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Original Research Article

Effect of two different doses of oral midazolam premedication on separation anxiety in children scheduled for herniotomy

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ABSTRACT

Background: Peri-operative separation anxiety in children adversely impacts on their cognitive function and behavioural outcome. The aim of the study was to assess the effect of two different doses of oral midazolam premedication on separation anxiety in paediatric patients scheduled for herniotomy.
Methods: Eighty-four eligible children aged 1-6 years, of American Society of Anesthesiologists (ASA) class I or II, scheduled for herniotomy, were randomized into two groups, A and B, of 42 each after ethical clearance and written parental consent. Children in group A and group B received 0.5 mg/kg and 0.75 mg/kg respectively of oral midazolam flavoured with paracetamol syrup, were observed, and later separated from parents at 30 min post-premedication. Premedicant acceptability was noted, and separation anxiety was assessed using the Richmond agitation sedation scale (RASS). Statistical significance was set at $p<0.05$.
Results: All 84 children completed the study. At 30 min post-premedication, 47.6% in group A and 19.1% in group B had light sedation, while 52.4% in group A and 80.9% in group B were moderately sedated, $p=0.0001$. Premedicant acceptability and agitation scores between the groups were comparable, $p>0.05$.
Conclusions: Oral 0.5 mg/kg and 0.75 mg/kg midazolam induced desirable sedation in children at the 30th min with comparable lower agitation scores; however, the 0.75 mg/kg dose achieved significantly faster onset and higher level of sedation in a greater proportion of the subjects.

Keywords: Midazolam, Premedication, Sedation, Separation anxiety

INTRODUCTION

Greater than 60% of children undergoing hospitalization for anaesthesia and surgery develop anxiety.[1] This anxiety which is usually multifaceted, arising from fear of needles and cannulae, pain of surgical procedures, previous traumatic perioperative experience and feeling of insecurity, may be suppressed in the child till maximally unmasked at the time of parental separation. Separation anxiety in the paediatric surgical patient is a phenomenon capable of precipitating significant early and late undesirable effects. Besides triggering immediate untoward physiological manifestations such as hypersalivation, dysrhythmias, breath holding and laryngospasm perioperatively, it can adversely alter long term behavioural outcome.[2,3] Blocking undesirable autonomic upheaval and preventing occurrence of long term altered behavioural pattern through effective preanaesthetic medication, therefore, is an integral part of paediatric anaesthetic practice with ethical imperativeness, especially when non-pharmacological behavioural management strategies prove unsuccessful.[4] Amongst pharmacological agents sedative premedicants are generally preferred for paediatric patients.[3] Midazolam, a water soluble agent, similar to other benzodiazepines has documented anxiolytic, muscle relaxant, anterograde amnesic and dose dependent sedative properties, but is unique from the rest due to its rapid onset and short

duration of action.[5] Given orally 1-2 hours before surgery, benzodiazepines generally have minimal effect on cardiorespiratory function but large doses can interfere with the speed and quality of recovery.[6] Due to its unique properties, midazolam ranks as the most commonly used drug for paediatric sedative premedication and a dose range of 0.25-1.0 mg/kg has been reported as effective in children.[7] The aim of the study was to determine the efficacy of 0.5 mg/kg versus 0.75 mg/kg oral midazolam premedication on presurgical anxiety in Nigerian paediatric patients.

METHODS

Following ethical approval (UPTH/ADM/90/S.II/ VOL.XI/533) for a prospective, randomized, double-blind, comparative study and written informed consent from the parents, 84 children aged 1-6 years scheduled for elective herniotomy were randomized into two groups, A and B, of 42 each. All 84 children completed the study which was conducted from April, 2019, to August, 2020, in the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. Sample size (N) was determined using power analysis formula for interventional study.[8]

$$N = \frac{(Z\alpha + Z_\beta)^2 P(1-P)}{d^2}$$

Z_α = 1.28 with power of 90% for this study; Z_β = 1.96 at 5% significance level; P1= proportion of outcome in study group 1. In a related study, the proportion of children that had desirable sedation in the group which received 0.5 mg/kg midazolam was 55% (0.55), P2= proportion of outcome in group 2. On the basis of the Null hypothesis, the proportion of outcome in group 1 was assumed to be equal to that in group 2; therefore, P1=P2=55% (0.55).[4]

p = average proportion=

$$\frac{P1+P2}{2} = \frac{0.55+0.55}{2} = 0.55;$$

d = effect size. For this study the effect size is 26% (0.26).

Substituting:

$$N = \frac{(1.28 + 1.96)^2 \times 0.55\ (1 - 0.55)}{(0.26)^2} = 38.4$$

With an allowance for 10% (3.84) attrition, adjusted sample size = 42 per group. Therefore, for the 2 groups, the study included a total of 84 subjects. Simple randomization and blinding were ensured by picking of opaque envelopes and recruitment of research assistants, keeping the lead researcher blinded to the subjects' group allocations and study drug preparation. The parents of the subjects as directed picked one out of 84 opaque envelopes from a bag on the morning of surgery under the supervision of a research assistant and a nurse. Each of these envelopes concealed an alphabet (A or B) in it with an equal number of 42 of each alphabet in the bag. The envelope picked was excluded from the rest and the patient allocated to that group designated by the alphabet picked. Another registrar anaesthetist blinded to the outcome of the premedication prepared the study agents according to the group and weight specifications. Different codes were utilized for each subject's group and drug dose against hospital number to facilitate rapid access to every child involved in the study, should any adverse effect occur. A pre-operative evaluation and preparation the day before surgery was done for all patients; the children were withheld from solid food 6 hours, breast milk 4 hours, but given clear glucose fluids up to 2 hours prior to the time for surgery. The inclusion criteria were paediatric patients in ASA class I or II, age 1-6 years and weight 10 to 20 kg scheduled for herniotomy, whose parents gave consent for the study, while children in ASA class >II, of age <1 or >6 years, scheduled for emergency surgery, with known history of allergy to study agents, with behavioural problems, on sedative medication or whose parents refused to give consent for the study constituted the exclusion criteria.

On the morning of surgery, a multi-parameter monitor (Dash 4000®) was attached to obtain and record patients' heart rate, blood pressure, SpO_2 and peripheral temperature. Subjects in group A received 0.5 mg/kg of midazolam (Pfizer Medicals) plus flavoured acetaminophen (paracetamol) syrup (Emzor Pharmaceuticals), while group B received 0.75 mg/kg of midazolam plus same flavoured acetaminophen syrup, administered by the parents under the supervision of the nurse. The lead researcher assessed level of sedation or agitation upon parental separation (the primary outcome measure) 30 minutes after oral midazolam using the Richmond agitation sedation scale (RASS), and rated medication acceptability (the study's secondary outcome measure) using a four-point Likert scale: 1= accepts readily, 2= dislikes (as depicted by facial expression) but accepts, 3= accepts with great difficulty, 4= could not be pre-medicated because of extreme resistance.[9,10] All children had general anaesthesia induced with sevoflurane and maintained with isoflurane 1-2% in oxygen via LMA. Caudal block was performed with the patient in the left lateral position using 1 ml/kg of bupivacaine 0.25%. Post-operatively, diclofenac suppository 1.5-2 mg/kg daily was commenced for postoperative analgesia and the patients were transferred to the recovery room for continued observation of vital parameters till fit for discharge to the ward. Lactated Ringer's was administered to all patients guided by the 4-2-1 rule.

RESULTS

The mean age of the children in years was 3.06±1.78, and their demographic data were comparable across the groups (Table 1). All the children in the two groups had baseline sedation score of zero (alert). A significant difference in their levels of sedation, however, occurred from the 15th and up to the 30th minute post premedication, with group

B showing higher sedation scores. Fifteen minutes following premedication, while 18 children (42.9%) were drowsy (RASS=1) and only 24 (57.1%) had light sedation (RASS=2) in the group which received 0.5 mg/kg midazolam (group A), as much as 26 children (61.9%) had light sedation (RASS=2), with 16 (38.1%) moderately sedated (RASS=3), in group B which received 0.75mg/kg midazolam, p=0.0001. Thirty minutes following oral midazolam, up to 34 children (80.9%) manifested moderate sedation in group B compared to 22 (52.4%) in group A, with 8 (19.1%) in group B and 20 (47.6%.) in group A showing light sedation; this difference between the two groups was statistically significant, p=0.0001 (Table 2). A significant difference in mean sedation scores was also noted at the different time points between the two groups following oral midazolam premedication (Table 3). In the two groups, the children showed comparable baseline agitation scores: 36 (85.7%) were alert (score = 0) and 6 (14.3%) restless in group A, while in group B, 38 (90.5%) were alert and 4 (9.5%) restless, p=0.500. Fifteen minutes after premedication, none in group B, while 7.1% in group A showed restlessness, with group B showing a faster rate of diminution in agitation score, though this difference was also not significant, p=0.078 (Table 4**)**. While the mean difference in agitation scores across the groups (Table 5) was comparable at 30 min post oral midazolam administration, an intragroup significant decrease in the agitation score at 15 min post premedication was observed in group A, but not in group B. Oral midazolam acceptability was comparable across the groups (85.7% in group A and 83.3% in group B), p=0.763 (Table 6). Group A and B were comparable in their baseline mean SpO_2 values of 97.8% and 98% respectively. Throughout the study period the values remained within the normal range, though group B had a slightly higher mean SpO_2 value compared to group A (Figure 1).

Table 1: Demographic characteristics of subjects in the two groups.

Variables	Study group				T test	P value
	Group A (N=42)		Group B (N=42)			
	Mean	SD	Mean	SD		
Age (years)	3.29	1.74	2.83	1.81	1.18	0.241
Weight (kg)	14.21	3.14	12.86	3.96	1.73	0.087
Height (cm)	92.93	12.60	88.92	14.64	1.35	0.182

Table 2: Level of the Richmond sedation scores of the study groups at different time points.

Duration (min)*	Group A (0.5 mg/ kg midazolam)				Group B (0.75 mg/ kg midazolam)				χ^2	P value
	Sedation score									
	0 (alert)	1 (drowsy)	2 (light)	3 (moderate)	0 (alert)	1 (drowsy)	2 (light)	3 (moderate)		
0	42 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	42 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		
15	0 (0.0)	18 (42.9)	24 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	26 (61.9)	16 (38.1)	34.1	0.0001
30	0 (0.0)	0 (0.0)	20 (47.6)	22 (52.4)	0 (0.0)	0 (0.0)	8 (19.1)	34 (80.9)	26.2	0.0001

Note: *- Duration from time of administration of premedication.

Table 3: Mean difference in sedation scores at different time points post-premedication.

Time (I)	Time (J)	Mean difference (I-J)	Standard error	P value	95% CI for difference	
					Lower bound	Upper bound
Group A						
0	15	-1.33	0.15	0.001*	-1.71	-0.96
	30	-2.33	0.17	0.001*	-2.75	-1.91
15	0	1.33	0.15	0.001*	0.95	1.71
	30	-1.00	0.13	0.001*	-1.33	-0.67
Group B						
0	15	-1.00	0.00		-1.00	-1.00
	30	-1.62	0.08	0.001*	-1.81	-1.43
15	0	1.00	0.00		1.00	1.00
	30	-0.62	0.07	0.001*	-0.81	-0.43

Note: *- Statistically significant.

Table 4: Agitation scores of the study groups at different time points.

Time (mins)*	Group A (0.5 mg/ kg)		Group B (0.75 mg/ kg)		χ^2	P value
	Agitation score N (%)					
	0	1	0	1		
0	36 (85.7)	6 (14.3)	38 (90.5)	4 (9.5)	0.454	0.500
15	39 (92.9)	3 (7.1)	42 (100.0)	0 (0.0)	3.11	0.078
30	42 (100.0)	0 (0.0)	42 (100.0)	0 (0.0)	-	-

Note: *- Duration from time of administration of premedication.

Table 5: Post-premedication mean difference in agitation scores at the different time points.

Time (I)	Time (J)	Mean difference (I-J)	Standard error	P value	95% CI for difference	
					Lower bound	Upper bound
Group A						
0	15	0.071	0.040	0.250	-0.029	0.172
	30	0.143	0.055	0.037*	0.006	0.279
15	0	-0.071	0.040	0.250	-0.172	0.029
	30	0.071	0.040	0.250	-0.029	0.172
Group B						
0	15	0.095	0.046	0.132	-0.019	0.210
	30	0.095	0.046	0.132	-0.019	0.210
15	0	-0.095	0.046	0.132	-0.210	0.019
	30	0.000	0.000	.	0.000	0.000

Note: *- Statistically significant.

Table 6: Acceptability of oral midazolam in the two groups.

Variables	Study group				χ^2	P value
	Group A (N=42)		Group B (N=42)			
	N	%	N	%		
Accepts readily	36	85.7	35	83.3	0.091	0.763
Dislikes but accepts	6	14.3	7	16.7		
Total	42	100	42	100		

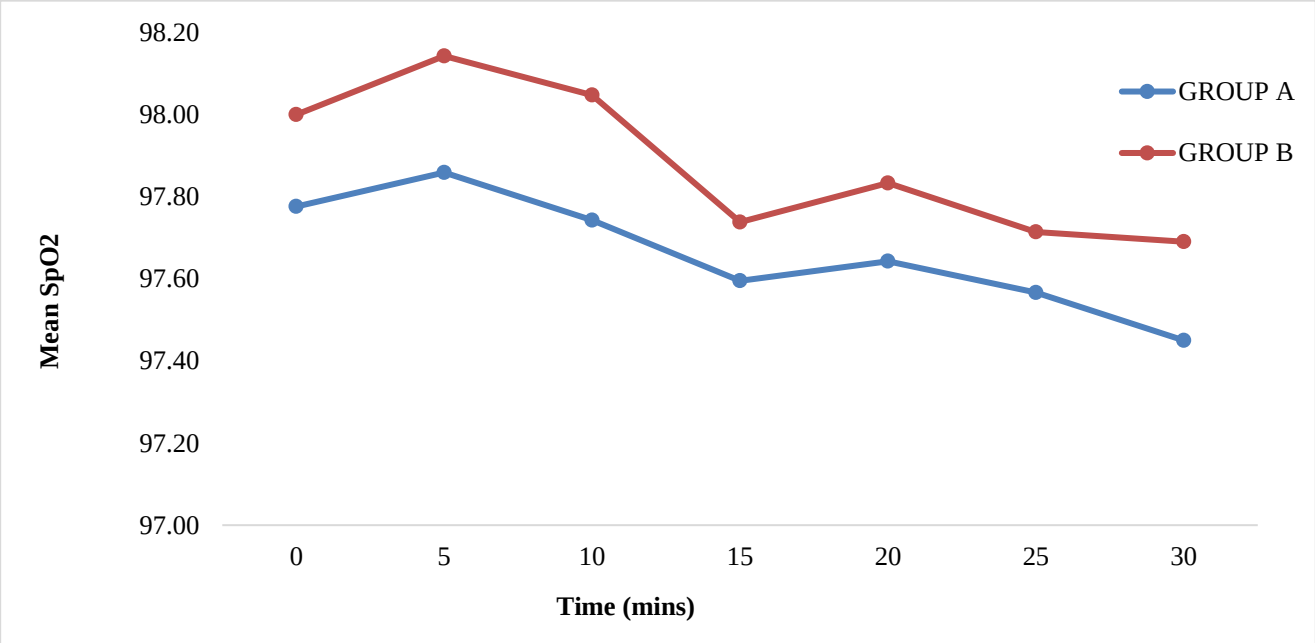

Figure 1: Line graph showing mean SpO_2 of participants in the two groups over study period.

DISCUSSION

The use of oral midazolam, as a sedative premedicant, greatly reduced the children's anxiety and circumvented a psychologically traumatising scenario, at the time of separation from their parents in the preoperative period; this was comparable in the two groups. However, a significantly higher level and faster onset of sedation was observed at the 15th and 30th minutes in group B that had 0.75 mg/kg oral midazolam premedication, compared to group A which received a dose of 0.5 mg/kg. Medication acceptability was similar in the two groups.

Clinical sedative effect of oral midazolam, as reported by Pandit et al, is evident within 10 to 30 min after its administration, and agrees with the decreased RASS scores from the 15th minute in this study.[10] The occurrence of a significantly faster onset of sedation in a greater proportion of subjects in group B, relative to group A, indicates a direct relationship between a higher dose of oral midazolam and faster onset of higher sedation level in children.

Sheta et al had similarly observed that the number of children with the desired sedation score was higher (80%) and similar among those who received 0.75 and 1 mg/kg oral midazolam compared to 65% in the group which received 0.5 mg/kg.[4] This was corroborated by Phaltankar and Shar et al.[11] The more rapid onset of sedation associated with the 0.75 mg/kg oral midazolam also lends evidence to the fact that a higher plasma bioavailability of midazolam was achieved with the higher of the two doses within a shorter time. Orally administered drugs undergo first pass metabolism which negatively affects bioavailability and, consequently, the minimum effective concentration that is necessary to produce the desired pharmacologic actions. Benzodiazepines undergo a significant first-pass metabolism.

Available literature documents that, consequently, of orally administered midazolam, only about 36% reach the systemic circulation in children aged 2 to <12 years.[12] Thus, based on its pharmacokinetics, a higher clinical dose of oral midazolam should compensate better for a high enterohepatic extraction and, theoretically, achieve a higher bioavailability than a lower dose within a shorter time frame. Sheta et al also reported deep sedation in 0%, 5% and 20% of the children in the 0.5 mg/kg, 0.75 mg/kg and 1 mg/kg oral midazolam groups respectively.[4] Similarly Beirami et al documented that undue sedation occurred in their group C subjects following the administration of 1 mg/kg oral midazolam.[13] Inferentially, a dose of 0.75 mg/kg or 0.8 mg/kg of injectable midazolam given orally as premedication, when compared to a 0.5 mg/kg dose, provided a rapid onset of a more desirable sedation, while a dose of 1.0 mg/kg produced an undue over sedation, thereby, posing threat of more harm than benefit in a proportion of children. Combining the documentation by Beirami et al with the report of Sheta et al 0.75 mg/kg oral midazolam empirically is associated with minimal or no causation of deep sedation.[4,13] In the two groups of this study, 0% deep sedation was observed supporting Beirami et al and of Sheta et al.[4,13] Excellent sedation is critical to achieving zero agitation level and circumventing the attendant short term and long term sequelae of preoperative anxiety in children. The evidence that children aged 1 to 5 years exhibit the highest level of separation anxiety, and the efficacy of oral midazolam premedication in decreasing the incidence of preoperative and emergence agitation among children has been documented.[14,15] Thus, pre-operatively, anxiolytic premedication for susceptible paediatric patients is warranted on ground of ethical imperativeness.

Although the mean agitation scores compared between the two groups in this study did not differ significantly, a decrease from baseline values in the two groups occurred at the 30th minute post premedication, with this reduction showing an intragroup significance in group A only. The slightly higher mean baseline agitation score (0.14) of group A than that (0.09) of group B explains this intragroup finding. This observation indicates a relatively more pronounced anxiolytic effect of midazolam in children with higher RASS score.[9]

Despite the nondetection of a significant difference in the agitation scores between the two groups of this study, there is derivable benefit in administering 0.75 mg/kg oral midazolam over 0.5 mg/kg in terms of actual reduction of separation anxiety in children. This can be inferred from the faster attainment of desired lower mean agitation score of 0.00 in all 42 (100%) children in Group B at the 15th min, compared to 39 (92.9%) in group A with same score, as seen in this study.

In their assessment of the effect of different doses of oral midazolam premedication on separation anxiety, Sheta et al reported that more children (75%) were comfortable at parental separation with corresponding better general anaesthesia induction process in the group that received 0.75 mg/kg dose compared to 55% in the group given 0.5 mg/kg.[4] Furthermore, an association between a significantly reduced apprehension in children and 0.75 mg/kg oral midazolam premedication in comparison with 0.5 mg/kg dose was established by Feld et al.[16] This dose related attenuation of agitation following enteral midazolam was also empirically corroborated by Phaltankar et al and Shar et al.[11] The failure to detect a significant difference in agitation scores between the groups in this present study, therefore, could be due to concealed physiological factors in the subjects used.

Some studies searching for the ideal dose of oral midazolam for premedication have reported varying results, owing largely to heterogeneity in drug preparation, sedation scales used, patient characteristics and time between premedication and separation from parents.[4] However, a careful analysis of the various reports reveals a consensus that oral midazolam 1 mg/kg is excessive, while a dose less than 0.5 mg/kg is ineffective in producing

desirable sedation needed to allay fear and anxiety in children caused by parental separation in the preoperative period.

The pharmacodynamic actions of midazolam have been linked to its intrinsic binding affinity to the $GABA_A$ receptor in the central nervous system and consequent enhancement of GABAergic neuronal activity. Besides $GABA_A$ the actions of midazolam are also mediated via interaction with benzodiazepine specific receptors (BZ1, BZ2 and BZ3) located in the brain. Activation of BZ receptors has been reported to cause a stronger $GABA_A$ mediated response.[17] Therefore, commensurate with the degree of activation of GABAergic and benzodiazepine receptors, correspondingly anxiolysis, sedation, hypnosis, and fatality can result at low doses, moderate doses, high doses, and at overdose of midazolam. Agitation and sedation are inversely related, with sedation being physiologically antagonistic to agitation; this underpins the design of the Richmond agitation sedation scale (RASS).[9] Therefore, since excellent attenuation of agitation is the desired goal of the paediatric anaesthesiologist, then a faster onset of optimal sedation that is devoid of respiratory compromise is strategic to a quicker attainment of the goal, as observed in this study; in this regard, an oral midazolam dose of 0.75 mg/kg is found to be superior to 0.5 mg/kg.

Children naturally have dislike for oral medication and may prove uncooperative, necessitating the use of sweeteners to improve drug acceptance. The bitter taste of injection midazolam was masked in this study with sweet tasting syrup acetaminophen, rendering it acceptable to all the children with no recorded incidence of vomiting. Sheta et al and Feld et al who did flavouring with apple juice in their midazolam study reported comparable drug acceptability.[4,16]

Kamel et al similarly concluded that oral midazolam mixed with sweetened acetaminophen syrup was much more acceptable to the children compared to nasal midazolam and ketamine.[18] Significant alterations in respiratory parameters were not observed in this study similar to the study by Phaltankar et al and Shar et al as well as by Mcmillan et al.[11,19] The majority of the children in the present study readily accepted the medication; comparison of the acceptability (85.7% in group A and 83.3% in group B), showed no statistically significant difference between the groups.

Phaltankar et al and Shah et al reported higher incidence of nausea and vomiting in association with the 0.75 mg/kg group in their study, an occurrence obviously due to their use of nitrous oxide.[11]

This study excluded nitrous oxide and observed zero incidence of nausea and vomiting. There is literary evidence that in relation to postoperative nausea and vomiting nitrous oxide is causative, while midazolam is both preventive and curative.[20]

CONCLUSION

The attainment of desired attenuation of preoperative separation anxiety in paediatric patients aged 1-6 years was comparable between 0.5 mg/kg and 0.75 mg/kg oral midazolam; however, the anxiolysis and a significantly higher level of desirable sedation were achieved faster in a greater proportion of the subjects who received the 0.75 mg/kg dose, without any respiratory derangement or significant adverse effects, but with similar medication acceptability in the two groups.

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