

COMPARATIVE STUDY BETWEEN INTRANASAL AND ORAL MIDAZOLAM AS PRE MEDICATION IN PEDIATRIC PATIENTSSowmya G¹, Nalinakshamma Sajjan²**HOW TO CITE THIS ARTICLE:**

Sowmya G, Nalinakshamma Sajjan. "Comparative Study between Intranasal and oral Midazolam as Pre Medication in Pediatric Patients". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 04 January 12; Page: 667-681, DOI: 10.14260/jemds/2015/98

ABSTRACT: BACKGROUND: Premedication in paediatric patients undergoing surgery is essential to lessen the trauma of separation from parents, to allay apprehension regarding anaesthesia and surgery, to co-operate for venepuncture, mask acceptance and to facilitate induction of general anaesthesia. Midazolam is an ideal premedicant with 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. **AIMS AND OBJECTIVES:** To compare onset of sedation, effectiveness and safety of midazolam as premedicant by intranasal and oral route. **MATERIALS AND METHODS:** 100 patients aged between 2-8 yrs posted for various elective surgeries were randomly divided into 2 groups of 50 patients each. Group A: Receiving intranasal midazolam 0.2 mg/kg. Group B: Receiving oral midazolam 0.5 mg/kg. Pre and intra operatively parameters like onset of sedation, anxiolysis, acceptance of mask, co-operation for venepuncture, heart rate, respiratory rate and post operatively restlessness and vomiting were assessed. **RESULTS:** Demographic profile was comparable in both groups. Mean time of onset of sedation was rapid in group A (7.44 ± 1.30) compared to group B (32.60 ± 4.07) Satisfactory anxiolysis was seen in both groups. Children in both group co-operated for mask acceptance and venepuncture.. Hemodynamic parameters were stable in both groups. No statistical significance was seen with respect to these parameters. **CONCLUSION:** Onset of sedation was significantly faster with intranasal administration compared with oral route. Midazolam administration by either route was equally effective, 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, this may prolong the induction of anaesthesia and lead to onset of postoperative negative psychologic effects such as nightmares, eating disturbances and enuresis.^{2,3} Therefore, an effective preanaesthetic medication 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

Benzodiazepines by facilitating actions of gamma amino butyric acid (GABA), the principal inhibitory neurotransmitter in CNS. GABA_A is receptor complex consisting of 5-glycoprotein subunits, when benzodiazepine bind to GABA_A α - subunits, results in enhanced opening of chloride gating channels, producing hyperpolarization of post-synaptic cell membrane and rendering them resistant to excitation. GABA_A receptors occurs almost exclusively on post synaptic nerve endings in CNS. Highest density is in cerebral cortex followed in decreasing order by hypothalamus, cerebellum, midbrain, hippocampus, medulla and spinal cord.

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The receptor occupancy of 20% produces anxiolysis, >30-50% receptor occupancy is associated with sedation and >60% receptor occupancy is required for unconsciousness.

Midazolam is a water soluble benzodiazepine. It possesses desirable properties such as dose dependent anxiolytic effect achieving a sedation which is usually not sleep, but rather a compliant, happy state.⁵ It produces minimal cardiovascular and respiratory effects and brings about an anterograde amnesia which helps to reduce the psychological trauma of anaesthesia and surgery.

Various routes of administration include – intranasal, oral, intramuscular, rectal, sublingual, intravenous.

INTRANASAL:

1. Rich vascular plexus of nasal cavity provides a direct route into the blood stream.
2. Hepatic first pass metabolism are avoided, allowing more drug to be bioavailable.
3. Ease and convenience: Essentially painless, does not require sterile technique.
4. Due to close proximity of olfactory nasal mucosa to CNS, CSF drug concentrations may exceed plasma concentrations, rapidly achieving adequate CSF drug concentrations for centrally acting medications.⁶

ORAL ROUTE:

Advantages of oral route include;

- Convenience of administration.
- Better acceptance.
- Economic.
- More safe.

METHODOLOGY: After approval from institutional ethical committee, this study was conducted on 100 ASA grade 1 and 2 patients aged 2-8 yrs posted for various elective surgeries, Patients were randomly divided into 2 groups of 50 patients each.

Group A: Receiving intranasal midazolam 0.2 mg/kg.

Group B: Receiving oral midazolam 0.5 mg/kg

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.

PRE-ANAESTHETIC ASSESSMENT: A detailed pre anaesthetic evaluation was done. During this visit, the procedure of the study planned was explained to the parents. Informed consent was also obtained from the parents for conducting the study on children.

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PRE-OPERATIVE FASTING: Preoperative fasting guidelines for children.

- No oral liquids 3 hours before the procedure.
- Avoidance of milk and solids 6 hours prior to the procedure.

DRUG AND DOSAGE: In the preoperative room, baseline recordings of heart rate, respiratory rate, systolic blood pressure and activity of child were noted.

For Group-A, intranasal midazolam, diluted midazolam 1mg/ml preservative free was administered intranasally with dropper as per dosage of 0.2 mg/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 venepuncture).

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 changes in heart rate, respiratory rate and systolic blood pressure. Adequacy of sedation, anxiety and response to painful stimulus. Also evaluated for vomiting, 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.⁷

Children were observed for any signs of upper airway obstruction, respiratory depression, apnoea and oxygen desaturation.

SEDATION WAS GRADED AS FOLLOWS: (5 POINT SCALE)

- | | |
|------------|--|
| Grade I: | Agitated, crying |
| Grade II: | Alert, awake, but not crying. |
| Grade III: | Calm, sitting or lying comfortably. |
| Grade IV: | Drowsy eyes spontaneously closing but responds to minor stimulation. |
| Grade V: | Sleep, eyes closed does not respond to minor stimulation. |

Anxiety score: (4 point scale)

- | | |
|------------|------------------------|
| Grade I: | Very anxious, crying |
| Grade II: | Anxious, crying |
| Grade III: | Calm, not co-operative |
| Grade IV: | Calm, co-operative. |

Sedation and anxiety levels were recorded every 2 minutes in intranasal midazolam group and every 5 minutes in oral midazolam group, until satisfactory sedation was obtained and observed for a maximum period of 45 minutes in both groups.

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.

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Children were connected to cardiac monitor for recording the ECG, baseline HR and BP.

All the patients were pre-oxygenated with 100% oxygen for 5 minutes. Intraoperative mask acceptance and venepuncture score were recorded using the following scoring system.

Ability to perform venepuncture was graded as follows – (4 point scale)

- Grade I: Crying and un-cooperative, not able to start IV line.
 Grade II: Withdrawal for painful stimulus but allows to start IV line – No crying.
 Grade III: Calm, awake but not crying, no withdrawal for painful stimulus or IV cannulation.
 Grade IV: Asleep, no response to painful stimulus and IV cannulation.

Mask acceptance was graded as follows – (5 point scale)

- Grade I: Combative, crying
 Grade II: Moderate fear, not easily calmed
 Grade III: Co-operative with reassurance
 Grade IV: Calm, cooperative
 Grade V: Asleep.

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.

Children were maintained on nitrous oxide and oxygen and non-depolarizing muscle relaxant Inj. Atracurium 0.5 mg/kg was provided intraoperatively. Vital like pulse rate / heart rate, blood pressure, oxygen saturation, respiratory rate were observed regularly and recorded every 10 minutes interval. Neuromuscular blockade reversed with neostigmine (50µg/kg) and atropine (10-20 µg/kg), extubated and shifted to recovery room.

POSTOPERATIVE PERIOD:

Restlessness Score:

- Not restless – satisfactory – 1
- Restless – Unsatisfactory – 0

Vomiting Score:

- No vomiting or vomited once – Satisfactory – 1
- Repeated vomiting – Unsatisfactory - 0

STATISTICAL ANALYSIS: The age, sex distribution and body weight of the children in each group was analysed statistically.

Time for onset of sedation was recorded.

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Onset of sedation was assessed on a 5 point sedation scale. Grade III, IV and V of sedation scale were considered as adequate sedation, whereas Grade I and II were considered inadequate sedation for statistical evaluation.

Grade III and IV of anxiety scoring was considered as satisfactory and grade I and II as unsatisfactory for statistical evaluation.

Grade II, III and IV of venepuncture grading were considered successful and grade I was considered as failed venepuncture for statistical evaluation.

Grade III, IV and V of mask acceptance grading was considered successful and grade I and II as unsuccessful for statistical analysis.

Vital parameters such as heart rate, respiratory rate and systolic blood pressure were assessed before and after administering the sedative premedication and was statistically analyzed.

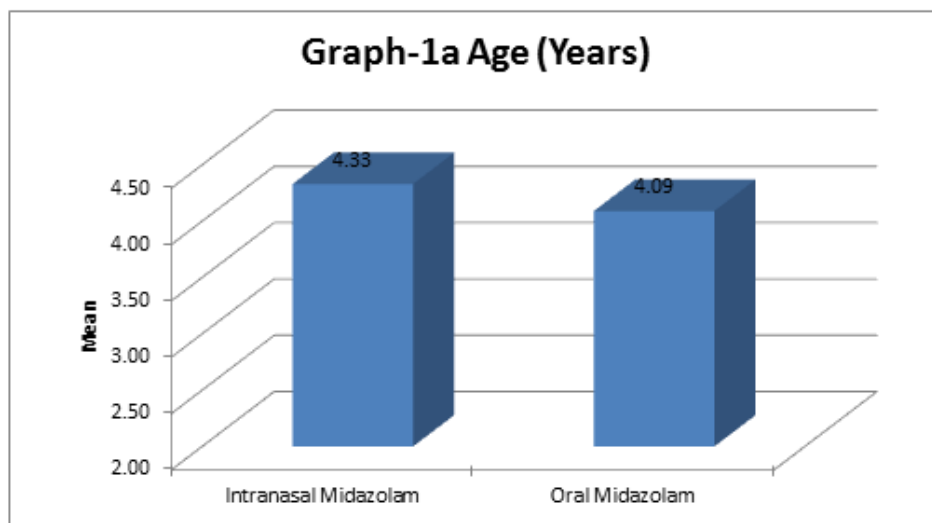
In the postoperative period; restlessness, vomiting were assessed.

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.

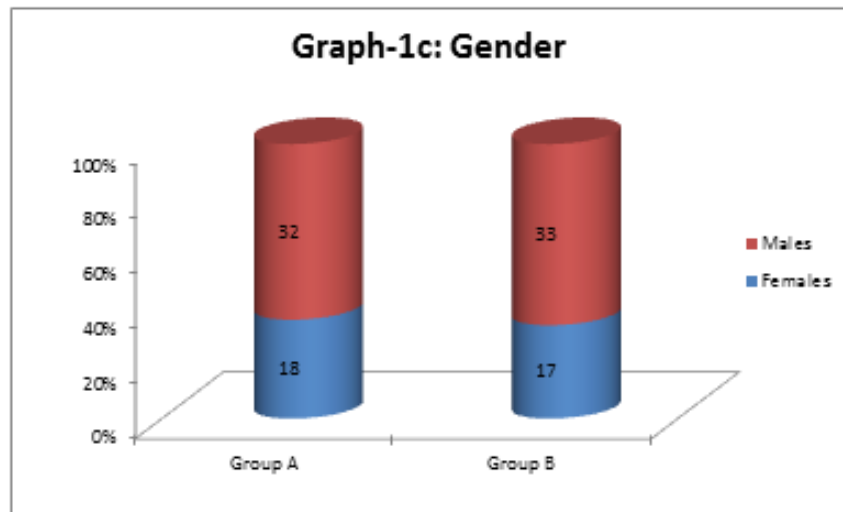
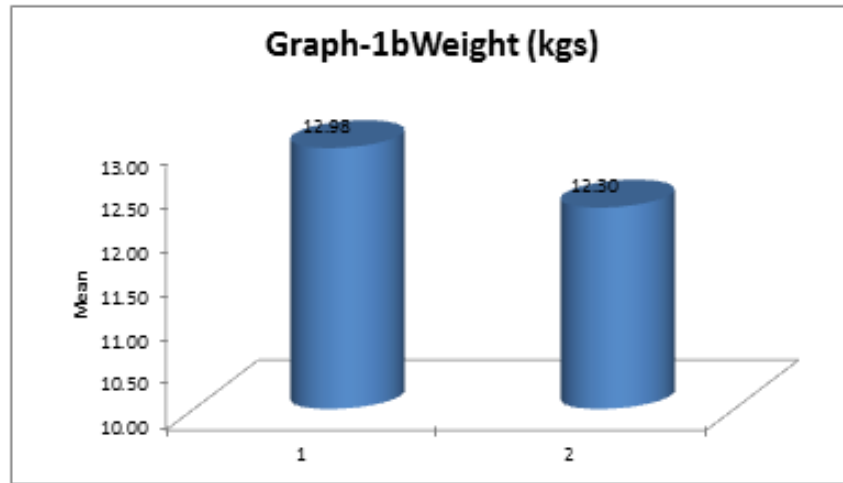
RESULTS: The two groups were comparable in age, sex and weight distribution.

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

TABLE 1: DEMOGRAPHIC DATA



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	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		

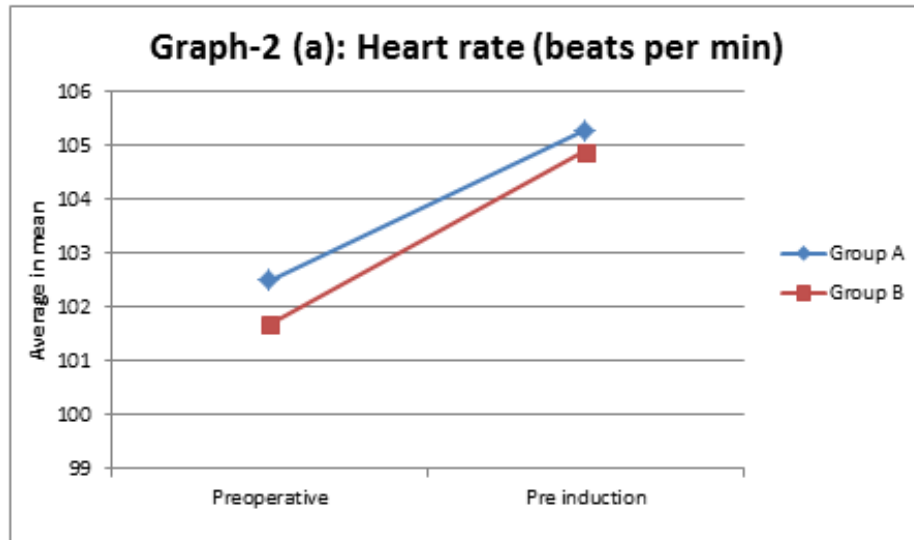
TABLE 2: VITAL PARAMETERS 2(a) Heart rate (beats per minute)

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, but the increase in both groups were similar and the increase in Group A was not statistically significant when compared to Group B [Table-2(a)]

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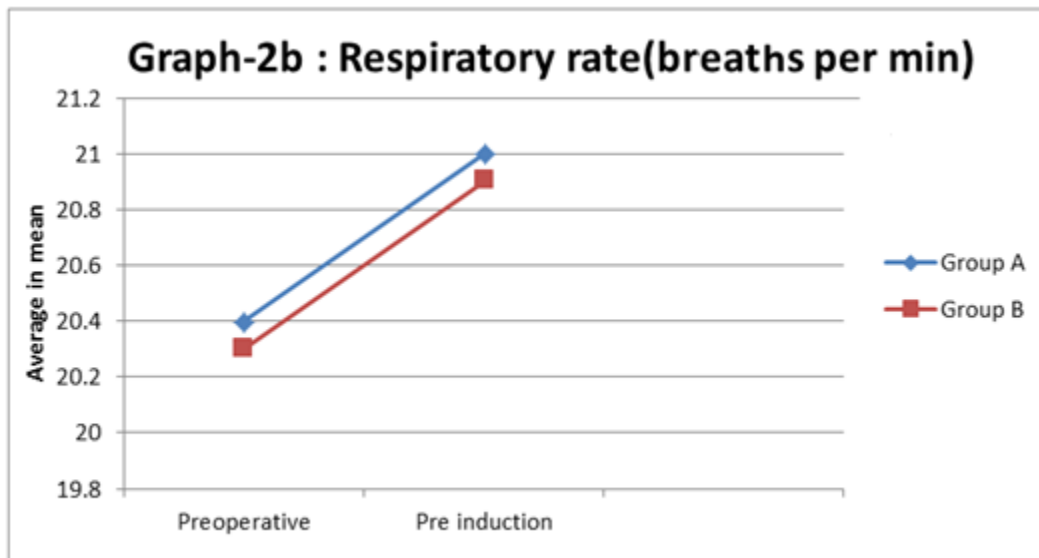


	Group A (mean \pm SD)	Group B (mean \pm SD)	Mean difference	P** value
Preoperative	20.4 \pm 0.6	20.3 \pm 0.5	0.08	0.47 NS
Pre induction	21.0 \pm 0.8	20.9 \pm 0.7	0.16	0.27 NS
Mean difference	0.66	0.58		
P*value	P<0.001 HS	P<0.001 HS		

Table 2(b) Respiratory rate (breaths per minute)

P* Students paired 't' test.

P** Students unpaired 't' test.



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There was a statistically significant increase in respiratory rate in both groups, group A and group B, but the increase in both groups were similar and the increase in Group A was not statistically significant when compared to Group B [Table-2(b)]

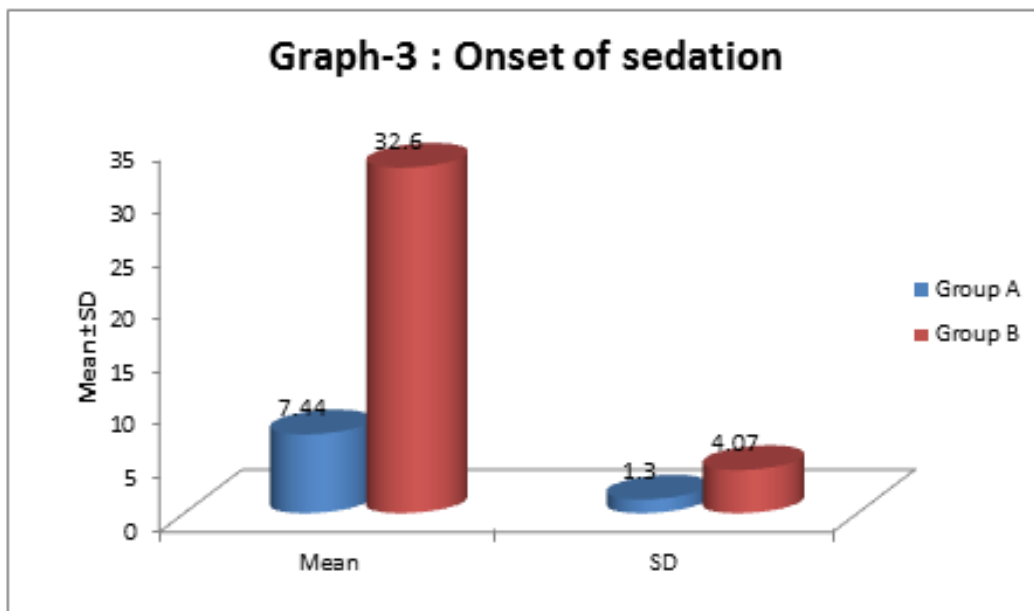
Onset of sedation	Group A	Group B
Mean	7.44	32.60
SD	1.30	4.07
Range (min)	5-9	25-40
Mean difference	25.16	
P*	P<0.001 HS	

TABLE 3: ONSET OF SEDATION

P* Students unpaired 't' test.

There was significant difference between 2 groups. Mean time of onset of sedation in group A was 7.44 min. Mean time of onset of sedation in group B was 32.60 min.

Onset of sedation was significantly faster in group A (7.44 ± 1.30) compared to group B (32.60 ± 4.07). This was found to be statistically and clinically highly significant with p-value of <0.001 . [Table-3].



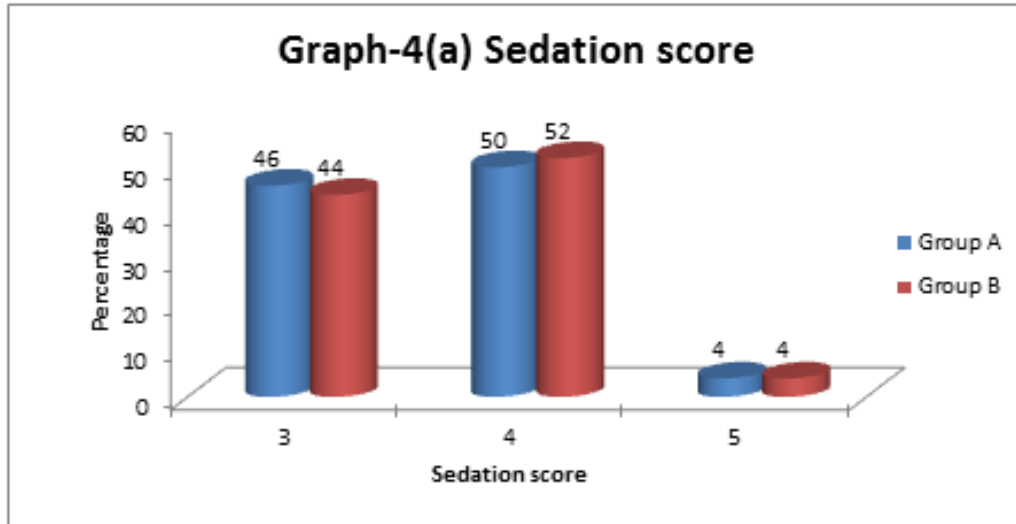
Groups	Sedation score			Total
	3	4	5	
Group A	23 (46%)	25 (50%)	2 (4%)	50 (100%)
Group B	22 (44%)	26 (52%)	2 (4%)	50 (100%)

TABLE 4(a): SEDATION SCORE

$X^2 = 0.04$, $P=0.97$ NS

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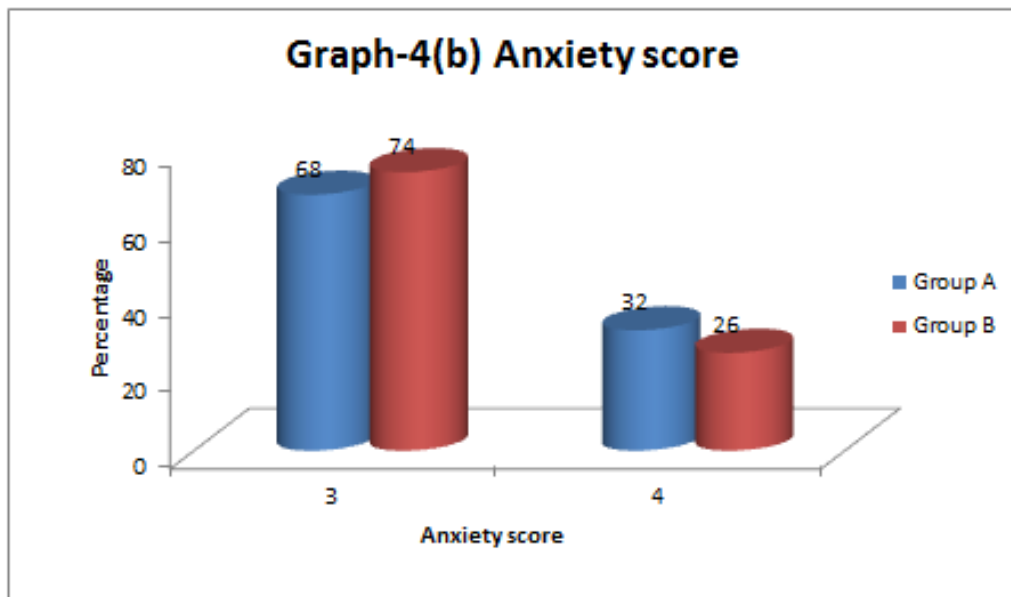
Sedation was assessed on a 5 point sedation scale, score-1 was agitated and crying upto score 5 was asleep. Children achieved satisfactory sedation in both the groups but in comparison, values were found to be statistically insignificant with p-value of 0.97. [Table 4(a)]



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

TABLE 4(b): ANXIETY SCORE

$X^2 = 0.6, P=0.74$ NS.



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Anxiety was assessed on a 4 point scoring system. Satisfactory anxiolysis was seen in both groups of children but in comparison, values were found to be statistically insignificant with p-value of 0.74 [Table 4(b)].

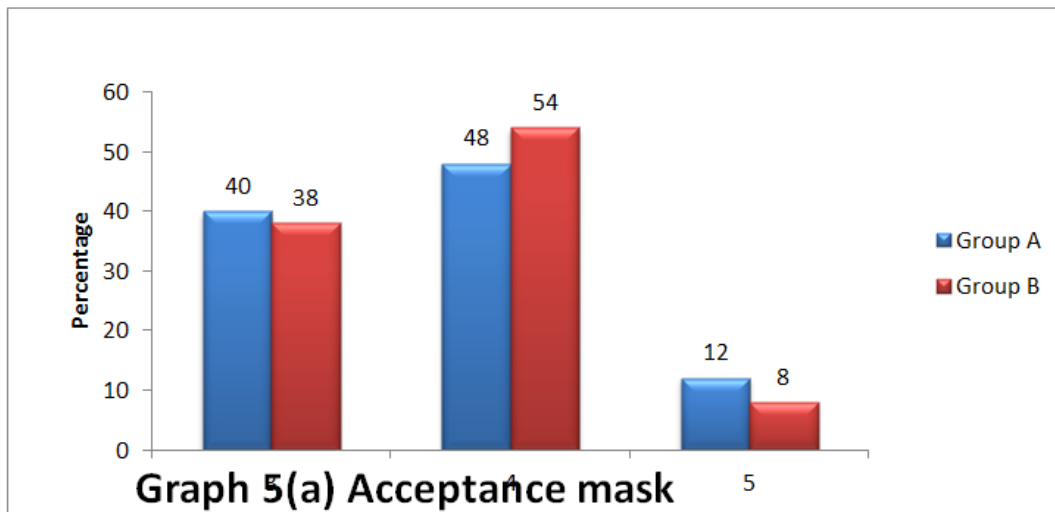
TABLE 5: OBSERVATION ON ARRIVAL IN OPERATION THEATRE:

Groups	3	4	5	Total	X ²	p
Group A	20 (40%)	24 (48%)	6 (12%)	50 (100%)	0.6	0.74 NS
Group B	19 (38%)	27 (54%)	4 (8%)	50 (100%)		
Acceptance of mask (a)						

Groups	2	3	4	Total	X ²	P
Group A	15 (30%)	27 (54%)	8 (16%)	50 (100%)	1.0	0.60 NS
Group B	14 (28%)	31 (62%)	5 (10%)	50 (100%)		
Venepuncture score (b)						

Mask acceptance was assessed on a 5 point scoring system. Children in both groups cooperated for mask acceptance but in comparison values were found to be statistically insignificant with p-value of 0.74 [Table 5(a)].

Venepuncture score was assessed on a 4 point scale. Children in both the groups co-operated for IV cannulation but in comparison values were found to be statistically insignificant with p-value of 0.60 [Table-5(b)].



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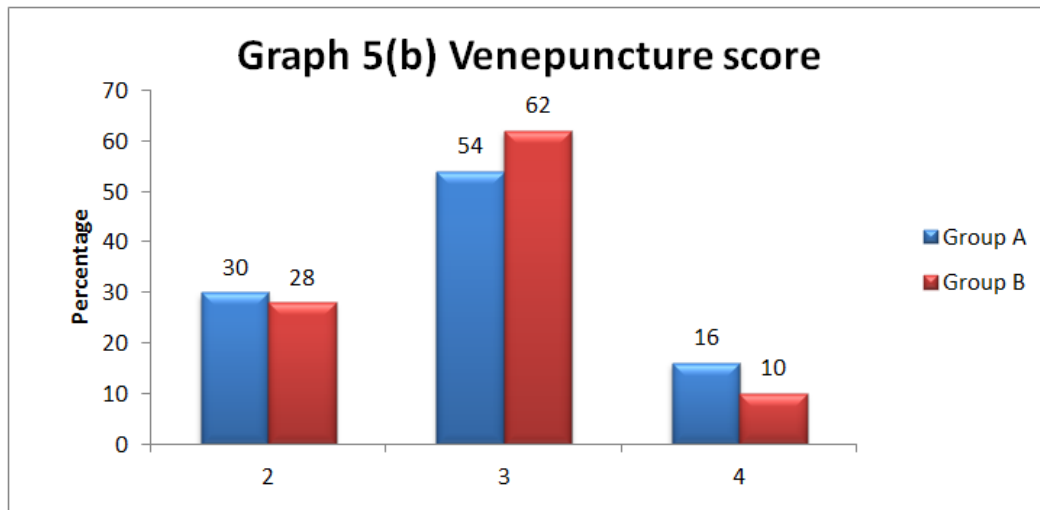


TABLE 6: POSTOPERATIVE:

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

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%)		
Vomiting score (b)					

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

In group A only 3 (6%) children had vomiting. In group B only 2(4%) children had vomiting. Values were found to be statistically insignificant with p-value of 0.65 [Table 6(b)].

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, 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.⁸

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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 ± 3.7 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.⁹

Lee Kim et al⁹ 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 ($P \leq 0.05$) 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.

They concluded that mean onset was approximately 3 times faster with IN administration compared to PO administration.

Overall behaviour under PO and IN was similar and all vital signs were stable throughout the procedures and showed no significant differences between PO and IN administration.

VITAL PARAMETERS:

a) Heart rate: There was a statistically significant increase in heart rate in both groups.

In group A 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 . 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.¹⁰

b) 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.¹¹

ONSET OF SEDATION: Onset of sedation was significantly faster in group A with a mean of 7.44 ± 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.⁹ Malinovsky JM et al¹² and Rose E. et al¹³

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 McCluskey et al,² (43 min) , McMillan CO et al¹¹ (30 min) and Weldon BC et al¹⁴ (15-50 min).

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SEDATION AND ANXIOLYSIS:

In both the groups satisfactory sedation and anxiolysis was seen.

In group A 46% of children reached sedation score of 3, 50% children reached score of 4 and 4% children reached score of 5. In group B, 32% children reached anxiolysis score of 4 and 68% children reached score of 3.

In group B 44% of children reached sedation score of 3, 52% children reached score of 4 and 4% children reached score of 5. In group B, 26% children reached anxiolysis score of 4 and 74% children reached score of 3. Children in both groups were easily separated from their parents.

MASK ACCEPTANCE: In group A, 40% children reached score of 3, 48% children reached score of 4 and 12% reached score of 5. In group B 38% children reached score of 3, 54% of children reached score of 4 and 8% children reached score of 5. This was in comparison with studies of Alderson et al¹⁶ (80%).

VENEPUNCTURE SCORE: In group A 30% children reached a score of 2, 54% children reached score of 3 and 16% children reached score of 4. In group B, 28% children reached score of 2, 62% children reached score of 3 and 10% children reached score of 4.

Pan AK et al,¹⁷ in their study on comparison of oral midazolam, ketamine and midazolam plus ketamine for premedication, achieved a success rate of 85% in venepuncture in the midazolam group (0.5 mg/kg) as against ketamine (70%) or midazolam plus ketamine (80%).

Mc Erlean et al,¹⁸ studied the effect of midazolam 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 al¹⁷ and McErlen et al.¹⁸ Children in both the groups co-operated for IV cannulation.

CARDIORESPIRATORY STATUS: Intraoperatively the changes in heart rate, and respiratory rate were less than 15% in all the cases studied and hence satisfactory. This was in comparison with studies of Lee Kim et al⁹ and Connors K. et al.¹⁵

POSTOPERATIVE SIDE EFFECTS: Postoperatively patients in both groups had minimal restlessness in 6% of children. Only 6% of children in group A and 4% of children in group B had vomiting. This was in comparison with studies of Alderson PJ et al.¹⁶

Only adverse effect seen with intranasal group is crying of child due to irritation and burning sensation of nasal mucosa following administration of drug. This was in comparison with studies of Milnovsky M et al.¹²

CONCLUSION: On comparison between intranasal route and oral route of administration of midazolam, Onset of sedation was significantly faster with intranasal administration compared with oral route, equally effective and no statistical differences were seen between them. All vital signs were stable throughout the procedure.

REFERENCES:

1. Cote CJ. Preoperative preparation and premedication. *Br J Anaesth* 1999; 83: 6-28.
2. McCluskev A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-care anaesthesia. *Anaesthesia*, 1994; 49: 782-785.
3. Kain ZN, et al. Midazolam effects on amnesia and anxiety in children. *Anesthesiology* 2000; 93: 676-684.
4. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric out patients. *Anaesthesia* 1990; 73: 831-834.
5. Cote CJ. Paediatric Anaesthesia. In Miller RD (editor), *Anaesthesia*, 5th edition, New York, Churchill Living Stone, Vol. 2, 2000,2088-2117.
6. Chien YW, Su KSE, Chang SF. Anatomy and physiology of the nose. Chapter-1 In : *In nasal systemic drug delivery*. Dekker, New York: 1989.p.1-26.
7. Ashwani K. Chhibber, Kenneth Fickling and Stewart J. Lustik. Pre-anaesthetic midazolam: A randomized trial with three different routes of administration. *J Anaesth Clin Res* 2011; 2(1):e1000118.
8. Suresh C, Kulshrenstha S, Jain A, Kohli P. Oral premedication for pediatric ambulatory anaesthesia: A comparison of midazolam and ketamine. *Ind J Anaesth*, 2000; 44: 41-46.
9. Lee-Kim SJ, Fadavi S, Punwani, Koerber A. Nasal versus oral midazolam sedation for paediatric dental patients. *J Dent Child* 2004 May-Aug; 71(2):126-130.
10. Levine MF, Spahr-Schopfer IA, Hartley E, MacPherson B. Oral midazolam premedication in children: The minimum time interval for separation from parents. *Can J Anaesth*, 1993; 40 (8): 726-729.
11. McMillan CO, Spahr-Schopfer IA, Sikich N., Hardey E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth* 1992; 39 (6): 545-550.
12. Malinovsky M, Poplaire C, Cozian A, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children: effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia* 1995; 50: 351-354.
13. Rose E, Simon D, Haberer JP. Premedication with intranasal midazolam in pediatric anesthesia. *Ann Fr Anesth Reanim* 1990; 9(4):326-30.
14. Weldon BC, Watcha MF, White PF. Oral midazolam in children: Effect of time and adjunctive therapy. *Anesth Ana/g*, 1992; 75: 51-55.
15. Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. *Ann Emerg Med*, 1994 Dec; 24(6):1074-1079.
16. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia : a comparison of Midazolam and Ketamine. *Can J Anaesth* 1994; 41 (3): 221-226.
17. Pan AK, Rudra A, Ghosh M, Biswas BN, Sen A, Kar A. Oral preanesthetic medication for children: A comparison of midazolam, ketamine and midazolam plus ketamine. *J Ind Asso Pediatr Surg* 2001 Oct; 6:135-142.
18. Mc Erlean M, Bartfield J, Karunakar TA, Whitman MCW, Turlev DM. Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion *J Pediatr*, 2003, 142: 429-30.

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Date of Submission: 03/12/2014.
Date of Peer Review: 04/12/2014.
Date of Acceptance: 02/01/2015.
Date of Publishing: 10/01/2015.