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Comparative evaluation of atomized intranasal midazolam and intranasal ketamine as sedative premedication in children for child-parent separation

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***Abstract*---**Background: In this study we wanted to compare intranasal atomized spray of midazolam 0.5 mg/kg with ketamine 5 mg/kg, as sedative premedicants for a child patient to treat separation

anxiety in paediatric surgical procedures with regard to the quality and rate of onset of sedation, sedation score, and behaviour score at the time of separation from parents and during gas induction of anaesthesia. we also wanted to compare any perioperative adverse effects of the premedication like airway obstruction, desaturation, bradycardia, sneezing, vomiting etc., acceptance of nasal spray and any delay in recovery from anaesthesia. Methods: This prospective study was undertaken in 60 paediatric patients aged between 1 and 6 years, belonging to both sexes of ASA grade 1 or 2 undergoing elective surgical procedures under general anaesthesia. The study was conducted at Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu. Group 1 received intranasal ketamine 5 mg/kg and Group 2 received intranasal midazolam 0.5 mg/kg. Patient's heart rate, SpO2, sedation score, behaviour score and any side effects like nausea, vomiting, airway obstruction etc. were noted at 5 min intervals for a duration of 20 minutes. Results: The mean and standard deviations of heart rates in the ketamine and midazolam group from 0-20 min. P-value was < 0.05 at the end of 20 mins and this was statistically significant. Heart rate was relatively lesser in the midazolam group. The mean and standard deviations of behaviour score at separation in ketamine and midazolam group. P-value was 0.003 (< 0.05) and this was statistically significant. The mean and standard deviations of behaviour score at induction in the ketamine and midazolam group. P-value was < 0.05 and this was statistically significant. In the ketamine group, there were 8 incidences of sneezing and 2 incidences of vomiting whereas in the midazolam group, only one had sneezing. The P-value was 0.011, this was statistically significant. Conclusions**:** Intranasal atomized spray of midazolam 0.5 mg/kg is a safer and more effective alternative than ketamine 5 mg/kg for premedication in ASA 1 and 2 children between 1-6 years for smooth child-parent separation and smooth induction of anaesthesia without any delay in postoperative recovery and hospital discharge.

***Keywords*---**atomized intranasal midazolam, intranasal ketamine, sedative premedication, child-parent separation.

Introduction

"Premedication refers to a drug treatment given to a patient before any surgical or invasive procedure".[1] Premedication in children will relieve mental trauma and anxiety, which occur when a child is separated from its parents. It also facilitates inducing anaesthesia smoothly with short recovery time. Numerous premedicants are being used to reduce the anxiety associated with the separation of a child from its parents. "*However, an ideal premedicant should provide good patient and parent acceptance, predictable results, and nil/minimal side effects".*[2] Premedication also minimizes postoperative negative behavioural changes. Since the 1990s, preparation of children during the preoperative period has undergone a massive change. Premedication via the painful intramuscular injection, Until the 1980s, IM injections were used for premedication which were very painful. It

has hence been replaced by transmucosal route (rectal, nasal or oral) ketamine, fentanyl, midazolam, or a combination of these. Intramuscular ketamine in reserved to cases where the child is uncontrollably agitated.

"Oral midazolam is the most commonly used premedicant in the United States since the 1990s due to its sedative and anxiolytic properties". [3] *"There is significant reduction in postoperative recall and establishment of anterograde amnesia".*[4] Alternative non-parenteral routes of administration have been studied, including oral, nasal, transmucosal, and rectal. "*Oral administration remains the most commonly used and best tolerated for the majority of children. Oral and transmucosal fentanyl have been used with success as well. Both the oral administration of the intravenous preparation and oral transmucosal fentanyl "lollypop" are effective, but postoperative nausea may be increased compared with other agents, limiting its usefulness in the outpatient setting (Howell et al., 2002; Tamura et al., 2003). Similar results have been seen with nasally administered sufentanil"* [4], less useful than others which cause nasal burning and chest wall rigidity.

Oral medication is less useful as it takes a long time to start acting and its delivery is unreliable if patient has vomiting and impossible when the patient is unable to take medications orally. Also, if the child refuses to swallow oral medications, this route is useless. In young children, medications can be given by rectal route, but older children and adolescents may not be comfortable with it. Giving medications by intravenous route needs a high level of expertise. Intraosseous delivery should be reserved for serious emergencies which usually are rare.
Intranasal delivery has several advantages like rapid absorption, higher patient compliance, higher convenience to the provider, more effective use of resources, it is painless, and the provider need not be highly trained. "*The highly vascularised nasal mucosa and the olfactory tissue in direct contact with the central nervous system allow nasally administered drugs to be rapidly transported into the bloodstream and brain, with the onset of action approaching that of the intravenous route".* [5,6] First-pass drug metabolism via the liver is also bypassed, resulting in high bioavailability of medications.

Midazolam is being used through the intranasal route since a long time for paediatric procedures and for providing sedation during surgeries. However, with the recent availability of the Nasal-Mucosal Atomization Device (MAD) this route of administration has been revisited. In this study, I am comparing the effects of atomized intranasal midazolam and intranasal ketamine used as sedative premedication in children for child-parent separation.

Objectives

- To compare between intranasal atomized spray of midazolam 0.5 mg/kg and ketamine 5 mg/kg, as sedative premedicants for a child patient to treat separation anxiety in paediatric surgical procedures.
- To compare the quality and rate of onset of sedation, sedation score and behaviour score at separation from parents and during gas induction of anaesthesia.

- To compare any perioperative adverse effects of the premedication like airway obstruction, desaturation, bradycardia, sneezing, vomiting etc., acceptance of nasal spray and any delay in recovery from anaesthesia.

Materials and Methods

After obtaining hospital ethics committee approval and informed consent from parents, this prospective study was undertaken in 60 paediatric patients aged between 1 and 6 years, belonging to both sexes of ASA grade 1 or 2 undergoing elective surgical procedures, with weight <20 kgs under general anaesthesia with estimated surgery time <90 mins. Were included in the study. We excluded patients with known allergy to study medications, those with upper respiratory tract infection with nasal discharge, obvious nasal deformities and those with aspiration risk. The study was conducted at Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu.

"The calculated sample size for the study using the mean behaviour score at separation from a parent as 1.5 with an SD of 0.4 and a difference in mean behaviour score as 0.3 between the two groups with 95% confidence interval and 80% power of the study is 28 rounded off to 30 in each study group".[7,8]

Patients were randomly allocated into one of the following groups using the envelope method to either of the two groups.

1. Group 1 - Ketamine
2. Group 2 – Midazolam

The study drug for a particular patient was drawn up by the consultant anaesthesiologist and administered by the trainee anaesthesiologist who was blinded to the nature of the study drug. The trainee anaesthetist did the data collection. The nature of the drug used in each patient was revealed to the investigator (trainee anaesthetist) only at the end of the whole study.

Statistical Analysis

Statistical analysis was done using SPSS version 20 software. Mean and standard deviation were calculated for continuous variables and percentage (%) for categorical variables. The student's t-test was used to test the mean difference of continuous variables and the chi-square test was used to test the association between categorical variables. P-value < 0.05 was considered statistically significant.

Results

We studied total of 60 patients. 30 patients were given intranasal midazolam and 30 were given ketamine. The groups were comparable with respect to age and weight. Statistically, no significant difference was observed with respect to age and weight. (Table 1)

Table 1: Comparison of mean age and weight among the two groups

Parameter	Group	Number	`Mean	SD	P value
Age	1	30	2.80	±1.32	0.73
	2	30	2.93	± 1.60	
Weight	1	30	13.06	±3.32	0.94
	2	30	13.13	±3.72	

Heart rate was relatively lesser in the midazolam group compared to ketamine group. However, this difference was not statistically significant when t-test was applied ($p>0.05$) except at 20 mins which was statistically significant. SpO2 was comparable in both the groups in all 20 mins. (Table 2)

Table 2: Mean Heart rate and mean SPO2 among the two groups

Parameters	Time (min)	Ketamine		Midazolam		P
		Mean	SD	Mean	SD	Value
Heart Rate	0	122.3	±17.08	123.5 6	±15.26	0.715
	5	121.5	±16.80	119.9 3	±12.28	0.682
	10	120.5 6	±16.22	115.6 6	± 12.67	0.198
	15	119.8 3	±17.7	113.1	±11.87	0.081
	20	119.5 6	±16.10	110.9	±11.7	0.02
SPO2	0	100	±0.00	100	±0.00	1.00
	5	99.93	±0.37	99.93	±0.25	1.00
	10	99.90	±0.31	99.57	± 2.07	0.377
	15	99.90	±0.31	99.93	±0.25	0.647
	20	99.83	±0.46	99.80	±0.55	0.800

The behaviour score and sedation scores in 20 minutes among two groups was not statistically different when t-test was applied. (Table 3)

Table 3: Difference in mean Behaviour scores and mean sedation scores among the two groups

Scores	Time (min)	Ketamine		Midazolam		P
		Mean	SD	Mean	SD	Value
Behaviour Score	0	3.90	±1.97	3.93	±1.98	0.953
	5	3.33	±0.61	3.50	±0.51	0.253
	10	2.60	±0.50	2.67	± 0.48	0.60
	15	2.0	±0.45	2.00	±0.37	1.00
	20	1.50	±0 .63	1.27	±0.52	0.12
Sedation Score	0	3.866	±1.97	3.90	±1.97	0.94
	5	3.37	±0.61	3.50	±0.51	0.36
	10	2.57	±0.50	2.67	± 0.48	0.43
	15	2.03	±0.41	2.00	±0.26	0.71
	20	1.50	±0 .63	1.27	±0.52	0.12

Behaviour score at separation and at induction was higher in ketamine group compared to midazolam group and this difference was statistically highly significant when t-test was applied. (Table 4)

Table 4: Association between Behaviour score at separation and at induction among the two groups

Behaviour Score	Ketamine	Midazolam	P Value
At Separation	1.40 ± 0.62	1.03± 0.18	0.003
At Induction	1.23 ± 0.57	1 ± 0	0.028

When we compared duration from extubating to wake-up in recovery, we found the duration was much higher in ketamine group and also, the duration from wake-up to discharge from recovery was higher in ketamine group. This was statistically highly significant.(Table 5)

Table 5: Difference in duration of extubating to wake up and wake-up to discharge in the two groups

	Ketamine	Midazolam	P Value
Duration from Extubating to Wake up in Recovery	40.67± 14.72	21.3± 7.30	0.001
The Duration from Wake up in Recovery to Discharge from Recovery	32.33± 12.64	21 ± 7.12	0.001

There were higher incidences of adverse events in ketamine group when compared to midazolam group. When chi-square test was applied, this difference was statistically significant. (Table 6)

Table 6: Comparison of adverse events in the two groups

Adverse Events	Ketamine (n=30)	Midazolam (n=30)	P Value
Vomiting	2 (6.7%)	0 (0%)	0.011
Sneezing	8 (26.7%)	1 (3.3%)	
Total	10 (33.45%)	1(3.3%)	

Discussion

Patients of age 1– 6 years were included in our study. Our study population consisted of 60 patients out of which males were 85 % and females were 15 %. Azeri Appeal, (2005), used ketamine 5 mg/kg intranasal in his study on comparison of intranasal midazolam versus ketamine as premedication. They found the dose to be safe. Ramesh Koppal et al. (2011), using either oral (0.5 mg/kg) or transnasal (0.5 mg/kg) midazolam evaluated the "*safety and effectiveness of midazolam by the transnasal and oral routes for paediatric sedation. He concluded that both the routes were equally effective and provided adequate sedation scores and they eased the separation of the child from the parents/guardian. With the availability of atomizers that allow the delivery of*

transnasal midazolam in a calculated dose (0.5 mg/metered dose), it may be preferred over oral midazolam."[9]

Hence in our study, the dosage of midazolam 0.5 mg kg^{-1} and ketamine dosage of 5 mg kg^{-1} were chosen as an optimal dose for children on premedication between 1-6 years, given 20 min before surgery. At the end of 20 mins of an intranasal atomized spray of either ketamine or midazolam, there was a better sedation score and behaviour score among the midazolam group than in ketamine. This was in concordance with the study done by Hosseini Jahromi SA, et al. (2012), who did "*a study to compare the effects of intranasal midazolam versus ketamine on reducing preoperative paediatric anxiety*." [10] There was no significant fall in saturation among both the groups and this is in concordance with Louon A, et al. (1994), who did "*a study for sedation in children, with a mixture of midazolam (0.56 mg/kg-1) and ketamine (5 mg/kg-1) given intranasally"*. [11]

In the ketamine group, there was a delay in duration from extubation to wake up in recovery and from wake up to discharge from recovery when compared to the midazolam group. This is in concordance with Davis, Peter J, et al. (1995) who concluded that "*nasal midazolam provided satisfactory anxiolysis without delaying anaesthesia recovery and hospital discharge"*. [12] The ketamine group had more incidences of vomiting (2) and sneezing (8) and prolonged duration from extubation to wake up in recovery and from wake up in recovery to discharge from recovery. This observation concurs with a study done by Lin, S. M., K. Liu, et al. (1990).[13]

With regard to Mucosal Atomizer Device (MAD), our experience was similar to a study done by Pandey RK et al. (2011) on "*comparative evaluation of drops versus atomized administration of intranasal ketamine for the procedural sedation of paediatric dental patients"*. [14] The effective delivery of the drug through the atomizer in the form of droplets which measure 30 –100 microns in size, help in a larger dispersion of the drug over the mucosa and hence result in better absorption. This was in concordance with Ramesh Koppal, et al. (2011), who evaluated "*the safety and effectiveness of midazolam by the transnasal and oral routes for paediatric sedation"*. [9]

Hepatic clearance of midazolam is very high. Hence, when midazolam is given intransnasally first-pass hepatic metabolism is avoided. This increases the bioavailability of midazolam. "*The elimination half-life of intranasal midazolam and ketamine is similar to that when the drug is given intravenously"*,[15] this is in concordance with Timothy R, et al. (2010).[15] In the midazolam group, nasal irritation and sneezing were found in 1 patient, which may be due to the acidic nature of midazolam formulation (pH 3.34). This observation concurs with the study done by Ramesh Koppal et al. in his published article on "Comparison of the Midazolam transnasal atomizer and oral Midazolam for Sedative Premedication in Paediatric Cases". Unexpectedly, in our study, 8 patients given intranasal ketamine had sneezing- much more than the midazolam group (it may be due to preservative benzethonium chloride).

Conclusions

We conclude that intranasal atomized spray of midazolam 0.5 mg/kg is a safer and more effective alternative than ketamine 5 mg/kg for premedication in ASA 1 and 2 children between 1-6 years for smooth child-parent separation and smooth induction of anaesthesia without any delay in postoperative recovery and hospital discharge.

Limitations of This Study

- This study was conducted only in paediatric ASA 1 and 2 patients, between 1-6 years old, not in other groups.
- Our study was not conducted in patients with difficult airways and a weight of more than 20 kgs.
- Our study was not conducted on emergency cases.
- Our study was not conducted on surgeries for more than 2 hours.

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