

Original Research Article

Study of intranasal midazolam versus intranasal ketamine as a premedication in children undergoing surgical procedures

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ABSTRACT

Background: Usage of premedication in children undergoing surgery is almost imperative and various medications have been used with varying success. The present study was aimed at comparison of intranasal midazolam and intranasal ketamine as a premedication in children by assessing acceptability of the drug by patients, ease at parent separation, level of sedation at the time of induction and facilitation of intravenous cannulation.

Methods: In this comparative observational study, 60 eligible participants were randomly divided into two groups of 30 each on the basis of preanaesthetic medication received: those intranasal midazolam group and intranasal ketamine group. At 30 minutes after intranasal dose, sedation, separation from parents and intravenous cannula acceptance was evaluated on four point score scale. Children were constantly observed for occurrence of possible adverse effects and the same were duly noted.

Results: The two groups were similar with respect to age, gender and body weight distribution. Twenty four patients (80%) in both ketamine and midazolam groups were observed to become drowsy, while 6 patients (20%) in ketamine group were asleep, compared to 0 patients in midazolam group ($p=0.024$). Thirteen (43.3%) patients from midazolam group had poor parenteral separation, as compared to 0 patients from ketamine group. And Comparison of intravenous cannula acceptance revealed the acceptance to be good in 26 (86.7%) patients in ketamine group as compared to 10 (33.3%) patients in midazolam group ($p<0.001$).

Conclusions: Ketamine when given in a dose of 5 mg/kg via intranasal route is better than midazolam given in a dose of 0.2mg/kg intranasally, as a premedication in children.

Keywords: Children, Intranasal ketamine, Intranasal midazolam, Premedication, Sedation, Induction

INTRODUCTION

The preoperative period is a stressful occurrence for most people undergoing surgery. Children in particular are more susceptible for obvious reasons, with fear and anxiety having been observed in nearly half of the children.¹ Symptoms like nightmares, enuresis and post-operative behavioral regression along with physical signs like significant fluctuations in heart rate and blood

pressure have all been reported.^{2,3} To respond effectively to the scenario is imperative on the part of anesthesiologist.

The major objectives of preanaesthetic medication are to decrease the stress response with preservation of haemodynamic parameters, facilitate anaesthesia induction and produce amnesia. Adult patients can mostly be reasonably managed by psychological preparation. But

a medicinal adjunct is advisable in children, considering immature age. Various medications like promethazine, ketamine, morphine, midazolam etc. have been used with varying success and they all come with their individual advantages/disadvantages.⁴⁻⁶ The ideal premedicant in children should be readily acceptable and have a rapid and reliable onset of action along with sedative and anxiolytic effect with minimal side effects. Going by these criteria, ketamine and midazolam seem to be two agents fitting the bill.^{7,8} Plus, both the drugs can be used intranasally as drugs for premedication, a route which is preferred in case of children.

Aim of the present study was to compare between intranasal midazolam and intranasal ketamine as a premedication in children by assessing acceptability of the drug by patients, ease at parent separation, level of sedation at the time of induction and facilitation of intravenous cannulation.

METHODS

This was a comparative observational study to determine the better drug between midazolam and ketamine, when given intranasally as premedication in children. The study was carried out at a tertiary care center in south India over the period of two years (August 2009 to July 2011).

After obtaining approval from Institutional Ethics Committee and written, informed consent from patient's parents, 60 patients fulfilling the selection criteria mentioned below were enrolled into the study.

Inclusion criteria

- American society of anesthesiologists (ASA) Grade I or II⁹
- Age of 1-6 years.

Exclusion criteria

- Emergency surgery cases
- Neurosurgery
- Nasal atresia
- History of recent nasal bleeding or discharge
- Refusal to consent.

The participants were randomly divided into two groups of 30 each on the basis of preanaesthetic medication they received:

- Group 1- Patients received intranasal midazolam (IM) (0.2mg/kg) (prepared from parenteral formulation of midazolam (1mg/ml) vial).
- Group 2- Patients received intranasal ketamine (IK) (5mg/kg) (prepared from parenteral formulation of ketamine (50mg/ml) vial).

All the participants were assessed thoroughly before surgery. Demographic data including age, gender, and

weight were recorded. Children were allowed to have milk up to 4 hours prior to surgery, if breastfed. Otherwise, only plain water was allowed up to 2 hours prior to surgery. No premedication was given in the wards. Children were kept in holding area in comforting presence of their parents. A baseline heart rate and oxygen saturation were measured before premedication. Readings were taken at 5 minutes interval until 30 minutes, when child was separated from parents. Intranasal dose of the drug was given in presence of parents using a sterile dropper. Children were constantly observed for the possible side effects like nausea, vomiting and increased salivation. At 30 minutes after intranasal dose, sedation, ease of separation from parents and intravenous cannula acceptance was evaluated on a four point score scale as follows;⁸

Sedation score scale

1. Agitated
2. Awake
3. Drowsy
4. Asleep

Separation score

1. Poor (crying, clinging)
2. Fair (crying but not clinging)
3. Good (whimpers, easily reassured)
4. Excellent (easy separation).

Scores of 1 or 2 were considered as unsatisfactory sedation or separation while scores of 3 or 4 were considered as satisfactory sedation or separation from parents. In operation theatre, intravenous cannulation was done before induction of anaesthesia. A four point evaluation system was used to evaluate acceptance of intravenous cannula.

Intravenous cannula acceptance scale

1. Poor (terrified, crying)
2. Fair (fear of needle, not reassured)
3. Good (slight fear of needle, easily reassured)
4. Excellent (unafraid, accepts intravenous cannula readily).

Scores of 1 or 2 were taken as unsatisfactory acceptance while scores of 3 or 4 were considered as satisfactory acceptance.

The statistical analysis was performed using SPSS (version 17) and Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between the groups.

RESULTS

A total of 60 participants, divided in two groups formed on the basis of premedication received [intranasal

midazolam (IM) and intranasal ketamine (IK), 30 participants each] were considered for final analysis. The two groups were similar with respect to age and gender. Majority of the children (56.7% in ketamine group and 60% children in midazolam group) were between 1 to 2 years old with 73.3% children in ketamine group being females as compared to 66.7% children in midazolam group. There was no difference with respect to weight of the children between the two groups, with 46.7% children in ketamine group having their weight between 7 and 10 kg as compared to 43.4% children in midazolam group (Table 1).

Table 1: Demographic details of the participants.

Demographic variable	Group IM (n=30)		Group IK (n=30)	
	No.	%	No.	%
Age				
1-2 years	18	60.0	17	56.7
3-4 years	9	30.0	8	26.7
5-6 years	3	10.0	5	16.7
Gender				
Male	10	33.3	8	26.7
Female	20	66.7	22	73.3
Body weight				
5-6 kg	11	36.7	8	26.7
7-10 kg	13	43.3	14	46.7
11-13 kg	6	20.0	8	26.7

A total of 53.3% children in ketamine group were in ASA grade I as compared to 56.7% children in midazolam group, and 46.7% children in ketamine group were in ASA grade II as compared to 43.3% children in midazolam group; the difference being statistically insignificant ($p=0.795$). As for the major indications for surgery, 53.3% children in midazolam group got operated for Patent Ductus Arteriosus (PDA) as compared to same number of children in ketamine group. Tetralogy of Fallot (TOF) (16.7% in midazolam group, 23.3% in ketamine group) and Ventral Septal Defect (VSD) (20% in midazolam group, 23.3% children in ketamine group) were the other common indications. One case each of total anomalous pulmonary venous connection (TAPVC), VSD+PDA and aorto-pulmonary window (AP window) were operated in the ketamine group during the study. There was no significant statistical difference ($p=0.891$) between the groups for the indications of surgery. Similarly, insignificant difference ($p=0.862$) was observed in the surgical procedures performed in the study, with ligation (53.3% in each group) and closure (23.3% in each group) being the commonest procedures performed in both the groups (Table 2). Twenty four patients (80%) in both ketamine and midazolam groups were observed to become drowsy, while 6 patients (20%) in ketamine group were asleep, compared to 0 patients in midazolam group who all remained awake. This difference was statistically significant ($p=0.024$), indicating relatively better sedation in ketamine group.

Significant difference ($p<0.001$) was observed in parenteral separation assessment, with 13 (43.3%) patients from midazolam group having poor separation, as compared to 0 patients from ketamine group.

Table 2: Comparison of indications for surgery and procedures performed.

Surgery details	Group IM (N=30)		Group IK (N=30)	
	No.	%	No.	%
Indication for surgery				
PDA	16	53.3	16	53.3
TOF	7	23.3	5	16.6
VSD	7	23.3	6	20.0
TAPVC	0	0.0	1	3.3
VSD+PDA	0	0.0	1	3.3
AP window	0	0.0	1	3.3
Procedures performed				
Ligation	16	53.3	16	53.3
Closure	7	23.3	7	23.3
Left modified blalock-taussig (LMBT) shunt	2	6.7	2	6.7
Intra-cardiac repair (ICR) for TOF	3	10.0	2	6.7
Repair	0	0.0	2	6.7
Right modified blalock-taussig (RMBT) shunt	2	6.7	1	3.3

And Comparison of intravenous cannula acceptance revealed the acceptance to be good in 26 (86.7%) patients in ketamine group as compared to 10 (33.3%) patients in midazolam group, indicating significantly better acceptance in in ketamine group ($p<0.001$) (Table 3).

Table 3: sedation, parental separation and intravenous cannula acceptance scores (30 minutes after premedication).

Score	Group IM (n=30)		Group IK (n=30)	
	No.	%	No.	%
Sedation score				
Agitated	0	-	0	-
Awake	6	20.0	0	-
Drowsy	24	80.0	24	80.0
Asleep	0	-	6	20.0
Parenteral separation score				
Poor	13	43.3	0	-
Fair	14	46.7	16	53.3
Good	3	10.0	14	46.7
Excellent	0	-	0	-
Intravenous cannula acceptance scores				
Poor	6	20.0	0	-
Fair	14	46.7	2	6.7
Good	10	33.3	26	86.6
Excellent	0	-	2	6.7

Tachycardia and salivation were seen after ketamine while respiratory depression was seen after giving midazolam, with 6 (20%) patients having nystagmus and 10 (33.3%) patients having tachycardia, as compared to 0 and 1 patients from midazolam group respectively, while 3 patients developed respiratory depression following midazolam administration (Table 4).

Table 4: Adverse effect following premedication.

Adverse effect	Group IM (n=30)	Group IK (n=30)	p value
Vomiting	2 (6.7%)	1 (3.3%)	1.000
Nystagmus	0	6 (20.0%)	0.024
Salivation	2 (6.7%)	3 (10.0%)	1.000
Tachycardia	1 (3.3%)	10 (33.3%)	0.006
Bradycardia	2 (6.7%)	0	0.492
Respiratory depression	3 (10.0%)	0	0.237

DISCUSSION

The purpose of using preanesthetic medication in paediatric patients, is the control of pain, fear and anxiety, thereby creating behavior that will facilitate the provision of quality medical care. The search for a rapidly acting sedative tranquilizer, free of adverse effects and with short duration of action, however, is still on. Many drugs or combinations of drugs via various routes of administration have been studied by numerous researchers over years. Intranasal administration of sedatives/analgesics is lately being explored as a possible alternative route of promise.

With the present study, a comparative evaluation between intranasal midazolam and intranasal ketamine, using relevant parameters detailed above, was undertaken to determine which of the two drugs is better as a premedication in children. Sixty children were enrolled and distributed randomly between the two groups in equal numbers (30 each). Emergency cases were excluded; as in emergency cases, intranasal administration of the drugs in the stipulated time interval may not have been possible; and emergency cases would have presented with full stomach and thus could have resulted in increased incidences of perioperative vomiting. Intranasal route was used for administration of preanesthetic drugs, similar to Henderson et al, and Wilton et al, believed to be the initial proponents of the method, who had studied the efficacy and safety of the route for premedication and found it to be effective and safe.¹⁰ The intranasal route would not have been suitable in cases of neurosurgery or in patients with nasal atresia, history of recent nasal bleeding or discharge, and hence such cases were duly excluded.

Demographics of the participants were well matched between groups, strengthening validity of the observations. The preschool age group studied is

common with previous similar studies.^{8,10,11} There was no significant statistical difference between the two groups for the indications of surgery or the procedures performed as well.

The level of sedation, ease at parental separation and intravenous cannula acceptance were the parameters assessed in the present study. All the three studied parameters were in favour of the ketamine group and the differences were significant. Diaz et al, had compared the outcome of intranasal ketamine premedication with a placebo in paediatric outpatients and observed ketamine to help pleasant and rapid separation of children from their parents, acceptance of monitoring and mask inhalation induction, along with no delay in post-operative recovery and discharge to home.¹² Gharde et al, in their strikingly similar study of efficacy of intranasal midazolam, ketamine and their mixture as premedication in children undergoing TOF repair, also reported ketamine to fair better, either alone or in mixture. Infact, the parameters used were also similar to the ones employed in the present study, adding further validity to the comparisons.⁸ Weksler et al, had also reported similar observations.¹³

There has been some conundrum over the dose of intranasal ketamine as premedication. In the present study, ketamine was used in a dose of 5 mg/kg body weight and the dose was observed to be adequate for required level of sedation. Weber et al, studied plasma concentration of ketamine after intranasal administration at a dose of 2 mg/kg and observed that rapid and high level drug absorption after nasal drug administration at that dose is possible without fluctuations in hemodynamic parameters. But the level of sedation was not monitored.¹⁴ Weksler et al, (1993) studied intranasal ketamine in paediatric patients at a dose of 6 mg/kg and had found excellent sedation in significant number of patients.¹³

Tachycardia, nystagmus and salivation was seen more with ketamine while respiratory depression was seen after giving midazolam, findings corroborative of the observations of previous researchers.^{5-7,10,12}

In conclusion, it can be said that ketamine when given in a dose of 5 mg/kg via intranasal route is better than midazolam given in a dose of 0.2mg/kg intranasally, as a premedication in children.

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