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Original Article

A comparative study of intranasal Midazolam and intranasal Ketamine as a preanaesthetic medication in paediatric surgical patients

Author
Dr Abhishek Tiwari
Assistant Professor, Department of Anaesthesiology, Integral Institute of Medical Sciences and Research, Kursi Road, Lucknow
Corresponding Author
Dr Abhishek Tiwari

Abstract
Objective: *To compare intranasal Midazolam and intranasal Ketamine as a preanaesthetic medication in paediatric surgical patients.*
Methods: *This was an open label randomized controlled trial study. Children weighing 05-20 kg scheduled for routine surgeries were participated in the study. Children were randomly assigned into two groups: Group M (n=50): Received intranasal midazolam spray in doses of 0.3 mg/kg and Group K (n=50): Received intranasal ketamine in doses 6 mg/kg. Acceptance of drug, response to drug administration, sedation scale, separation score, ease of cannulation score, vital parameters and side effects of drug was noted.*
Results: *There was no significant (p>0.05) difference in basic characteristics between the groups. There was no significant (p>0.05) difference in baseline hemodynamic parameters between the groups. Moderate fear/crying not quite with reassurance was the most common separation score in Intranasal Midazolam (38%) and Slight fear/crying quite with reassurancewas the most common separation score in Intranasal Ketamine (42%). Good acceptance of cannulation score was among more than half of patients in both Intranasal Midazolam (44%) and Intranasal Ketamine (70%). Hypotension was the most common side effect in both the groups constituting 8%.*
Conclusion: *Preanaesthetic medication with intranasal ketamine and intranasal midazolam are both equally effective for the purpose of sedation. Intranasal ketamine achieved better quality of sedation enabling easier parental separation. This study found that intranasal route was convenient and safe route for premedication in children.*
Keywords: *Preanaesthetic medication, Intranasal Midazolam, Intranasal Ketamine.*

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 postoperative behavioral regression along with physical signs like significant fluctuations in heart rate and blood pressure have all been reported. To respond effectively to the scenario is imperative on the part of anesthesiologist[2].

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[3,4].

Intranasal premedication provides good conditions for induction of anesthesia in preschool children[5]. Intranasal midazolam for premedication in preschool children was first described by Wilton et al[6] and later studied by García-Velasco et al[7]. The objective of this study was to compare intranasal Midazolam and intranasal Ketamine as a preanaesthetic medication in paediatric surgical patients.

Material and Methods

This was an open label randomized controlled trial study conducted in a tertiary care hospital in north India. The study was approved by the Ethical Committee of the Institute and the consent was taken from patient's guardian before enrolling in the study. Based on the statistical calculation a total 100 patients belonging to ASA (American Society of Anaesthesiologists) physical status I and II, within the age group of 1 to 6 years, scheduled for elective minor operation were recruited for the study. Patients were into two groups each consisting 50 patients by using computer generated random number table.

Paediatric patients in age group of 01 to 06 years belonging to ASA physical status I and II were included in the study. Patients undergoing emergency surgery, patients whose parents refused to take part in this study and any patient having infection, nasal pathology, and allergy to any of the study drugs were excluded from the study.

Methods

Children weighing 05-20 kg scheduled for routine surgeries were participated in the study. Children were randomly assigned into two groups: Group M (n=50): Received intranasal midazolam spray in doses of 0.3 mg/kg and Group K (n=50): Received intranasal ketamine in doses 6 mg/kg. Acceptance of drug, response to drug administration, sedation scale, separation score, ease of cannulation score, vital parameters and side effects of drug was noted. Medications were administered 30 min prior to induction, in preanaesthetic room with the parent(s) attendance. Intranasal drug was administered in both nostrils with child in recumbent position.

Measurements

Baseline heart rate, respiratory rate, oxygen saturation and blood pressure was measured before and every 10 min after intranasal drug administration for 30 minutes until transfer to operating room (OR). Degree of sedation was assessed every 5 minutes for 30 minutes by using a five point sedation scale. Scores 1, 2 & 3 were considered satisfactory whereas score 4 & 5 were considered unsatisfactory.

The response to the child-parent separation was assessed and graded according to a 4 Point scale at 30 minutes. Children with score 1, 2 & 3 were considered satisfactory and score of 4 was considered unsatisfactory.

In the operation room, an empirical four point score was used for evaluation of acceptance of Intravenous cannulation. Acceptance of intravenous cannulation score 3 or 4 was designated as having a, satisfactory score, while score 1 or 2 was considered unsatisfactory.

Data Collection

Charts were used for patient data recording for all cases and the following was noted:

1) Pre-operative: Demographic data which were include name of the patient, age of the patient, sex and weight of the patient and particulars.

2) Post-operative adverse effects as nausea, vomiting, increased secreation and bradycardia were reported.
3) The various Quality and Quantity indicators which was used in the study include five point sedation score, four point separation score, acceptance of intravenous cannulation score and vital parameters which include heart rate, respiratory rate, blood pressure and arterial oxygen saturation.

Statistical Analysis

The results are presented in frequencies, percentages and mean±SD. The Chi-square test was used to compare categorical variables between the groups. The Unpaired t-test was used to compare continuous variables between the groups. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

Results

The mean age of patients of Intranasal Midazolam and Intranasal Ketamine was 5.14±1.65 and 4.82±1.43 years respectively. More than half of patients of both Intranasal Midazolam (68%) and Intranasal Ketamine (60%) were males. Majority of patients of both Intranasal Midazolam (70%) and Intranasal Ketamine (72%) had ASA grade I. The mean weight of patients of Intranasal Midazolam and Intranasal Ketamine was 9.26±3.53 and 9.76±3.69 kgs respectively. There was no significant (p>0.05) difference in basic characteristics between the groups (Table-1).

There was no significant (p>0.05) difference in baseline hemodynamic parameters between the groups (Table-2).

Moderate fear/crying not quite with reassurance was the most common separation score in Intranasal Midazolam (38%) and Slight fear/crying quite with reassurance was the most common separation score in Intranasal Ketamine (42%). Slight fear/crying quite with reassurance the second most common separation score in Intranasal Midazolam (34%) and Slight fear/crying quite with reassurance was the second most common separation score in Intranasal Ketamine (28%). Good acceptance of cannulation score was among more than half of patients in both Intranasal Midazolam (44%) and Intranasal Ketamine (70%). There was no significant (p>0.05) difference in Separation and Acceptance of Cannulation Score between the groups (Table-3).

Agitated and alert score became nil in both the groups after 15 minutes. Calm, drowsy and asleep were nil from 0 minute to 10 minutes (Fig.1).

Hypotension was the most common side effect in both the groups constituting 8%. Urinary Retention was the second most common side effect in Intranasal Midazolam (6%) and Nausea & Vomiting was the second most common side effect in Intranasal Ketamine (6%) (Table-4).

Table-1: Basic characteristics of patients between the groups

Basic characteristics	Intranasal Midazolam (n=50)	Intranasal Ketamine (n=50)	p-value[1]
Age in years, mean±SD	5.14±1.65	4.82±1.43	0.30
Gender, no. (%)			
Male	34 (68.0)	30 (60.0)	0.40
Female	16 (32.0)	20 (40.0)	
ASA grade, no. (%)			
Grade I	35 (70.0)	36 (72.0)	0.82
Grade II	15 (30.0)	14 (28.0)	
Weight in kgs, mean±SD	9.26±3.53	9.76±3.69	0.49

[1]Unpaired t-test/Chi-square test

Table-2: Comparison of baseline hemodynamic parameters between the groups

Baseline hemodynamic parameters	Intranasal Midazolam (n=50)	Intranasal Ketamine (n=50)	p-value[1]
HR	79.48±12.80	50.78±11.65	0.69
RR	16.88±2.89	17.28±2.71	0.47
SPO_2	98.92±0.85	98.82±1.21	0.63
SBP	93.12±11.53	92.66±11.44	0.84
DBP	60.38±8.14	59.54±7.74	0.59

[1]Unpaired t-test

Table-3: Comparison of Separation and Acceptance of Cannulation Score between the groups

Score	Intranasal Midazolam (n=50)		Intranasal Ketamine (n=50)		p-value[1]
	No.	%	No.	%	
Separation score					
Unafraid/cooperative/asleep	9	18.0	10	20.0	0.74
Slight fear/crying quite with reassurance	17	34.0	21	42.0	
Moderate fear/crying not quite withreassurance	19	38.0	14	28.0	
Crying need for restraint	5	10.0	5	10.0	
Acceptance of Cannulation Score					
Poor	7	14.0	3	6.0	0.27
Fair	14	28.0	9	18.0	
Good	27	54.0	35	70.0	
Excellent	2	4.0	3	6.0	

[1]Chi-square test

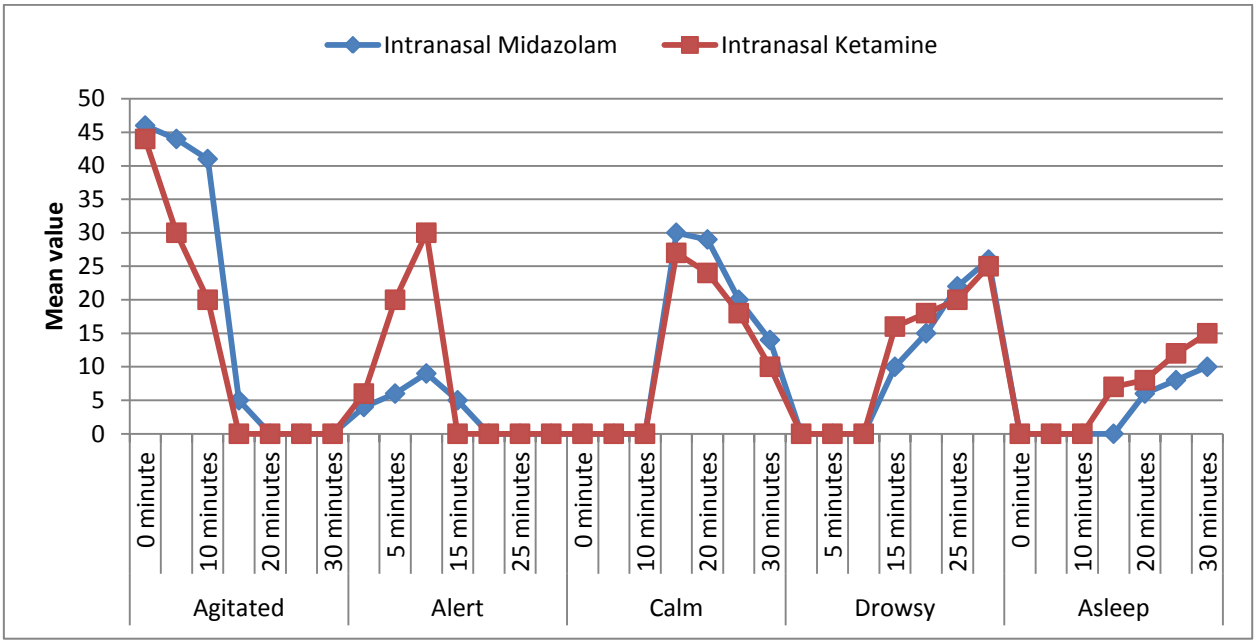

Fig.1. Comparison of different sedation score between the groups across the time periods

Table-4: Comparison of side effects between the groups

Side effects	Intranasal Midazolam (n=50)		Intranasal Ketamine (n=50)		p-value[1]
	No.	%	No.	%	
Bradycardia	2	4.0	2	4.0	NA
Hypotension	4	8.0	4	8.0	
Sedation	2	4.0	2	4.0	
Urinary Retention	3	6.0	2	4.0	
Itching	0	0.0	3	6.0	
Nausea & Vomiting	0	0.0	3	6.0	
No Side Effect	39	78.0	34	68.0	

[1]Chi-square test, NA-Not applicable as >1 0s in a column

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 was undertaken to determine which of the two drugs is better as a premedication in children. Intranasal route was used for administration of preanesthetic drugs, similar to Henderson et al[8] and Wilton et al[6] 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.

Demographics of the participants were similar between the groups, strengthening validity of the observations. The preschool age group studied is common with previous similar studies[9,8].

Acceptance of drug, response to drug administration, sedation scale, separation score, ease of cannulation score, vital parameters and side effects of drug were assessed in the present study. All the studied parameters were in favour of the ketamine group, however, the differences were statistically insignificant. Diaz et al[10] 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 postoperative recovery and discharge to home. Gharde et al[9] 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. Weksler et al[11] had also reported similar observations.

There has been some conundrum over the dose of intranasal ketamine as premedication. In the present study, ketamine was used in a dose of 6 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[12]. Weksler et al[11] studied intranasal ketamine in paediatric patients at a dose of 6 mg/kg and had found excellent sedation in significant number of patients.

Hypotension was the most common side effect in both the groups constituting 8%. Urinary Retention was the second most common side effect in Intranasal Midazolam (6%) and Nausea & Vomiting was the second most common side effect in Intranasal Ketamine (6%), findings corroborative of the observations of previous researchers[4,3,13].

This study had a few limitations but every effort was made to minimize their effects on the study outcomes. This study did not objectively measure the depth of sedation. Some researchers suggested the utility of bispectral index in PSA. Although early evidence is supportive, there is insufficient evidence to advocate its routine use in preanaesthetic sedation. This study could not ‘blind‘ the intervention.

Conclusion

Preanaesthetic medication with intranasal ketamine and intranasal midazolam are both equally effective for the purpose of sedation. Intranasal ketamine achieved better quality of sedation enabling easier parental separation. This

study found that intranasal route was convenient and safe route for premedication in children.

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