A study to determine the effectiveness of rectally administered Midazolam for premedication in children.

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Citation

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Abstract

This prospective double blind and randomized study was undertaken to evaluate the efficacy of rectally administered midazolam for premedication of paediatric patients. 100 ASA grade I and II children in the age group of 5-10 years were randomly allocated to two groups of 50 patients each. Group I (midazolam group) received 0.3mg/kg midazolam rectally and group II (saline group) received 5 ml of normal saline rectally.The results of the study showed that midazolam in the dosage of 0.3mg/kg given rectally was acceptable to children, produced satisfactory sedation, provided easy separation of children from parents, maintained stable cardio respiratory status preoperatively as well as postoperatively and produced smooth emergence from anaesthesia but with delayed recovery.

INTRODUCTION

Surgery and anaesthesia can cause considerable distress and psychological consequences for both parents and children. Psycho social factors such as anxiety, fear of separation from parents especially in children justify the use of premedication. Premedication with sedatives may alleviate this anxiety. However with children the intramuscular route for agent administration may in itself produce anxiety. Thus premedication administered via alternate routes is beneficial in this setting. [134] Different non invasive routes of administration have been described producing acceptable or good sedation, reducing the anxiety of separation from parents and facilitating induction of anaesthesia. [5]

Midazolam is a safe and effective drug for premedication of children scheduled for ambulatory surgery. It is a short acting water soluble benzodiazepine with a short half life and it can be given through all routes, and has ability to be absorbed transmucosally. [67] There have been several previous investigations involving rectal administration of midazolam for premedication. [8] Rectal administration of midazolam may offer similar sedation and relief of anxiety without the discomfort and fear associated with intramuscular administration in children. [9]

Keeping in view the above considerations, our study was designed to determine the effectiveness and safety of rectally administered midazolam for premedication of children, and its effect on post anaesthetic recovery.

MATERIAL AND METHODS

This prospective, randomized double blind study included 100 patients belonging to grade ASA I or II, aged 5-10 years undergoing different elective surgical procedures. The study was approved by hospital ethical committee, and written informed consent was taken from parents of all patients. Exclusion criteria included patients with respiratory, cardiac, renal or haematological diseases and allergy to benzodiazepines. Children were allocated into two groups of 50 patients each. Group I (midazolam, GM) included 50 children who were given midazolam as premedicant 0.3mg/kg diluted in 5 ml saline solution and administered per rectally with a lubricated feeding tube and inserted 7-10 cms beyond anal opening, 15 minutes prior to taking to operating room. Group II (saline, GS),included 50 children who were given only 5 ml of normal saline per rectum and acted as control.

Before administration of drug, children were brought to reception area of operation theatre along with their parents.

Heart rate, oxygen saturation and respiratory rate were monitored before and at 5, 10, and 15 minutes after administration of drug. Patient's response was noted and degree of sedation was assessed before premedication and at 5, 10 and 15 minutes after administration of drug using 5 point sedation scale. (Wilton, 1993)(Table 1)Anaesthetists who administered the drug and who assessed sedation scores were blinded to the study. At 15 minutes child was separated from the parents and taken to operating room and response to separation from parents was recorded for each patient using 4 point separation and induction score. (Peter Davis, 1995)(Table 2)

In the operating room, IV line was secured and IV infusion of N/2 DNS started. Heart rate, blood pressure and Spo_2 were monitored throughout the procedure. After preoxygenation for 3 minutes children were induced with sodium thiopentone 5mg/kg body wt.Endotracheal intubation was facilitated with atracurium 0.5mg/kg and anaesthesia was maintained with 60% nitrous oxide in 40% oxygen with 1% halothane. Morphine 0.1mg/kg was given as analgesic and diclofenac sodium suppository 1mg/kg was given per rectal for post operative pain relief. At the end of surgery residual neuromuscular block was reversed with neostigmine 50 micrograms/kg and glycopyrrolate 4 microgram/kg and patients were extubated.Patients were shifted to recovery room and assessed by post anaesthesia recovery score at 5,10,15 and 30 minutes after extubation.(Table 3).

All data was collected and comparison between the two groups for continuous variables was expressed as mean ± standard deviation of mean and analyzed using standard statistical tests and inference drawn accordingly. P value <0.05 was taken as statistically significant.

Figure 1

Table 1: (Sedation Score)

Sedation Level	Score
Agitated, clinging to parents	1
Alert, awake but not clinging to parent	2
Calm, sitting or lying with eyes open, relaxed	3
Drowsy, eyes close but responding to minor stimulation	4
Asleep, not responding to minor stimulation	5

Figure 7

Figure 2: Comparison of Heart rate (mean±SD) at various time intervals between the 2 groups

Criteria	Score
1. Patient unafraid, cooperative asleep	Excellent
2. Slight fear, crying, quiet on reassurance	Good
3. Moderate fear, crying, not quiet on reassurance	Fair
4. Crying, need for restrain	Poor

Figure 3

Table 3: (Post anaesthesia recovery stage)

Stage I	Awake, does not feel sleepy and initiates conversation
Stage II	Awake, but feels sleepy
Stage III	Asleep, but responds to both verbal &painful Stimulation
Stage IV	Asleep responds to painful stimuli
Stage V	Asleep does not respond to painful stimuli

RESULTS

There was statistically no significant difference in age, weight and sex between the two groups. (Table 4, Fig 1)All children accepted rectally administered drug.

The mean heart rate in the midazolam group at5, 10, and 15 minutes after premedication was 95±5.1, 90.6±4.1 and 88.2±2.8 respectively. In the control group the mean heart rate was 108.7+7.2, 108.6+7.7 and 108.7+7.5 respectively. The difference between the two groups was statistically significant at all time intervals. ($p<0.001$) table 5, fig 2.

The sedation was judged to be adequate if the preoperative levels were 3, 4 or 5. By this standard at 5 mts 1 child(2%) was calm,24 children(48%)were awake and 25 children (50%) were agitated, while as in control group only I child(2%) was awake and 49 children(98%) were agitated. The difference between the two groups was statistically significant($p<0.001$).At 10 mts 20 children(40%) were calm and relaxed while as 30children(60%) were not anxious in midazolam group whereas 44 children (88%) were agitated and only 6 children(12%) were not anxious but awake in the control group .The difference was statistically significant.

At 15 minutes 84 % children were calm and relaxed whereas 16% children were drowsy but responded to minor stimulation in the midazolam group while as 46% children were alert and awake but not crying and 46% were agitated and only 8% were calm and relaxed, none of the children was drowsy in the control group. The difference was statistically significant.($p<0.001$) Table 6.

Child behaviour separation score: In midazolam group

excellent score was seen in 10% of children, good (satisfactory) score in 90% of children. None of the children had a fair or poor score, whereas fair and poor score was seen in94% of children and good (satisfactory) score in 6% children in the control group. None of the children had excellent score. The difference between the two groups was statistically significant (p<0.001).Table 7, Fig 3.

In our study post anaesthesia arousal was delayed in midazolam group. At 5 mts 100% children in midazolam group had post anaesthesia arousal stage V as compared to 84% children in control group. The difference was statistically significant(p<0.001).At 10 mts 96% patients in midazolam group and 60% in control group had grade IV post anaesthesia arousal stage. The difference was significant statistically. At 15 mts 70% patients in midazolam group and only 4% patients in control group had grade IV post anaesthesia arousal stage. The difference was statistically significant (p<0.000). Similarly at 30 mts post anaesthesia, about 78% children in midazolam group were asleep but responded to painful and verbal stimulation while as, in control group only 4% children were asleep. The difference was statistically significant (p<0.001).(table 8)

Figure 4

Table 4: Comparison of Demographic data between two groups

	Midazolam group	Control group	Result
	Mean ± SD	Mean± SD	P value
Age(Yrs)	7±1.6(5,10)	6.9±1.7(5,10)	0.717(NS)
Weight(Kg)	20.8±5.0(15,45)	20.6±4.5(14,32)	0.818(NS)
Male (%)	47(94.0)	42(84.0)	0.112(NS)
Female (%)	3(6.0)	8(16.0)	

Figure 5

Figure 1: Bar diagram showing demographic data between two groups

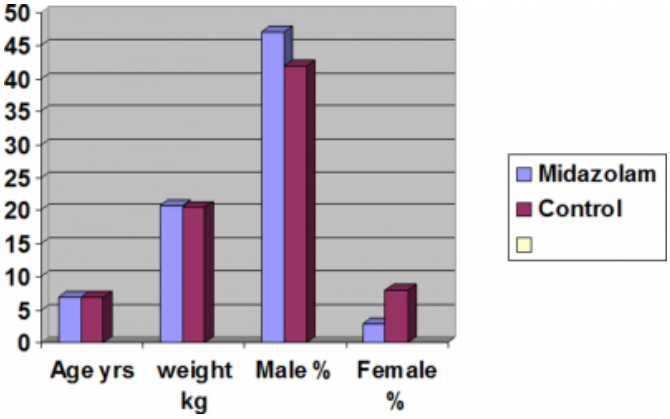

Figure 6

Table 5: Comparison of Heart rate(beats/min) at various time interval between two groups.

Heart Rate (Beats/min)	Midazolam Group	Control Group	Result
	Mean±SD	Mean±SD	p value
Before premedication	98.5±5.5(90,110)	108.9±7.4(98,130)	0.000 (sig)
At 5 mts	95.0±5.1(85,105)	108.7±7.2(98,130)	0.000 (sig)
At 10 mts	90.6±4.1(82,102)	108.6±7.7(92,130)	0.000 (sig)
At 15 mts	88.2±2.8(80,92)	108.7±7.5(98,130)	0.000 (sig)
Overall (friedmann test)	X^2=141.025, p=0.000(sig)	X^2=5.961 p=0.000(sig)	

Figure 8

Table 6: Comparison of sedation Scores after premedication at various time intervals between two groups.

Time After Premedication.	Sedation Score	Midazolam		Control		P value
		n	%	n	%	
5 mts	1	25	50.0	49	98.0	0.000 (sig)
	2	24	48.0	1	2.0	
	3	1	2.0	0	0.0	
	Mean± SD	1.52±0.54(1,3)		1.02±0.14(1,2)		0.000 (sig)
10 mts	1	0	0.0	44	88.0	0.000 (sig)
	2	30	60.0	6	12.0	
	3	20	40.0	0	0.0	
	Mean± SD	4.40±0.49(2,3)		1.12±0.33(1,2)		0.000 (sig)
15 mts	1	0	0.0	23	46.0	0.000 (sig)
	2	0	0.0	23	46.0	
	3	42	84.0	4	8.0	
	4	8	16.0	0	0.0	
	Mean± SD	3.16±0.37(3,4)		1.62±0.63(1,3)		0.000 (sig)
Overall (friedmann test)		X^2=91.292 p=0.000(sig)		X^2=49.143 p=0.000(sig)		

Figure 9

Table 7: Comparison of Child Behaviour Separation Scores between two groups.

Child Behaviour Separation Score	Midazolam Group		Control Group		P value
	n	%	n	%	
Excellent	5	10.0	0	0.0	0.000 (sig)
Good	45	90.0	3	6.0	
Fair	0	0.0	27	54.0	
Poor	0	0.0	20	40.0	

Figure 10

Figure 3: Comparison of Child behaviour Separation scores in two groups.

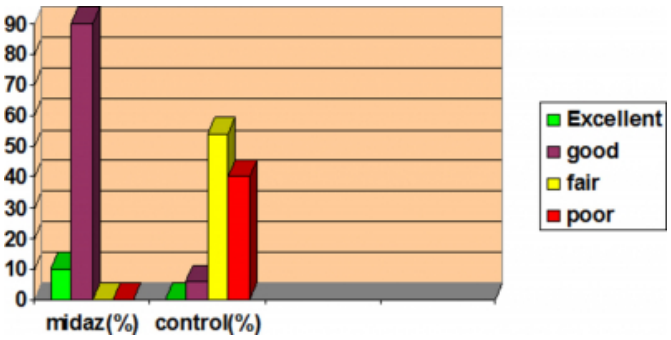

Figure 11

Table 8: Comparison of post anaesthesia Arousal Stage at different time intervals between the two groups.

Post anaesthesia Arousal Stage	Grade	Midazolam Group		Control Group		P value
		n	%	n	%	
5 minutes	Grade I	0	0.0	0	0.0	0.003 (sig)
	Grade II	0	0.0	0	0.0	
	Grade III	0	0.0	2	4.0	
	Grade IV	0	0.0	6	12.0	
	Grade V	50	100.0	42	84.0	
10 minutes	Grade I	0	0.0	0	0.0	0.000 (sig)
	Grade II	0	0.0	7	14.0	
	Grade III	0	0.0	10	20.0	
	Grade IV	48	96.0	33	66.0	
	Grade V	2	4.0	0	0.0	
15 minutes	Grade I	0	0.0	1	2.0	0.000 (sig)
	Grade II	0	0.0	36	72.0	
	Grade III	12	24.0	11	22.0	
	Grade IV	38	76.0	2	4.0	
	Grade V	0	0.0	0	0.0	
30 minutes	Grade I	0	0.0	27	54.0	0.000 (sig)
	Grade II	9	18.0	21	42.0	
	Grade III	39	78.0	2	4.0	
	Grade IV	2	4.0	0	0.0	
	Grade V	0	0.0	0	0.0	
Overall(Friedmann test)		X^2=141.923 p=0.000(sig)		X^2=140.648 p=0.000(sig)		

{image:11}

DISCUSSION

The most common reason for administering premedication presently is to make the experience of anaesthesia and surgery more pleasant and less traumatic for our patients especially children [10] . Midazolam is an effective drug for premedication both in adults and children. [11] The rapid and reliable onset of action, avoidance of painful injections, ease of administration and predictable effects of transmucosal administration of midazolam, like rectal route have become popular with anaesthesiologists. The degree of sedation 20 to 30 minutes after rectal administration of midazolam is sufficient for smooth induction of anaesthesia via halothane and nitrous oxide. Like other benzodiazepines, midazolam is rapidly absorbed by rectal route. [9]

In our study, we used midazolam 0.3mg/kg rectally as doses less than 0.2mg/kg appeared to be ineffective. [12] Saint Maurice in 1987, in his study showed dose of 0.35-0.45mg/kg to be suitable for the preoperative medication of children between 2-10 years.

All children in our study accepted rectally administered drug in both groups which is consistent with the study done by Roelofs JA et al. [13] The acceptance of premedication is somehow similar to that of the study of Piotrowski R etal [14] in 1986 where out of 80 children, 68 accepted rectal

instillation well. In contradiction to our results Tolksdorf in 1991 found that oral midazolam to be better accepted than rectal midazolam. [15]

Children were sedated satisfactorily with midazolam, their number increased to 40% at 10 mts and 84% at 15 mts which was statistically significant ($p<0.05$). The results were consistent to those observed by Niall CT etal [12] .Kretz et al compared 0.5mg/kg rectal midazolam to 1.5mg/kg rectal diazepam and found that peak plasma concentration of midazolam was seen after 15 mts of administration. [16] Piotrowski R in his study observed optimal time for sedato-hypnotic action to be 20-30 minutes. [14] Tolksdorf found fastest onset of action with rectal midazolam when compared to oral and nasal route. [15]

In our study number of children who behaved satisfactorily at the time of separation of patients was 90% in midazolam group as compared to 6% in the control group. This observation was similar to study by Peter J Davis et al [17] who proved in his study that midazolam caused better and easier child separation than those who received normal saline.(90% Vs 54%)Similar results were shown by Helen W Karl etal and David S Bee in 1992, [1819] who showed that midazolam was effective premedicant in children for easy child separation.

With respect to heart rate significant differences were seen between the two groups, which implied that midazolam decreased preoperative anxiety. Evidence for the same was seen in the study conducted by Pohl B, who showed premedication leads to decrease in arterial blood pressure and heart rate, [20] but Niall et al in 1988 [12] and Geopfert in 1996 [21] showed that heart rate did not change much during administration of midazolam in paediatric patients. Our study failed to show any impact of midazolam premedication on respiratory rate. Evidence for the same is seen in literature also. [2122]

Our study showed delayed post anaesthesia arousal in midazolam group, as 78% of children were asleep but arousable at 30 minutes post anaesthesia as compared to 4% children in control group. This was consistent with the study done by David S Beebe [19] who found rectal midazolam to prolong recovery. Our study differed from study by Spear et al [23] where rectal midazolam at dose up to 1.0mg/kg was found not to prolong recovery, however all of the children in their study received inhaled induction of general anaesthesia rather than IV induction. The delayed recovery in our study could partly be explained by residual sedation of midazolam after brief anaesthesia. This is supported by many studies. [8] One of the limitations of our study was that post anaesthesia period follow up was limited to 30 minutes only, which should have been more.

We conclude that rectal midazolam is an effective and acceptable premedication in children, with stable cardio respiratory status and provides smooth emergence from general anaesthesia.

References

1. Krane FJ,DavisPJ,Smith RM: Preoperative preparation. Smith,s Anaesthesia for infants and children.Edited by Motoyama EK,Davis PJ,St Louis,CV Mosby,1990,pp 211-216.
2. Eckenhoff JE: Relationships of anaesthesia to post operative personality changes in children. Am J Dis Child.1953: 86:587-591.
3. Twersky RS,Hartung J,Berger BJ,Mc Clain J,Beaton C. Midazolam enhances Anterograde but not retrograde amnesia in paediatric patients. Anaesthesiology 1993:78:51-55.
4. Holm-Knudsen R, Clausen TG, Eno D. Rectal administration of midazolam vs diazepam for preanaesthetic sedation in children. Anesth prog:1990 Jan-feb:37(1):29-31.
5. Lejus C,Renaudin M, Testa S, Malinovsky JM, Vigier T,and Souron R. Midazolam for premedication in children:Nasal Vs Rectal administration. European J of Anaesthesiology 1997:14:244-249.
6. Vadim khazin, Shaul Ezra, Major Amram Cohen,Mc Army. Comparison of rectal to intranasal administration of midazolam for premedication of children. Military Medicine 1995.160:11:579-581.
7. Julia JM, Rochette A, Ricard C, Jullien Y, du cailar J. Comparaison du midazolam et du flunitrazepam en premedication par voie rectale chez le hourrisson. Ann Fr Anesth Reanim 1984:3:185-188.
8. De Jong PC and Verburg MP. Comparison of rectal to intramuscular administration of midazolam and atropine for premedication of children. Acta Anaesthesiol Scand 1988:32:485-489.
9. Maurice CS, Meistelman C, Rey E, Esteve C, Lauture de D, Olive G.The pharmacokinetics of rectal midazolam for premedication in children. Anesthesiology 1986:65:536-538.
10. Paul F White et al. Pharmacological and chemical aspects of preoperative medication. Anesthesia & Analgesia 1986:65:96-71.
11. Rita L, Seleny FL, Mazurek A, Rabins S. Intramuscular midazolam for paediatric preanesthetic sedation.A double blind controlled study with morphine. Anesthesiology 1985:63:528-531.
12. Wilton NCT,Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology 1988:69:972-975.
13. Roelofse JA, VanDer Bijl P. Comparison of rectal midazolam and diazepam for premedication in paediatric dental patients. Oral Maxillofac Surg 1993 May:5(5):525-9.
14. Piotrowski R,Petrow N. Rectal premedication with midazolam in children. A comparative clinical study. Anesthetist 1989 Jan:38(1):16-21.
15. Tolksdorf W, Eick C. Rectal,oral and nasal premedication using midazolam in children aged 1-6 years.A comparative clinical study. Anesthetist 1991 Dec:40(12):661-7.

16. Kretz FJ, Liegl M, Heinemeyer G, Eyrich K. Die rektale Narkoseeinleitung bei kleinkindern mit Diazepam und Midazolam. Anasth Intensivmed 1985:26:343-346.
17. Peter Davis ,Julie A et al. Preanesthetic medication,extranasal midazolam for brief pediatric surgical proceedures . Anaesthesiology 1995:82:2-5.
18. Helen W Karl,James I Rosenberg. Transmucosal administration of midazolam for premedication of pediatric patients. Anesthesiology 1993:78:885-891.
19. Beebe DS,Belani KG,Chang PN,Hesse PS,Schuh JS, et al. Effectiveness of preoperative sedation with rectal midazolam,ketamine,or their combination in young children. Anesth Analg 1992:75:880-884.
20. Pohl B, Schmicker F, Hofmockel R. Oral and rectal premedication of children with midazolam. Anesthesio Reanem 2002:27(3):60-67.
21. Goepert A,Schwab A et al. Intranasal administration of midazolam in young children in emergency medicine. Anesthesia intensive Med 1996:31(1):26-28.
22. Geldner G,Hubmann M et al. Comparison between three transmucosal routes of administration of midazolam in children. Pediatric Anesthesia 1997:7(2):103-109.
23. Spear RM,Yaster M, Berkowitz ID et al.Preinduction of anesthesia in children with rectally administered midazolam. Anesthesiology 1991:74:670-674.

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