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COMPARISON OF THREE DIFFERENT DOSES OF ORAL MIDAZOLAM FOR PREANAESTHETIC MEDICATION IN PAEDIATRIC PATIENTS

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Abstract:

Background and Aims: Preoperative anxiety is shown to be associated with release of stress hormones that affect the haemodynamics of the patients intra-operatively and postoperatively. An effective premedication facilitates smooth induction of general anaesthesia with reduced hemodynamic disturbances. Elevated anxiety causes psychological problems in children. Midazolam has been demonstrated to be a very good sedative, anxiolytic and amnesic premedicant. This study was aimed to make use of the readily available intravenous Midazolam as a substitute for oral Midazolam in three different doses to assess ease of separation from parents, co-operation for venepuncture, preoperative and post operative sedation score.

Settings and Design: A prospective, double blind, randomized study

Material and Method: 90 paediatric patients of 2-8 years of age undergoing different types of surgeries under general anaesthesia were randomly divided into three groups of 30 each. Preoperatively they received Midazolam 0.5mg/kg, 0.75mg/kg and 1.0mg/kg body weight, commercially available intravenous preparation for oral administration. It was diluted in apple juice and given 40 minutes prior to the induction of anaesthesia Ease of separation from parents, level of sedation ,cooperation of patient for venepuncture were recorded.

Result: Mean heart rate, blood pressure, respiratory rate and SpO2 in Group A, Group B and Group C were statistically comparable(p value=0.170, p value = 0.063, p value = 0.73 respectively). After 40 minutes of oral Midazolam; in Group A, 53.33% were comfortable; whereas in Group B, 90% were comfortable and in Group C, all the patients were comfortable. Sedation score was more in Group C than in Group B than in Group A. In Group A, only 26.67% patients had good cooperation; whereas in Group B, 56.67% had good and 20% had excellent co-operation. In Group C, 70% patients had excellent cooperation for venepuncture.

Conclusion: 0.75 mg/kg and 1 mg/kg body weight dose provided better results than 0.5mg/kg in terms of ease of separation from parents and co-operation for venepuncture. 1 mg/kg body weight dose did not provide any added benefit over the 0.75 mg/kg. The patients receiving 1 mg/kg dose were more sedated while being taken into the operation theatre.

Key words: Oral midazolam, preanesthetic sedation, Paediatric patients

Introduction

The process of undergoing a surgery can be a real unpleasant experience for children, with a great psychological impact that can affect them for lifetime.[1-3] They are uncooperative due to fear of pain, unfamiliar environment, parental separation or a previous unpleasant experience. This preoperative anxiety is shown to be associated with release

of stress hormones that affect the haemodynamics of the patients intra-operatively & postoperatively.[3-5] Children who are fearful and uncooperative can be managed with behavioural techniques but still pharmacological sedation and anxiolysis are widely practised techniques to allay the anxiety and achieve best co-operation in the paediatric patients.[5, 6]

An effective premedication facilitates smooth induction of general anaesthesia with reduced hemodynamic disturbances. Over the years many drugs have been used for effective premedication in paediatric patients such as Benzodiazepines, Antihistamines, Chloral Hydrate , α-2 agonists, Ketamine and opioids.[7-9] Of all the benzodiazepines studied, Midazolam has been demonstrated to be a very good sedative, anxiolytic and amnesic premedicant.[10, 11]

Midazolam is rapidly and completely absorbed after oral administration. It is rapidly excreted, with a half-life of only about 2 hours. Due to the substantial first-pass effect, absolute bioavailability of oral Midazolam ranges between 30-70%.[12-14] The pharmacokinetics of Midazolam is linear in the 7.5-20 mg oral dose range. Due to its rapid onset and relatively short duration of action, it has proven to facilitate easy separation from parents with very few side effects as compared to other drugs.[11, 12]

Midazolam is available in many formulations like intravenous, intramuscular, rectal, oral and intranasal. There are advantages and disadvantages of all these routes of administration. Intramuscular & intravenous routes are associated with pain and discomfort. Both intranasal and rectal routes are associated with local irritation, erratic absorption; whereas the latter has slower time of onset.[6,10-12]

Oral Midazolam is not readily available at all places in our country. Remote areas do not have access to oral Midazolam, whereas intravenous Midazolam is available at most places. The drug can produce highly water-soluble salts (pH less than 4) or exist in lipophilic diazepine ring-closed form (pH greater than 4). Therefore intravenous preparation of Midazolam has been used by oral route by many workers after mixing with clear fluid eg. apple juice.[6,13,15] An oral preparation is well absorbed due to acidic gastric pH and easily acceptable by a child, more so if it is blended with a sweetener or fruit juice.[6,10,11]

Thus this study was aimed to make use of the readily available intravenous Midazolam as a substitute for oral Midazolam in three different doses to assess ease of separation from parents, co-operation for venepuncture, preoperative and post operative sedation score.

Materials and Methods:

This study was a prospective, double blind, randomized study carried on 90 paediatric patients of 2-8 years of age in tertiary care hospital. After obtaining approval from the institutional ethics committee, ASA I and II patients undergoing different types of surgeries lasting from 30 to 120 minutes under general anaesthesia were included. Written, informed and valid consent was obtained from each patient's parent and assent from the patients as and when required. Patients with congenital anomalies, physical disabilities, patients on anticonvulsants or sedatives, history of nausea, vomiting or vomited after giving oral premedication, patients requiring dose > 20 mg and parents' refusal were excluded. Calculated sample size using the OpenEpi software considering α error 5% and β error 20% were 83 (Kelsey).

Preanaesthetia evaluation of the patients were done one day prior to the surgery and the patients satisfying the inclusion criteria were selected. These patients were randomly divided into three groups of 30 each according to computerised random tables as Group A, Group B and Group C. Preoperatively patient's heart rate, respiratory rate and SpO2 were recorded. These children were given IV Midazolam 0.5mg/kg, 0.75mg/kg and 1.0mg/kg body weight orally 40 minutes prior to the induction of anaesthesia by one of the parent according to the group. Commercially available intravenous Midazolam (5mg/ml ampoule) was used to prepare the required oral formulation to be administered to the patients. The calculated dose was diluted in apple juice, twice its volume to make it acceptable for the patient by senior resident who was blind. The maximum dose that was administered to any patient was 20 mg.[13,14,16] Patient's vitals were again recorded at every ten minutes till 40 minutes after administration of the drug.

Ease of separation from parents, level of sedation ,cooperation of patient for venepuncture were recorded after 40 minutes of oral Midazolam administration.The response of the children when taken away from their parents was graded as:[16,17]

Grade 1 - inconsolable cry
Grade 2 - complaining
Grade 3 - quiet but awake
Grade 4 - sleepy

The degree of sedation based on five points Modified Ramsay Sedation Score was noted.[17,18] (Table 1) Cooperation of patient for venepuncture was graded depending upon the individual child's response in the operation room:

1. Poor (1)
2. Fair (2)
3. Good (3)
4. Excellent (4)

All children were given general anaesthesia for further surgical procedure. Patients vitals were recorded at induction, at intubation, at 5 minutes interval till 20 minutes and at 10 minutes interval till the end of surgery, at extubation and at 10 minutes interval post extubation for 30 minutes. Patients sedation score were recorded at extubation and at 10 minutes interval for 30 minutes after extubation.

All data are presented as mean ± standard deviation, and/or number. Demographic data were analyzed by *t*-test and Chi-square test. Acceptance of drug, response to drug administration, sedation scale, parental separation was analyzed by Chi-square test. Hemodynamic changes and anesthesia recovery was assessed by standard error of difference between two means and *t*-test. $P < 0.05$ was considered statistically significant.

Results:

The three groups were comparable with respect to age, weight, gender, ASA grade and duration of surgery. (Table 2)

The mean heart rate, mean blood pressure and respiratory rate in Group A, Group B and Group C were statistically comparable in all three groups (p value=0.170, p value = 0.063, p value = 0.73 respectively).There were no variation in the mean SpO_2 (p value=0.153) from 'Premedication zero minute' till '40 min' interval in all three groups (p value= 0.153, 0.089, 0.237, 0.544and 0.089 at respective intervals).

After 40 minutes of administration of Midazolam orally, children were observed with respect to ease of separation from parents. Since the assessment of ease of separation from parents is more subjective, to make it more objective and to simplify, Grade 1 and Grade 2 were combined together and named as 'Uncomfortable' and Grade 3 and Grade 4 as 'Comfortable'. In Group A, 16 patients (53.33%) were comfortable; whereas in Group B, 27patients (90%) were comfortable and in Group C, all the patients were comfortable. It suggests that higher the dose of Midazolam, better the grade of ease of separation from parents.(Graph 1)

It was observed that before induction, all patients from Group A had a sedation score of 2; in Group B, 12 patient had a score of 2 and 18 patients had a score of 3; whereas in Group C, one patient had a score of 2, 26 patients had a score of 3 and 3 patients had a score of 4.Thus the sedation score gradually increased and the increase was more in Group C than in Group B than in Group A (Group C>Group B>Group A).(Graph 2)

When ease of venepuncture was assessed at 40 minutes, in Group A, only 26.67% patients had good cooperation; whereas in Group B, 56.67% had good and 20% had excellent co-operation. In Group C, 70% patients had excellent cooperation.(Graph 3)

The mean heart rate and blood pressure changes were similar in all three groups throughout the study period and was statistically comparable at all the time intervals intraoperatively (p value>0.05).

Ten minutes and 20 minutes after extubation all patients had sedation score of 4 and 3 respectively. This can be explained by the added effect of anaesthetic agents such as Fentanyl, Sevoflurane used for maintenance of anaesthesia in the intra-operative period in the three groups.

30 minutes after extubation, sedation score in Group A, 25 (83.33%) patients had of 2 and 5 (16.67%) patients had a score of 3; in Group B, 17 (56.67%) patients had a score of 2 and 13 (43.33%) patients had a score of 3; and in Group C, 8 (26.67%) patients had a score of 2 and 22 (73.33%) patients had a score of 3.It was thus observed that the children in Group C had a higher sedation score 30 minutes after extubation than children in Group B and Group A. This can be attributed to the higher dose of Midazolam used in Group C.

Discussion:

The mental stability of children who undergo any surgical procedures is a major concern for anaesthesiologists and other health care providers. It is a necessity and of utmost importance to preserve a child's psychic safety and take into account their emotional needs, as well as their physical security. Elevated levels of preoperative anxiety have been associated with difficulty in anaesthetic induction, emergence agitation and the development of negative postoperative behavioural changes.[1,2]

The hostile hospital environment, anaesthesia, surgery, pain and other stress constitute a major cause for mental distress that may lead to short or even long-term psychological consequences. Common behavioural problems after surgery include nightmares, waking up crying, sleep disorders, disobeying parents, separation anxiety, and temper tantrums.[2,3] More serious behavioural changes, such as new-onset enuresis are not uncommon. Because trauma affects the child's ability to self regulate both physically and emotionally, post traumatic symptoms in infants and young children may encompass one or more of a broad range of behaviours, including terrified responses to sights, sounds or other sensory input.[1,2,3]

McMillan CO[8] et al evaluated the safety and efficacy of three doses of oral Midazolam (0.5mg/kg. 0.75mg/kg and 1mg/kg) and observed that the heart rate, respiratory rate and blood pressure was unchanged during the study. There was no fall in the saturation or respiratory depression. Coté CJ[17] et al studied the efficacy, safety and taste acceptability of three doses (0.25, 0.5 and 1 mg/kg) in children and observed that oral Midazolam produced minimal effects on respiration and oxygen saturation. Sheta A. S. et al[5] 45% of patients who received 0.5mg/kg Midazolam were uncomfortable, whereas 75% of patients who received 0.75mg/kg and 90% of patients who received 1 mg/kg Midazolam were comfortable at the time of separation from parents. Various studies compared oral midazolam with oral clonidine, ketamine , diazepam , droperidol or trimeparazine and reported that Midazolam provide a more predictable and effective sedation, faster and smoother recoveryand greater anxiolysis.[19, 20]Anxiolysis at the time of separation from parents have been rated excellent in 80-90% of the children by most authors.[6,9,18]

Feld LH et al conducted a similar study with 0.25mg/kg or 0.5mg/kg or 0.75mg/kg of Midazolam along with Atropine 0.03mg/kg mixed with apple juice and found that Midazolam 0.75mg/kg produced significant sedation at 30 minutes. Satisfactory sedation before induction of anaesthesia has been demonstrated in the 0.75mg/kg and 1.0mg/kg dose by other authors.[6, 18, 25] Sheta A. S. et al observed that 20 % of patients who received 1mg/kg had excellent cooperation for venepuncture or mask holding as compared to 10% of patients who received 0.75mg/kg oral Midazolam. 75% of children who received 0.5mg/kg Midazolam had poor co-operation.[6] Thus the findings with respect to co-operation for venepuncture in the present study were in concurrence with above study.

From the present study it was concluded that 0.5mg/kg, 0.75 mg/kg and 1mg/kg body weight doses of oral Midazolam can be safely administered as premedication to paediatric patients. 0.75 mg/kg and 1 mg/kg body weight dose provided better results than 0.5mg/kg in terms of ease of separation from parents and co-operation for venepuncture. 1 mg/kg body weight dose did not provide any added benefit over the 0.75 mg/kg. The patients receiving 1 mg/kg dose were more sedated while being taken into the operation theatre.

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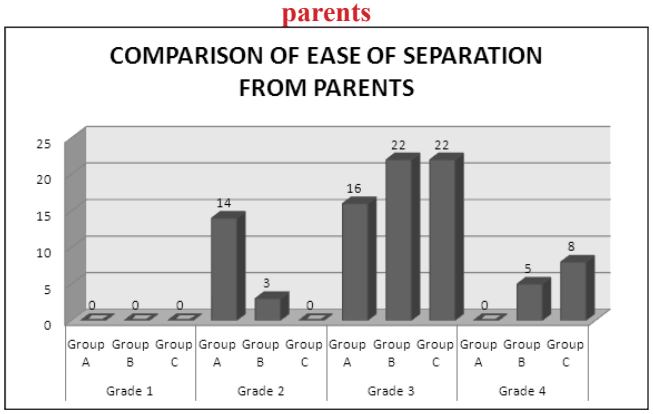
Table-1 : Sedation score

Modified Ramsay Sedation Score	
1	Patient agitated and anxious or restless or both
2	Patient cooperative, oriented and tranquil
3	Patient responds to commands only
4	Brisk response to a light glabellar tap or auditory stimulus
5	Sluggish response to light glabellar tap or auditory stimulus
6	No response

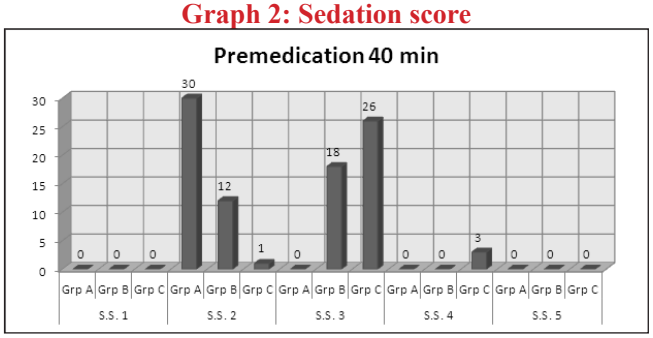
Table 2: Demographic data

Group	A	B	C	P value
Mean Age (years)	5.47	5.6	5.27	0.923
Mean Wt (kg)	13.8	14.8	14.03	0.859
Male/ Female	25/5	23/ 7	24/ 6	0.812
ASA I/ ASA II	22/08	23/07	23/07	0.942
Duration of surgery (minute)	56	56.33	57.83	0.962

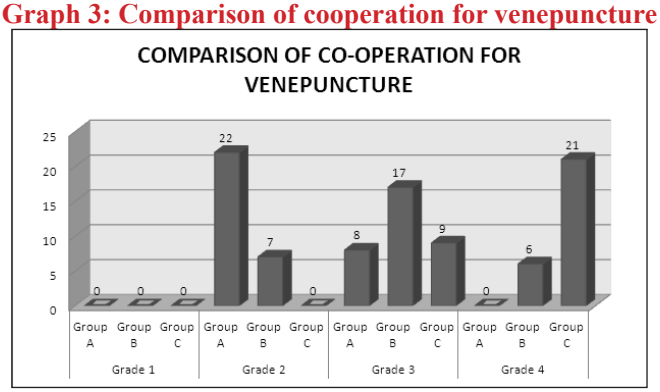
Graph 1: Comparison of ease of separation from parents



Graph 2: Sedation score



Graph 3: Comparison of cooperation for venepuncture



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