Original research article

Comparative Study between Intranasal and Oral Midazolam as Premedication in Paediatric Patients

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Abstract

Background and Objectives: Premedication in paediatric patients undergoing surgery is very much essential to lessen the trauma of separation from parents, to allay apprehension regarding anaesthesia and surgery, to co-operate for venipuncture, mask acceptance and to facilitate induction of general anaesthesia. Midazolam is an ideal premedicant with many desirable properties such as sedation, anxiolysis, minimal cardiovascular and respiratory effects, anterograde amnesia. Hence the present study was undertaken to compare between intranasal midazolam and oral midazolam with respect to onset of sedation, effectiveness and safety. **Methodology:** The study population consisted of 100 ASA grade I and II patients aged between 2-8 years posted for various elective surgeries at NMCH, Patna. The study population was randomly divided into 2 groups of 50 patients each.

Conclusion: Thus from the above study, we conclude that Onset of sedation was significantly faster with intranasal administration compared with oral route. Midazolam administration by either route was equally. effective and no statistical differences were seen between them. All vital signs were stable throughout the procedure in both groups and no significant differences were seen.

Keywords: Premedication, Midazolam, Sedation.

Introduction

Children have the same anxiety as adults[1]. Hospital admission, anaesthesia and surgery are stressful experiences for children, hence extreme preoperative anxiety in them may prolong the induction of anaesthesia and lead to onset of postoperative negative psychologic effects such as nightmares, eating disturbances and enuresis.[2,3] Of the various aspects of pediatric anaesthesia, the most neglected part is premedication. In most of the busy paediatric surgical theaters, it is very common to find children in waiting area, in various stages of anxiety and distress emitting various tones of crying. Most of the time, the anesthetist will struggle with the child to start the intravenous line or induce inhalationally. When we never induce anaesthesia in a struggling adult patient, fearing hypertensive response, we never bother to properly premedicate the paediatric patient before bringing the child to the operation theater. Therefore, an effective preanaesthetic medication for use in children undergoing surgery is required which will allay apprehension regarding anaesthesia and surgery, lessen the trauma of separation

from parents and facilitate induction of general anaesthesia without prolonging the postanaesthesia recovery period.[4] Premedication in children remains a controversial subject as various premedication and delivery systems have been developed using different routes of administration.

Objectives

To compare the onset of drug action by oral and intranasal routes
To compare the effectiveness and safety of drug as premedicant by two routes with respect to *Sedation score
*Anxiety score

Material and Method

The present study was conducted on patients admitted to Nalanda medical College and Hospital Patna, Bihar. Study duration of Two years, for elective surgery in Departments of General Surgery, Plastic Surgery, ENT and Orthopaedics. 100 patients of ASA Grade I and Grade II, of either sex aged between 2 to 8 years were included in this study. Children undergoing surgical procedure between 30 minutes to 2 hours duration were selected for the study. The children were divided into two groups of 50 each randomly. Children in Group-A received intranasal midazolam 0.2 mg/kg and children in Group-B received oral midazolam syrup of 0.5 mg/kg.

Pre-anaesthetic assessment : All patients were visited and evaluated for fitness for the intended procedure and anaesthesia on the day prior to the surgery. During this visit, the procedure of the study planned was explained to the parents. An attempt was made to alleviate the anxiety of patients. Parents were also instructed on nil per oral guidelines. General clinical examination of the patient was performed including a general physical and systemic examination.

Pre-operative fasting :

Preoperative fasting guidelines for children were as follows –
*No oral liquids 2 hours before the procedure.
*Avoidance of milk and solids 6 hours prior to the procedure.
The criteria for inclusion and exclusion were –

Inclusion criteria

*Patients coming for elective major / minor surgeries.
*Age between 2-8 years.
*ASA Grade 1 and 2.

Exclusion criteria

*ASA Grade 3 and 4.
*History of prematurity and chronic illness.
*History of developmental delay.
In the preoperative room, baseline recordings of heart rate, respiratory rate, systolic blood pressure and activity of child were noted. In our study, 100 cases were divided into two groups of 50 each; intranasal midazolam 0.2 mg/kg was given to Group-A and oral midazolam syrup of 0.5 mg/kg was given to Group-B. For Group-A, intranasal midazolam, diluted midazolam 1mg/ml preservative free was administered intranasally with dropper as per dosage of 0.2mg/kg, 45 min before induction of anaesthesia Children were evaluated for adequacy of sedation by sedation score and anxiety score and

response to painful stimulus for every 2 minutes 1,3,5,7,9,11,13,15,17,19 minutes and so on (Needle prick and ability to perform venipuncture). For Group-B, oral midazolam syrup 0.5 mg/kg administered 45 min before induction of anaesthesia and evaluated as stated above at 5 min interval at 5,10,15,20,25,30,35,40,45 minutes.
Children in both groups were evaluated for any changes in heart rate, respiratory rate and systolic blood pressure. Adequacy of sedation, anxiety and response to painful stimulus. Also evaluated for vomiting, excessive salivation, abdominal movement or rigidity and ability to maintain airway. The doses of midazolam that we used in this study were approximately equipotent and within the ranges that have been shown to be effective in producing sedation. The bioavailability of nasal and oral midazolam are approximately 64% and 26% respectively. Therefore total effective dose (bioavailability X dose) was approximately 0.13 mg/kg for each route.[52] Onset of sedation was defined as the minimum time interval necessary for the child to become drowsy and asleep. When a sedation score of 3,4 or 5 was reached, the child was transferred to the operating room. If no satisfactory sedation was achieved after the maximum time interval, anaesthesia induction was still performed. Parental separation was assessed. All children were secured with 22G canula and premedicated with Inj. Glyco 0.01 mg/kg and analgesia provided with Inj. Fentanyl 2 µgm/kg. General anaesthesia was induced with nitrous oxide (60%) and oxygen (40%) and halothane (0.5-3%). Acceptance of mask by the child was recorded and time from mask application to loss of eyelash reflex i.e., induction time was noted. Relaxed with depolarizing muscle relaxant succinylcholine 1-2 mg/kg i.v. laryngoscopy was done using rigid laryngoscope with standard Macintosh blade, endotracheal intubation done with appropriate sized high volume, low pressure cuffed endotracheal tube. Secretions at the time of intubation were scored as satisfactory or unsatisfactory. Descriptive data that included mean, standard deviation and percentage were determined for all the groups. Continuous data were analyzed by paired 't' test (for paired sample) and unpaired 't' test (for independent samples). Chi- square test was used for categorical data. P-value of <0.05 was considered for significant difference.

RESULTS

A total of 100 children were enrolled in the study. 50 children received intranasal midazolam 0.2 mg/kg Group A and other 50 children received oral midazolam 0.5 mg/kg Group B.

TABLE 1: DEMOGRAPHIC DATA

		Group A	Group B	
No. of patients		**50**	**50**	
Age (yrs)	Range	2-8	2-8	P=0.49 NS
	Mean ± SD	4.33 ± 1.74	4.09 ± 1.73	
Weight (kg)	Range	8-20	8-20	P=0.31 NS
	Mean ± SD	12.98±3.72	12.30±2.89	
Sex	Male	32 (64%)	33 (66%)	X^2=0.04
	Female	18 (36%)	17 (34%)	P=0.83 NS

The two groups were comparable in age, sex and weight distribution. In Group A there were 32 male and 18 female children with age ranging from 2-8 years (mean 4.33 ± 1.74) and body weight ranging from 8-20 kgs (mean 12.98 ± 3.72).In group B there were 33 male and 17 female children with age ranging from 2-8 years (mean 4.09 ± 1.73) and weight ranging from 8-20 (mean 12.30 ± 2.89).

TABLE 2: VITAL PARAMETERS

2(a) Heart rate (beats per minute)

	Group A (mean ±SD)	**Group B (mean ± SD)**	**Mean difference**	**P** value**
Preoperative	102.5 ± 3.7	101.7 ± 2.8	0.82	0.21 NS
Pre induction	105.3 ± 4.5	104.9 ± 4.3	0.36	0.36 NS
Mean difference	2.76	3.22		
P*value	P<0.001 HS	P<0.001 HS		

P* Students paired 't' test

P** Students unpaired 't' test

There was a statistically significant increase in heart rate in both the groups, Group A and B from baseline to pre induction levels, though it was not clinically significant. In group A, the heart rate increased from 102.5 ± 3.7 to 105.3 ± 4.5 and in Group B from 101.7 ± 2.8 to 104.9 ± 4.3.

TABLE 3: ONSET OF SEDATION

Onset of sedation	**Group A**	**Group B**
Mean	7.44	32.60
SD	1.30	4.07
Range (min)	5-9	25-40
Mean difference	25.16	
P*	P<0.001 HS	

P* Students unpaired 't' test.

TABLE 4(a) : SEDATION SCORE

Groups	**Sedation score**			**Total**
	3	**4**	**5**	
Group A	23 (46%)	25 (50%)	2 (4%)	50 (100%)
Group B	22 (44%)	26 (52%)	2 (4%)	50 (100%)

Sedation was assessed on a 5 point sedation scale, score-1 was agitated and crying upto score 5 was asleep.

TABLE 4(b) : ANXIETY SCORE

Groups	**Anxiety score**		**Total**
	3	**4**	
Group A	34 (68%)	16 (32%)	50 (100%)
Group B	37 (74%)	13 (26%)	50 (100%)

Anxiety was assessed on a 4 point scoring system. In group A, anxiety score of 3 was seen in 34 (68%) children and score of 4 was seen in 16 (32%) children In group B, anxiety score of 3 was seen in 37 (74%) children and score of 4 was seen in 13 (26%) children.

TABLE 5: CARDIORESPIRATORY

Groups	**Satisfactory**	**Unsatisfactory**	**Total**
Group A	50 (100%)	-	50(100%)

Group B	50 (100%)	-	50 (100%)

Intraoperatively changes in heart rate and respiratory rate were less than 15% in all the cases studied and hence was satisfactory

TABLE 6: POSTOPERATIVE

Groups	Restless	Not restless	Total
Group A	3 (6%)	47 (94%)	50 (100%)
Group B	3 (6%)	47 (94%)	50 (100%)

Groups	Vomiting	No vomiting	Total	X^2	P
Group A	3 (6%)	47 (94%)	50 (100%)	0.21	0.65 NS
Group B	2 (4%)	48 (96%)	50 (100%)		

In postoperative period, in both groups 47 (94%) children were not restless and only 3 (6%) children were restless.

TABLE 7: PARENTAL SATISFACTION

Groups	Yes	No	Total
Group A	48 (96%)	2 (4%)	50 (100%)
Group B	48 (96%)	2 (4%)	50 (100%)

Parental satisfaction regarding premedication was compared between both the groups. In both groups 96% of parents were satisfied.

DISCUSSION

Pre anaesthetic medication in children should relieve anxiety, reduce the trauma associated with separation from their parents and facilitate induction of anaesthesia without prolonging the recovery period. Midazolam has many desirable properties of a premedicant for children especially undergoing day care surgery. Its elimination half life is considerably shorter than those of diazepam or trimeprazine. It exerts a reliable dose dependent anxiolytic effect without over sedation and produces minimal cardiovascular and respiratory effects. Also anterograde amnesia produced by midazolam should help to reduce the psychological trauma of anaesthesia and surgery. Hence midazolam is considered as the drug of choice for premedication.[5] The present study was done to evaluate the onset, effectiveness and safety of midazolam administered by intranasal and oral route as preanaesthetic medication in paediatric patients and results have been compared in both the groups with respect to the following parameters.

Age, Sex and Weight : In present study, children in the two groups were in age group of 2-8 years with a mean age of 4.33 ± 1.74 in group A and 4.09 ± 1.73 in group B, weight of mean 12.98 ± 3.72 in group A and 12.30 ± 2.89 in group B and with almost equal male and female population. The two groups did not differ significantly in their age, sex and weight. This was in comparison with the study conducted by Lee Kim et al.[6] in children age group of 2-6 yr. Lee Kim et al[6] conducted a study to compare the onset time of 2 regimens (per oral (PO) and intra nasal (IN) midazolam) and also to compare the efficacy and safety of midazolam through a single dose of 0.7 mg/kg via oral route and 0.3 mg/kg by nasal route. There were no statistical differences in age, weight and gender between PO and IN administration (P□0.05) mean onset time of PO and IN routes was 15.5 (SD ± 5) minutes and 5.55 (± 2.2) minutes respectively. Their study

showed no statistically significant differences in overall behaviour in terms of sedation, anxiolysis and alterations of vital signs (HR, RR) between PO and IN midazolam regimens for paediatric dental patients, undergoing dental procedures. Subjects in IN however showed more movement and less sleep between 25-30 minutes after sedation began, indicating that subjects with IN administration were waking up from sedation about 5 to 10 minutes before the PO subjects. In group A heart rate increased from baseline of 102.5±3.7 to preinduction 105.3±4.5 and in group B from 101.7±2.8 to 104.9±4.3. And the increase in both groups were similar but this was clinically not significant. This was in comparison with studies of Levine MF et al,[7] in their study on oral midazolam, heart rate increased significantly from 105.4±10 to 120.9±16.9

Respiratory rate : There was statistically significant increase in respiratory rate in both groups. In group A it increased from 20.4±0.6 baseline to 21.0 ± 0.8 pre induction level. In group B it increased from 20.3 ± 0.5 baseline to 20.9 ± 0.7 pre induction level and the increase in both groups were similar.
But this was clinically not significant. This was in comparison with studies of McMillan et al.[8]

Onset of sedation : Onset of sedation was significantly faster in group A with a mean of7.44 ± 1.30 compared to group B with a mean of 32.60 ± 4.07.
In children who received intranasal midazolam i.e., group A average time ranged 5-9 min and a mean (7.44 ± 1.30) was seen. This was comparable with studies conducted by Lee Kim et al (5.5±2.2 mins with 0.3mg/kg), Malinovsky JM et al[9] (6mins with 0.2mg/kg), Rose E. et al1[10] (6mins with 0.2mg/kg) and Niall CT et al (5mins with 0.2mg/kg). In children who received oral midazolam i.e., group B average time ranged 25-40 min and a mean of (32.60 ± 4.07) min. This was comparable with studies of Weldon BC et al[11] (mean 36 min), McMillan CO et al[8] (mean 30 min) and McCluskey et al[2] (mean 43 min), with same dose of midazolam 0.5mg/kg administered orally. McMillan CO et al[8] in their study showed excellent anxiolysis in 80-90% of patients who received oral midazolam after 30 mins of premedication, Weldon BC et al[11] (Mean 95% showed sedation and anxiolysis), Levine MF et al[7] (Mean 90% showed sedation and anxiolysis). McErlean et al,[12] studied the effect of midazoalm syrup as a premedication to reduce the discomfort associated with paediatric intravenous catheter insertion. Midazolam pain scores were lower than placebo scores. Midazolam scored 79% Vs Placebo which scored 48%. This was comparable with studies of Pan AK et al[13] and McErlen et al[12]. Children in both the groups co-operated for IV cannulation. Thus our study demonstrates that premedication with intranasal midazolam 0.2 mg/kg or oral midazolam 0.5 mg/kg provides satisfactory sedation and anxiolysis. Onset of sedation was significantly faster in intranasal group compared to oral route.

Conclusion

On comparison between intranasal route and oral route of administration of midazolam as preanaesthetic medication in paediatric patients, we concluded the following –
*Onset of sedation was significantly faster with intranasal administration compared with oral administration.
*Midazolam administration by either route intranasal or oral was equally effective as seen with sedation score, anxiety score, emotional status score, acceptance of mask and venipuncture score and no statistical differences were seen between them.

*All vital signs were stable throughout the procedure and showed no significant difference between intranasal and oral administration, thus establishing the safety of drug administration by either routes.

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