceptor agonist like clonidine and dexmedetomidine, each having its own specific advantages and disadvantages. In this study we use midazolam and ketamine as premedicant by intranasal route.

Midazolam is a useful drug in pediatrics for situations where anxiolysis and amnesia are needed.[2,3] It is used intranasally in doses ranging from 0.2mg/kg to 0.5mg/kg. Midazolam has a number of beneficial effects when used as premedication in children such as good sedation, fast onset, and limited duration of action.[4,5] Though midazolam has a number of beneficial effects, it is far from an ideal premedicant having untoward side effects such as paradoxical reaction, respiratory depression, cognitive impairment, amnesia, and restlessness and has no analgesic action.[6] It is a great choice when anxiolysis is needed but analgesia is not the main focus.[7,8]

Intranasal ketamine is used as a sedative analgesic and a premedication agent. It can achieve an adequate level of sedation when administered intranasally in doses ranging from 0.5mg/kg to 5mg/kg for anesthetic preinduction. Its most common side effect is vomiting with no serious adverse events.[9]

These premedicants can be delivered through oral, intramuscular (IM), rectal, and nasal routes.[10] 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 high vascularity of nasal mucosa, wide absorption area, bypasses the first pass hepatic metabolism, which increases the bio-availability of the drug, avoidance of intravenous placement and high patient tolerance of drug administration.[11-13]

In this prospective, randomized, double-blind study, we compared intranasal midazolam 0.2 mg/kg and intranasal ketamine 5mg/kg in terms of demographic, hemodynamic and respiratory parameters; sedation level, parental separation score, intravenous cannulation and face mask acceptance. We also assessed any adverse reactions to the drugs used in premedication.

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Materials & Methods

After obtaining approval from the Institutional Ethical Committee and written informed consent from the parents or legal guardians of the patients after explaining the study protocol to them. This study included 60 American Society of Anaesthesiologists (ASA) Grades I and II patients, patients of either sex between 2–10 years of age who were scheduled for elective abdominal surgeries. Parent's refusal, ASA Grades III and IV, congenital heart disease, upper respiratory tract infection, and requiring emergency surgeries were excluded from the study.

Pre-anaesthetic assessment included medical and surgical history; general and systemic examination; airway examination; and required routine investigations conducted on an outpatient basis. On the day of surgery, the nil by mouth status was confirmed, and parental consent was obtained.

Patients were divided into two groups of 30 each using a randomization chart. To avoid bias, observers and attending anaesthesiologists were blinded to the study drug.

Group M (n=30) - received intranasal midazolam 0.2 mg/kg (injectable preparation in the concentration 5 mg/ml) via LMA-MAD 30 minutes before surgery.

Group K (n=30) - received intranasal ketamine 5 mg/kg (injectable preparation in the concentration of 50 mg/ml) via LMA-MAD 30 minutes before surgery.

The intranasal drug was dripped into both nostrils using a 2-mL syringe attached to **LMA-MAD atomization device, (Figure I)** with the patients in the recumbent position or in parent's lap in recovery area. 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 standard 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 level of sedation and reaction to separation from parents was assessed, IV canula was inserted and reaction to venous cannulation was recorded. After attaching the appropriate monitor lines (electrocardiogram, NIBP, pulse oximeter) injection glycopyrrolate 0.01 mg/kg was given and general anesthesia was induced using sevoflurane 8% along with 100% oxygen. Simultaneously, the response to mask placement was assessed and recorded. Intubation was facilitated by atracurium 0.5 mg/kg, fentanyl 2 µg/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.

Figure I: LMA-MAD with drug in syringe demonstration the mist formation and application on the patient

The parameters measured were:

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.

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.

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.

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.

Haemodynamic parameters including, HR, NIBP, RR and SpO2 and **adverse effects**, if any.

Results

The demographic variables including age, weight, and sex distribution were comparable in both the groups with a statistically insignificant difference (P<0.01). [Table I]

Table I Demographic variables of two groups

Parameters	Group M (n=30)	Group K (n=30)	P- value
Age (years)	3.87± 1.09	4.55± 2.13	0.421
Sex (male: female)	21: 3	17:13	0.284
Weight (kg)	14.17± 2.83	15.77± 1.04	0.595

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 II].

Table II Heart rate of patients in two study groups (Mean± S.D)

Heart Rate (beats/min)	Group M (n=30)	Group K (n=30)
Baseline	110.23±6.53	111.30±6.49
10 minutes	102.13±6.45	115.37±6.89
20 minutes	108.50±6.61	118±6.66
30 minutes	102.63±5.51	116.30±6.38

There was no significant difference in the systolic blood pressure and respiratory rate between the two groups [Table III & IV].

Table III Systolic blood pressure (mmHg) between the two groups

Systolic Blood Pressure (mmHg)	Group M (n=30)	Group K (n=30)
Baseline	97.51±4.53	97.34±3.57
10 minutes	97.19±4.36	97.43±3.81
20 minutes	94.46±2.25	95.34±3.59
30 minutes	90.25±2.17	92.74±3.09

Table IV Respiratory rate (RR) between the two groups

Respiratory rate (Rate/min)	Group M (n=30)	Group K (n=30)
Baseline	22.07±0.87	22.20±0.85
10 minutes	19.93±0.74	18.60±1.92
20 minutes	18.57±0.50	16.80±1.75
30 minutes	18.93±1.73	17.80±1.75

There were no significant changes in the oxygen saturation of patients of both the groups throughout the study period [Table V].

Table V Oxygen saturation (SPO2) of patients of both the groups

Oxygen Saturation (%) SpO2	Group M (n=30)	Group K (n=30)
Baseline	98.03±0.85	98.13±0.86
10 minutes	97.03±0.81	97.33±0.76
20 minutes	98.03±0.81	98.07±0.78
30 minutes	98.03±0.65	98.15±0.76

Sedation Score: Mean onset of sedation was faster in group M but at the time of induction i.e. 30 mins after premedication overall mean sedation score was better in group K (3.87± 0.66) compared to group M (2.62± 0.69), with a statistically significant p- value ($p < 0.05$). [Figure II]

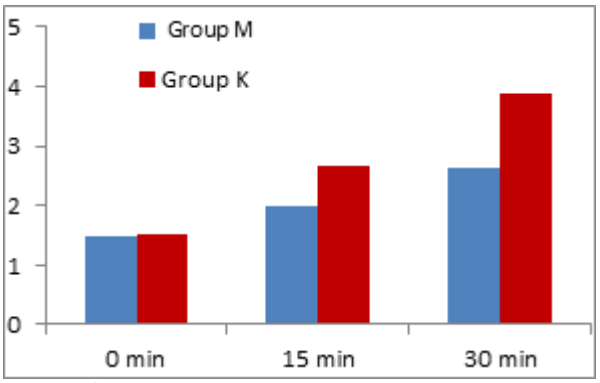

Figure II Comparison of mean sedation score between the two groups at the time of induction

Separation Score: The mean parental separation score of patients receiving ketamine (3.98 ± 0.76) as premedication was significantly higher than the patients who received midazolam (1.51± 0.76) ($p<0.002$) [Figure III].

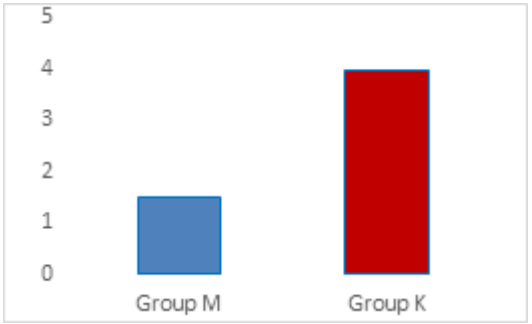

Figure III Comparison of mean separation score between the two study groups

Acceptance to intravenous cannulation was satisfactory in only 13.59% patients in midazolam group, while it was satisfactory in 52.3% patients in ketamine group and the difference was significant ($p<0.05$). [Figure IV]

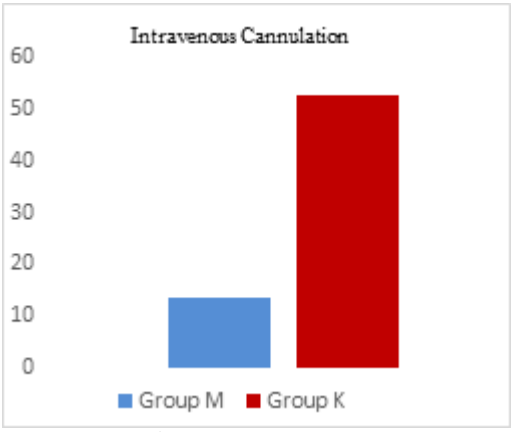

Figure IV Acceptance of intravenous cannulation in two study groups

Facemask acceptance Score: None of the patients in the study groups had poor acceptance to mask. Overall mean facemask acceptance score was better in group K (65.30%) compared to group M (33%), with a statistically significant p- value ($p < 0.05$). [Figure V]

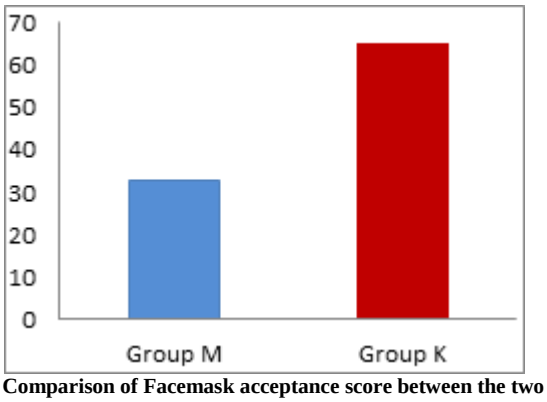

Figure V Comparison of Facemask acceptance score between the two groups

Discussion

Premedication is considered as administration of drug to the patient before surgery primarily to allay anxiety, produce analgesia, sedation and amnesia. Preoperative anxiety in children is associated with adverse outcomes, and thus it is imperative to treat with sedative premedication. Premedication for these children allows smooth separation from parents and induction without struggle. Appropriate drug is selected on the basis of child's age, weight, drug history, allergic history, emotional maturity, and personality, and anxiety level, physiological and psychological status. Children of 2-10 years age group are at high risk for developing extreme anxiety.[14] and the need for pharmacological premedication is highest.[15]

Intranasal drug administration has become more widely accepted with the availability of inexpensive atomizers such as the LMA MAD atomizer device.[16] Compared to dripping in the dose with a syringe, these devices improve drug absorption by delivering the dose to a wider surface area. Concentrated parenteral injections are preferred for intranasal administration, as volumes greater than 1 mL per nostril may saturate the nasal mucosal surface and drain out of the nasal cavity. The primary disadvantage of intranasal drug administration is transient nasal irritation, with some patients also experiencing cough, vocal cord irritation, or laryngospasm.[17]

Intranasal midazolam has been used as a sedative/anxiolytic and an antiepileptic. Baldwa and colleagues[18] in 2012 compared the effects of two intranasal midazolam doses (0.2 and 0.3 mg/kg) as a premedication in 60 children undergoing elective surgery. The two doses were compared for the level of sedation, ease of parental separation and face mask acceptance. Rawat et al. have also studied the effect of intranasal midazolam in children between 3-5 years of age and found it to be very useful and safe.[19]

Intranasal ketamine at a dose of 6 mg/kg is effective in sedating children within 20 to 40 minutes before induction of anesthesia. Only preservative free ketamine should be given nasally to avoid neurotoxicity, the 100 mg/ml concentration is preferable to minimize the volume administered in the nose. Weksler and Ovadia have also demonstrated the feasibility of intranasal ketamine for preoperative sedation.[20]

In our study, we compared effects of intranasal ketamine vs intranasal midazolam on preoperative sedation, separation from parents, mask induction and postoperative recovery. Both the study groups were comparable with respect to demographic and respiratory and hemodynamics parameters except significant tachycardia seen in ketamine group. Overall sedation, child-parent separation score, response to intravenous cannulation and facemask acceptance was better in group K compared to group M after 30mins of intranasal premedication. Our study results are concordant with Chakraverty P et al 2020.[21]

Conclusion

Intranasal route is convenient and safe for premedication in children. We observed that premedication with both intranasal ketamine and midazolam is effective for the purpose of sedation. Intranasal ketamine (5 mg/kg) achieved better quality of preoperative sedation, enabling easier child parental separation along with a better acceptance of venous cannulation and face mask induction with negligible side effects and better postoperative analgesia.

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