MIDAZOLAM SYRUP AS A PREMEDICATION IN PAEDIATRIC PATIENTS- A RANDOMISED, DOUBLE-BLIND, PARALLEL GROUP, PLACEBO-CONTROLLED STUDY

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ABSTRACT

BACKGROUND

Premedication is expedient in reducing the psychological trauma from recalling the unpleasant pre-anaesthetic phases; hence, inducing a trouble-free anaesthesia.

Aim- This study was done to evaluate commercially available midazolam syrup 0.25 mg/kg as a premedication in children with regard to sedation, anxiolysis and parental separation score.

MATERIALS AND METHODS

After IRB approval and written informed consent from parents, this study was conducted in 100 children (ASA I and II), aged 1 to 6 years who were scheduled for various elective and emergency surgeries. Patients were randomly divided into two groups (n= 50 each). Group A was control and Group B received midazolam syrup 0.25 mg/kg 45 minutes before surgery.

RESULTS

The acceptance of drug was very good. All children in Group A (without premedication) were extremely anxious and crying or thrashing, while in Group B 98% patients were calm and sleepy and separated happily from parents after 45 minutes. Midazolam did not impact the overall recovery time in children. None of the patients in either group developed any complication.

CONCLUSION

A dose of 0.25 mg/kg of commercially available midazolam syrup offers effective sedation and better emotional control facilitating better separation from parents.

KEY WORDS

Oral Midazolam, Children, Premedication.

HOW TO CITE THIS ARTICLE: Jaldeep BP, Shilpa M.D, Deepshikha CT. Midazolam syrup as a premedication in paediatric patients a randomised, double-blind, parallel group, placebo-controlled study. J. Evolution Med. Dent. Sci. 2018;7(28):3220-3223, DOI: 10.14260/jemds/2018/724

BACKGROUND

Surgery, in paediatric age group, can cause considerable distress and psychological consequences for both parents and children. Anxiety, in children undergoing surgery is characterised by subjective feelings of tension, apprehension, nervousness and worry. Children (1 - 5 years of age) are at the highest risk of developing anxiety than adults.^[1] Postoperative maladaptive behaviour (e.g. enuresis, sleep disturbance), delayed recovery and other complications due to postoperative pain may result from preoperative anxiety if child is not reassured properly.^[2] Before the induction of general anaesthesia, infants and preschool children frequently need medication to decrease their anxiety and to facilitate their separation from parents. Midazolam is most commonly used for this purpose.^[3]

'Financial or Other Competing Interest': None.
Submission 30-05-2018, Peer Review 24-06-2018,
Acceptance 30-06-2018, Published 09-07-2018.

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DOI: 10.14260/jemds/2018/724

Recent studies suggested that oral midazolam as pre-anaesthetic medication is as efficacious as intramuscular in paediatric patients.^[4,5] However, concerns have been raised regarding the potential of effective oral doses of midazolam to prolong recovery time.^[4,6,7]

The use of premedication in anaesthesia is historical. Although, it is recognised that preoperative visit by anaesthesiologist provides a beneficial effect in terms of anxiolysis,^[8] the use of drugs appear to be common. In 1998, Kain et al^[9] reported that premedication with midazolam was more effective in reducing anxiety in preschool children than was parental presence at the time of induction of anaesthesia.

Before the development of commercially prepared syrup, oral midazolam formulation was prepared by mixing the intravenous midazolam product with variety of additives like apple, grape juice, paracetamol syrup to mask its bitter taste.^[10,11] As the fat solubility of midazolam is pH dependant, non-standard oral formulations were prepared which have unpredictable absorption characteristic, bioavailability and stability.^[12,13] Commercially prepared midazolam syrup is recently being introduced in India (July 2010). In literature there are limited studies^[14,15] on using this preparation as premedication in children and there is need for further research to evaluate its efficacy and safety profile as premedication in children. This prompted us to undertake

this study with the purpose of examining the efficacy and safety of commercially prepared oral midazolam syrup as pre-anaesthetic medication in children.

MATERIALS AND METHODS

Ethics and Study Design

This prospective, randomised, double-blind, placebo-controlled, clinical study was conducted in 100 paediatric patients taken for convenience after the permission from Institutional Review Board (IRB) (IRB No. 184/2011), Govt. Medical College, Bhavnagar and obtaining written informed consent from the parents of children. The study was registered in Clinical Trial Registry of India (CTRI/2015/10/006234) and carried out as per guidelines of good clinical practice. Study was conducted in the Department of Anaesthesiology, Government Medical College and Sir Takhtasinhji General Hospital, Bhavnagar, Gujarat between 2010 - 12.

Recruitment Criteria

Paediatric patients aged 1 to 6 years, of ASA physical status I and II, undergoing surgery with general or regional anaesthesia were evaluated and recruited in the study. Patients with age less than 1 year and more than 6 years, ASA physical status more than II, psychological disturbances, unstable haemodynamic and respiratory function, gastrointestinal problems, taking sedative and anticonvulsants for treatment and those whose parents did not give consent were excluded from the study.

Patients were randomised in 1: 1 ratio using computer generated random number sequence into two groups (n= 50). Sealed envelope technique was used as method of concealment. Group A patients received placebo (Rose flavoured Rasna syrup) 5 mL, whereas Group B patients received midazolam syrup 0.25 mg/kg diluted in 5 mL distilled water, 45 mins before induction. Anaesthesiologist X had prepared the drug according to the group assigned. Anaesthesiologist Y (attending anaesthesiologist) was unaware about the content of the drug given and was also responsible for dispensing the drug to patients and recording observation.

Study Procedure

Patients were kept nil per oral for 4 hours before surgery. In pre-operative preparation room heart rate (HR), blood pressure (Systolic [SBP], Diastolic [DBP]), respiratory rate and peripheral arterial oxygen saturation (SpO₂) were recorded. Baseline sedation score, parental separation and anxiolysis score were recorded. After giving assigned treatment, anaesthesiologist Y recorded vital parameters, sedation score and parental separation and anxiolysis score immediately after giving drug and then at every five minutes interval till for forty-five minutes.

Outcome Measures

In the study HR, SBP, DBP, SpO₂, Sedation Score [1= Awake, active; 2= Awake, calm and quiet; 3= Drowsy- readily responds; 4= Asleep- responds slowly to gentle stimulation; 5= Asleep- not readily arousable]; Anxiolysis Score [1= Vocal display of fear-apprehension; 2= Moderate expression of fear;

3= Minimal expression of fear; 4= No fear] and Parental Separation Scores [Unsuccessful (1= Need for restrain; 2= Separate with crying); Successful (3= Separate without crying; 4= Happily separated)] were recorded just before giving the premedication and then after every 5 minutes up to 45 minutes. We recorded adverse drug reactions (ADRs) if any after giving the premedication in preoperative room, managed accordingly and reported to IRB.

Statistical Analysis

Overall, 100 patients were required to achieve 80% power at 5% significance level. Total number of patients required for each group were 50 patients. Quantitative data were expressed as mean and standard deviation, whereas descriptive statistics was used for categorical data. Comparison between two groups was done using GraphPad Prism 5 computerised software, unpaired t-test for quantitative data and chi-square test for qualitative data. P value < 0.05 is considered statistically significant.

RESULTS

Figure 1. Study Flow Chart

Figure 2. Changes in Sedation Score

Figure 3. Changes in Anxiolysis Score

Figure 4. Changes in Parental Separation Score

Patient Characteristics	Group A (n=50)	Group B (n=50)	P value
Age (years) (Mean ± SD)	3.94 ± 0.25	3.85 ± 0.24	0.98
Gender (M/F)	35/15	33/17	0.83
Weight (kg) (Mean ± SD)	12.34 ± 0.75	12.42 ± 0.67	0.94
ASA Physical Status (I/II)	22/28	24/26	0.84

Table 1. Patient Characteristics in Two Groups

The two groups were statistically similar in relation to age, gender, weight, ASA physical status (Table 1).

In Group A most of the patients were moderately apprehensive throughout the study period (Score 1 {28%}, 2 {72%}), while in Group B anxiolysis was achieved at 15 minutes and it continued to increase throughout the study (Score 3 {28%}, 4 {72%}), (P value < 0.05) (Figure 2).

In Group B sedation was induced at 15 minutes and continued to sedation score of 3 (78%) and 4 (20%) at the end of 45 minutes (P value < 0.05) (Figure 3).

In Group A all patients were crying when separated from their parents (Score 1 {20%}, 2 {80%}), while in Group B all patients were successfully separated from parents after 45 minutes of premedication (Score 3 {12%}, 4 {88%}) which was statistically significant (P value < 0.05) (Figure 4).

HR were uniformly decreasing in Group B as compared to baseline value, which was statistically significant (P value < 0.0001), but clinically insignificant. The SBP, DBP and SpO₂

were comparable in both the groups (P value > 0.05). None of the patients in both the groups developed any complication.

DISCUSSION

Children, aged 1 to 6 years, are difficult to handle in preoperative period before surgery as they are extremely uncooperative, fearful, anxious, physically resistant and do not want to get separated from the parents. The major objectives of pre-anaesthetic medication in this age group are to alleviate anxiety and provide adequate degree of sedation for ease of parental separation. While going through the literature, many studies are available which used different sedative premedications in children.^[16,17,18] However, there are reports of serious complications in the postoperative period while using some premedications.^[6,7,19,20] The selection of most effective pre-medicant with optimum sedation, minimum complications and having high degree of parental satisfaction is difficult.

Midazolam is found to be an effective pre-anaesthetic medication for children, administered either orally,^[21] rectally,^[17,22] intramuscularly,^[23] intranasally,^[24] sublingually^[25] and by jet injection.^[26] Of all the routes, oral is the most acceptable route in children because of its unique advantages.^[19] This tempted us to use oral midazolam (Commercial formulation, recently introduced in Indian market in July 2010) as premedication in children.

Previous studies showed 30 minutes delay in achieving good sedation, hence midazolam was given 45 minutes prior to induction in present study.^[27]

The results of the present study showed that with 0.25 mg/kg of oral midazolam premedication, all the patients had good anxiolysis (score 3 and 4), successful separation from the parents (score 3 and 4) and were adequately sedated (score 3 and 4) at the end of monitoring period as compared to placebo group.

Sjoval et al^[28] studied the effect of oral midazolam in a dose of 0.25 mg/kg and found it to be a satisfactory sedative agent. However, increased secretions were noted in their study. In another study,^[18] author used 0.4 - 0.6 mg/kg of oral midazolam and found only "fair" anxiolysis in children younger than 5 years of age. In contrast, oral midazolam 0.4 - 0.6 mg/kg produced good anxiolysis in older children of more than 5 years of age. In another study^[27] author used three doses of oral midazolam 0.25, 0.5 and 0.75 mg/kg and found them to be equally effective for sedation and anxiolysis without any circulatory, respiratory and long-term residual neurological defects in children. Results are comparable with the present study. There are other studies which used 1 mg/kg^[17] and 1.5 mg/kg^[29] of oral midazolam and found that the children were better sedated than with the standard dose (0.5 mg/kg) of midazolam.

In the study of McMillan et al,^[19] excellent anxiolysis at the time of parental separation was found in 80% - 90% of the children who received midazolam in a dose of 0.5, 0.75 and 1.0 mg/kg. They concluded that all three doses of midazolam are equally effective and provided sedation and anxiolysis in children at the time of separation from parents, 30 minutes after administration of premedication. In another study, the author reported only 3% - 7% incidence of excellent anxiolysis with 0.75 mg/kg of midazolam, while 0.25 and 0.5 mg/kg provided good anxiolysis in majority of patients, which is comparable to present study.

In the present study, none of the patients developed any circulatory or respiratory adverse events.

CONCLUSION

To conclude midazolam syrup in a dose of 0.25 mg/kg can be an optimum dose for relieving anxiety, achieving good degree of sedation and successful separation from parents with stable haemodynamics without any adverse events.

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