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Efficacy and safety of two doses of oral midazolam as premedication in paediatric patients: A prospective randomized and comparative study.

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Abstract : *The present study was conducted to assess and compare the efficacy and safety of two doses of oral midazolam as premedication in pediatric patients undergoing surgeries under general anesthesia. Forty children aged 1-5 years were enrolled and randomly assigned to one of the two groups and received oral preparation of midazolam in two doses of 0.5 mg/kg and 0.75 mg/kg in two groups respectively, 30 minutes before separation from parents. They were assessed for patient's acceptance of the medication , reaction to separation from parents, sedation scores and recovery conditions. With regard to children's reaction to separation from their parents, the number of comfortable children was more in group B (18,90%) as compared to group A (15,75%). On arrival to the operation room eight children (40%) had satisfactory sedation scores in group B as compared to 5(25%) in group A. Satisfactory sedation score was also higher in group B (10,50%) as compared to group A (4,20%) after reversal of residual paralysis. Time to spontaneous ventilation and extubation and time from pre-medication to full recovery were not different in two groups. Oral midazolam in a dose of 0.75 mg/kg is an acceptable, effective and safe premedication in children aged 1-5 years.*

Keywords: *anesthesia, midazolam, pediatric, premedication, ,sedation.*

I. INTRODUCTION

Effective premedication is an integral component of balanced anesthesia. As in adults, children also suffer from anxiety and separation from parents which may rise autonomic hyperactivity, dysrrythmias, hypersalivation, breath holding and laryngospasm perioperatively. Additionally it can also add to surgical stress response. Establishment of adequate pre-anaesthetic sedation and amnesia for pre and intraoperative event has thus assumed an important role in the anesthetic management of pediatric patients. An ideal premedication should allay apprehension regarding anesthesia and surgery, lessen the trauma of separation from family and facilitate induction of general anesthesia without prolonging the post-anaesthetic recovery period.[1]

As a general consensus pharmacological approach should be adopted only when behavioral (non-pharmacologic) management techniques fail. Midazolam has been found to be good pre-anaesthetic agent and also is the most commonly used benzodiazepine in pediatric patients. Its principal pharmacological effects are sedation, anxiolysis, anticonvulsant actions, spinal cord mediated skeletal muscle relaxation and anterograde amnesia. Midazolam in its syrup form has been shown to be an extremely safe premedication for children with a dose range of 0.25 to 1.0 mg/kg. [2,3] So this prospective, randomized and comparative study was undertaken to assess and compare the efficacy and the safety of oral midazolam in two different doses and to determine the optimal dose as a premedication in children of 1-5 years of age undergoing surgical procedures under general anesthesia.

II. MATERIALS & METHODS

In a randomized, prospective and comparative study, 40 children aged 1-5 years with American Society of Anesthesiologists (ASA) I & II status presenting for various surgical procedures under general anesthesia were included. After approval from institutional ethics committee, the study protocol was explained to the parents and informed consent was obtained from them. The children having upper respiratory tract infections, rhinopharyngitis, hypersensitivity to benzodiazepines, those treated with sedatives or anticonvulsants or if parents did not give consent were excluded from the study. The study patients were randomly assigned to one of the two groups according to the computer based randomization. Group A received oral midazolam in a dose of 0.5 mg/kg and Group B received oral midazolam in a dose of 0.75 mg/kg, 30 minutes before the procedure. The drug was prepared and administered by an anesthesiologist not involved in the study.

A standard general anesthesia protocol was followed for all the patients. All children were given atropine 0.01 mg/kg intravenously and induced with ketamine 1 mg/kg and propofol 2-3 mg/kg, intravenously. Orotracheal intubation was facilitated with intravenous succinylcholine 2.0 mg/kg. Children were taken on controlled ventilation and anaesthesia was maintained with a mixture of O_2 and NO_2 :: 50%:50% supplemented with sevoflurane (0.25-1.0%) and atracurium as and when required. Intrvenous fluids were administered as per standard protocol. After the completion of surgery, residual neuromuscular block was reversed with neostigmine .05 mg/kg and glycopyrrolate .01 mg/kg intravenously. Patient electrocardiogram, noninvasive blood pressure, pulse–oximetry and temperature were monitored intraoperatively. Paracetamol 10 mg/kg was given intramuscularly 30 minute before the end of the procedure. Tracheal extubation was done when normoventilation was achieved and the patients regained gag and cough reflex. Thereafter all patients were shifted to postoperative care unit and heart rate, blood pressure, arterial oxygen saturation were monitored. Children were also observed for the acceptance of the oral medication, reaction to the separation from parents, pre-induction and post extubation sedation scores and recovery conditions. Acceptance of the medication was defined as swallowing without immediate regurgitation. Reaction to the separation from parents was the response of the children when taken away from the parents, 30 minutes after the administration of the study syrups. It was graded as inconsolable cry, complaining, quiet but awake or sleepy. The degree of sedation when the child was first seen in the operative room and at the end after reversal of the residual paralysis was based upon 5 point sedation Score [4] as follows:

I. Anxious agitated
II. Oriented, calm and co-operative
III. Drowsy, responding to verbal commands
IV. Not responding to verbal commands but to the painful stimuli
V. Not responding to painful stimuli

With respect to recovery conditions, the children were also observed for spontaneous ventilation after giving the reversal and time required for establishing adequate spontaneous ventilation and extubation was noted. Time from pre-medication to full recovery was also noted.

Statistical analysis was performed using statistical package of social science (SPSS) version 20 . The percentage between the two groups were compared using two- sample proportion- Z test. Mean value were compared between the groups using student's unpaired T test. P value of < 0.05 was considered as significant.

III. RESULTS

The children in both groups were comparable with regard to age, sex, weight and ASA status. The duration of general anesthesia was also not statistically significant [Table-1].There were no incidence of bradycardia (heart rate< 20%), hypotension (mean blood pressure< 20% of baseline) or desaturation episodes (o_2 saturation< 95%), after premedication or in operation room. The children in both groups accepted oral medication well and did not vomit soon after the swallowing of premedication. Although, the number of comfortable children were more in group B (18,90%) as compared to group A (15,75%), there was no significant difference in level of reactions to separation from parents, 30 minutes after receiving premedication (p>.05). [Table- 2]

There was no significant difference in the preoperative sedation scores in the both groups (P >0.05). [Table-3] There were no incidences of children responding to painful stimuli in any of the group. After reversal of residual paralysis, the number of children with satisfactory sedation score i.e. drowsy but arousable was higher in the 0.75 mg/kg dose group (10,50%), than in .05 mg/kg group (4,20%) (p<.05)), whereas, the number of children with desirable sedation score i.e. oriented and calm was significantly higher in 0.5 mg/kg dose group (15, 75%) as compared to the group B (5,25%) (p<.05). There were 5 (25%) children in group B and none in group A, who responded to painful stimuli but not to verbal command (P<.05). [Table-4]

There was no significant difference in the time to spontaneous ventilation and extubation in both groups. Most of the children in both groups recovered spontaneous ventilation and could be extubated within 5 minutes. Average time interval from pre-medication to full recovery was also not significantly different in two groups(p>.05). [Table-5]

IV. DISCUSSION

As preanesthetic medication has become an essential component of current anaesthesia practice in children, several studies have reported that it can allay anxiety preoperatively and facilitate separation of children from their parents. [5,6,7] It has also been suggested in many previous studies that midazolam is an effective preanesthetic medication for children. When administered either intramuscularly,[8] rectally [9] Intranasally [10] or orally.[11,12] Oral midazolam is found to be safe and effective without altering the haemodynamics and oxygen saturation values in the pre-operative or immediate post operative periods. It produces good anxiolysis in a dose range of 0.4-0.6 mg/kg in older children (>5 years of age) allowing parenteral separation by 15-30 minutes.

In a comparative study done by Saarnivarra et al [13] on children (1-9 years of age) receiving oral midazolam or chloral hydrate (in combination with atropine), they concluded that midazolam 0.4-0.6 mg/kg per oral provided only "fair analysis in children younger than 5 years of age, but good anxiolysis in children more than 5 years of age. In the same context, our study has tried to compare two doses of oral midazolam (0.5 mg/kg and 0.75 mg/kg) in children of 1-5 years of age and we found that oral midazolam in the dose of 0.75 mg/kg was similar to dose of 0.5 mg/kg with respect to children,s separation from their parents, preoperative sedation scores and recovery conditions, whereas it was better in producing favourable sedation scores after reversal of residual paralysis.($p<.05$)

Administration of small amount of fluid (5 to 10 ml) to children prior to induction of general anesthesia does not pose a significant risk for aspiration of abdominal contents [14]. The limited bioavailability of oral midazolam due to its high first pass metabolism may explain the high dose requirement for sedation and anxiolysis after the oral route of administration. This combination of sedative and anxiolytic characteristics of midazolam is believed to create a calming effect which eases the separation of children from their parents [15]. Finley et al.[15] showed that midazolam induced decrease in anxiety was more pronounced for children with higher baseline levels of anxiety. Oral midazolam was reported to give a more predictable and effective sedation than oral diazepam [16]. It was also associated with a faster and smoother recovery, when compared with oral ketamine [17]. Patel and Meakin [18] also reported greater anxiolysis after oral midazolam (0.5 mg/kg) than after a combination of diazepam (0.25 mg/kg) with droperidol (0.25 mg/kg) or trimeparazine (2 mg/kg).

Age of the child is also an important variable. Separation anxiety usually peaks at approximately 1 year of age, but children at the age of 1-5 years are at the highest risk for extreme preoperative anxiety [19]. Clinical sedative effects are seen within 5 to 10 minutes of oral midazolam administration. The peak effect is achieved in 20 to 30 minutes [20]. In present study, separation time was set at 30 minutes and we found a satisfactory anxiolysis in 90% of children after 0.75 mg/kg dose and 75% of children in 0.50 mg/kg dose.

Preoperative oral midazolam has proved effective in treating preoperative anxiety. Orally administered midazolam can be given in a dose of 0.25 to 1 mg/kg up to a total dose of 20 mg depending on the duration of surgery and the anxiety level of the child. In this study, after reversal of residual paralysis, the satisfactory level of sedation score was achieved in 10 (50%) children in group B and 4 (20%) children in group A and the difference was statistically significant ($p<.05$), whereas the number of oriented and calm children was higher in group A (15, 75%) than in group B (5,25%)($p<..05$). There were 5(25%) children in group B and no children in group A, who were not responding to verbal command but to painful stimuli ($p<.05$). Feld et al [3] also reported a superior anxiolysis 30 minutes after a 0.75 mg/kg dose of midazolam as compared to 0.25 mg/kg and 0.5 mg/kg dose or placebo. Similarly, it was reported that the use of a 0.75 mg/kg dose of oral midazolam did not result in clinical respiratory depression or upper airway obstruction, but in some children caused an increased level of sedation beyond simple conscious sedation. [21] Our study correlates to this study.

According to Cox et al [22] oral midazolam effectively reduced both separation and induction anxiety in children with minimal effect on recovery times. There was no significant delay in recovery time of both groups in our study. Small sample size has been the limitation of our study and statistically significant difference could have been drawn with a relatively larger sample with respect to chlldren's reaction to parent's separation and preoperative sedation score as well.

V. CONCLUSION

It can be concluded that oral midazolam in a dose of 0.75 mg/kg is an optimal and effective premedication drug in children of 1 to 5 years of age with minimal effects on recovery time. There were no hemodynamic alterations and respiratory depression reported in this dose of midazolam. Other side effect like nausea, vomiting and hiccough were also not reported.

Table 1 : Demographic Profile

Variable	Group A	Group B
Age (years)	2.74±1.54	2.86±1.65
Sex (M/F)	13/7	12/8
Weight(kg)	15.25±6.98	14.78±6.28
ASA I/II	16/4	15/5
Duration of general anesthesia	62.0±21.4	54.8±23.5

Values are expressed as mean±standard deviation.

Table 2 : Reaction to parents separation

Reaction	**Group A (0.5 mg/kg)**	**Group B (0.75mg/kg)**	**P value**
Inconsolable cry	1(5%)	0(0%)	0.305
Complaining	4(20%)	2(10%)	0.371
Total number of uncomfortable children	5(25%)	2(10%)	0.203
Quiet-but-awake	13(65%)	13(65%)	1.000
Sleepy	2(10%)	5(25%)	0.203
Total number of comfortable children	15(75%)	18(90%)	0.203

Table 3: Preoperative Sedation score in operation room

Score	Group A (0.5 mg/kg)	Group B (0.75mg/kg)	P value
Anxious	3(15%)	0(0%)	0.060
Oriented, calm	11(55%)	8(20%)	0.337
Drowsy-RVC	5(11%)	8(20%)	0.305
Not RVC but to painful stimuli	1(5%)	4(20%)	0.141
Not responding to painful stimuli	0(0%)	0(0%)	

Table 4: Sedation score on reversal of residual paralysis.

Score	Group A (0.5 mg/kg)	Group B (0.75mg/kg)	P value
Anxious	1(5%)	0(0%)	0.305
Oriented, calm	15(75%)	5(25%)	0.000*
Drowsy-RVC	4(20%)	10(50%)	0.036*
Not RVC but to painful stimuli	0(0%)	5(25%)	0.010*
Not responding to painful stimuli	0(0%)	0(0%)	

*= significant (p<.05)

Table 5 : Recovery profile.

Time	Group A (0.5 mg/kg)	Group B (0.75mg/kg)	P value
Time to spontaneous ventilation and extubation <5 min	18(90%)	16(80%)	0.371
Time to spontaneous ventilation and extubation 5–10 min	2(0%)	2(10%)	1.000
Time to spontaneous ventilation and extubation 10–40 min	0(0%)	2(10%)	0.136
Time from premedication to full recovery (hours)	97.5±21.0	92.3±25.7	0.483

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