Original Article

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A comparative study on the efficacy of rectal diazepam and midazolam for reduction of pre-operative anxiety in pediatric patients

Seyed Mohammad Mireskandari[1], MD; Seyed Mohammad-Bagher Akhavirad[2], MD; Mohammad-Esmaiel Darabi*[1], MD; Reza Alizadeh[3], MD; Abbas Moghim-Beygie[4], MD; Ebrahim Davoodi[5], MD

1. Anesthesiologist, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, IR Iran
2. Pediatrician, Mostafa-Khomeini Hospital, Shahid University of Medical Sciences, Tehran, IR Iran
3. Anesthesiologist, Hospital 501, Military University of Medical Sciences, Tehran, IR Iran
4. Epidemiologists, Department of Biostatistics & Epidemiology, Hamadan University of Medical Sciences, IR Iran
5. General Physician , Mostafa-Khomeini Hospital, Shahed University of Medical Sciences, Tehran, IR Iran

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Abstract

Objective: Children, due to their great parental dependency, are amongst the cases that should receive preoperatively medication to reduce their fear and anxiety. The objective of this study was to compare the efficacy of rectal diazepam and midazolam for this purpose in pediatric patients scheduled for elective surgery.

Material & Methods: 60 children, aged between 1 and 6 years, scheduled for elective surgery, were included in this double blind, randomized controlled trial. Patients were randomly allocated into three equal groups. Patients in midazolam and diazepam groups received the drugs 0.3 mg/kg and 0.5 mg/kg respectively (in normal saline at a final volume of 2.5 ml) and placebo group received only 2.5 ml of normal saline 20 min before arriving operation room through rectal applicator. Sedation and anxiety scores at the time of separation from their parents before arriving operating room were recorded for all groups.

Findings: There was a significant reduction in anxiety level in midazolam and diazepam groups as compared to placebo group ($P<0.001$). Sedation rate was 65% for midazolam, 60% for diazepam, and 15% for placebo group ($P=0.007$). There were no significant changes in hemodynamic parameters in the three study groups.

Conclusion: With respect to effective anxiolytic and sedative activity, rectal midazolam (0.3 mg/Kg) and diazepam (0.5 mg/Kg) can be used as an anesthetic premedicant for children at pre-operative period and their use is safe regarding hemodynamic variables and related side-effects.

Key Words: Rectal diazepam, Rectal midazolam, Premedicant, Anxiety, Elective operation

*** Correspondence author.**
Address: Bahrami Children Hospital, Shaheed Kiaee St., Damavand Ave, Tehran, IR Iran
E-mail: me_darabi@yahoo.com

Introduction

Reduction of anxiety and fear at preoperative period in children as candidates of elective surgery is essential for surgical preparation. Anxiety is defined as a sensation of fear and apprehension with sensory signs indicative of sympathetic nervous system activity.

Separation of children from their parents before arriving operating room is very troublesome, and anxiety itself can enhance sympathetic nervous system activity during the process of anesthesia and surgery[1]. In addition, anxiety can adversely affect postoperative healing process with unpleasant sensation in the patient's mind. Therefore, anxiety reduction is of the main tasks of anesthesiologists at preoperative visit of the patients. Various therapeutic strategies including use of drugs and other methods have been employed for this purpose.

Although non-drug methods including the involvement of parents for reduction of anxiety and use of audio-visual training programs are very effective, but they are not enough and it is required to use drugs like ketamine, clonidine, benzodiazepines, and antihistamines to lower anxiety. Among these drugs, benzodiazepines are the most commonly used anesthesia premedicant in children[2]. Midazolam is a water-soluble drug that is used through oral, intravenous, intramuscular, sublingual, intranasal, and/or rectal routes[3]. Also diazepam is a lipid-soluble benzodiazepine that can be used through oral, intravenous, intramuscular, and rectal routes.

Rectal route is preferred in children due to its ease of administration, efficacy, better absorption, and lack of bad taste and odor. However, rectal application of diazepam is specifically recommended in children at preschool age[4]. The aim of this study was to compare the efficacy of rectal diazepam and midazolam for reduction of anxiety in children at preoperative period and their effect on hemodynamic variables before and after anesthesia.

Material & Methods

After obtaining written parental consent and agreement from research council, 60 patients aged 1-6 years scheduled for elective surgery, with no contraindication for the study were included in this trial.

This study was a double-blind randomized control trial that was carried out at Bahrami children's hospital from February to August 2006. Since there was no similar study regarding the applicable dose of the drugs, after collecting data and their analysis, it was verified that the selected sample size with regard to an error level of 0.05 and study power of 80% was enough for showing the efficacy of drugs in reduction of anxiety in children. Patients with a history of anorectal anomaly, use of sedatives and narcotics within 24 hours before surgery, and with cardiovascular and neurological disorders and/or unpredicted change in anesthetic protocol were excluded from the study.

Patients were randomly allocated into 3 groups through permuted blocked randomization. Patients in group 1 received 0.3 mg/kg of midazolam (5 mg/ml; Exir, Iran) that was diluted in normal saline to a final volume of 2.5 ml. Patients in group 2 received 0.5 mg/kg of diazepam (5 mg/2.5 ml; Alpharma) that was diluted in normal saline to a volume of 2.5 ml and patients in placebo group received only 2.5 ml of normal saline through rectal applicator 20 min before entering operation room.

Systolic and diastolic blood pressures, and heart and respiratory rates were measured before administering the drugs, and after anesthesia induction and tracheal intubation in patients of all three groups. Anesthesia was induced with 2 µg/kg Fentanyl, 5 mg/kg sodium thiopental, and 0.5 mg/kg atracurium. and maintained with 1% halothane, 1 µg/kg Fentanyl, 0.1 mg/kg atracurium every 30 min, and 70% N2O/30% O2. Lactate ringer (5ml/kg) was administered to all of patients before induction of anesthesia and during the surgery with regard to hemorrhage intensity and body fluid loss. Drugs preparation was

performed by one technician and premedicant administration and patients' evaluation by other operating room personnel.

For evaluation of sedation level at the time of entering into the operating room, the following scoring criteria were used: 1) Asleep, 2) Somnolent and responsive to oral commands and mild stimulation, 3) Awake and silent, and 4) Agitated, crying and intolerant. For evaluation of anxiety at the time of separation from parents, the following scoring criteria were used: 1) Asleep, 2) Calm and silent, and easy to separate from parents 3) Awake and agitated, can be calmed, and 4) Crying, can not be calmed. Scores 1, 2, and 3 for sedation and scores 1 and 2 for anxiety at the time of separation were considered acceptable.

Statistical analysis of age, weight, heart rate and arterial pressure data from the three groups was conducted using analysis of variance for repeated measurements (ANOVA). The sedation and anxiety scores data were analyzed with chi-square test. The level of significance was defined as a p-value of less than 0.05.

Findings

Sixty patients were evaluated in this study and no patient was excluded or lost from the study. 47 (77.16%) cases were male and 13 (22.84%) female. There were statistically no significant difference between groups with respect to age, weight, and gender distribution (Table 1). There were also no significant differences between groups with respect to systolic and diastolic blood pressures and heart rate before administering the mentioned drugs. Systolic blood pressure was significantly lower in midazolam group as compared to diazepam and placebo groups before induction of anesthesia (P=0.01). Diastolic blood pressure before induction of anesthesia and after tracheal intubation was lower, though not significantly, in midazolam group in comparison with the other two groups. Furthermore, heart rate was significantly lower in diazepam group as compared to other groups (P≤0.001). In placebo group, heart rate was significantly higher after inducing anesthesia and tracheal intubation in comparison with other groups (P≤0.001). Changes in hemodynamic variables in patients had no clinical importance and did not require any treatment.

In midazolam and diazepam groups, respiration rate was non-significantly lower when comparing data before induction of anesthesia and before drug administration (P=0.5), but no apneic period was seen in patients.

With respect to separation anxiety score at the time of entering to operating room 15, 20, and 80% of patients were anxious in midazolam, diazepam, and placebo groups respectively (Table 2). For anxiety score 65, 60, and 15 % of cases had an acceptable level of sedation at the time of entrance into the operating room in midazolam, diazepam, and placebo groups respectively (Table 2). Therefore, anxiety score was statistically lower for diazepam and midazolam groups as compared to placebo group (P=0.007), but the

Table 1: Characteristics of the patients in three groups

	Diazepam group	*Midazolam group*	*Placebo group*	*P-value*
Age (year)	3.45±1.56	2.83±1.6	2.66±1.67	0.2
Weight (kg)	16.9±4.7	16±5.2	15.2±1.5	0.6
Systolic blood pressure (mmHg)	94.7±6.28	91.7±9.03	93.95±9.34	0.5
Diastolic blood pressure (mmHg)	61.2±5.8	60.3±7.69	56.45±8.81	0.11
Heart rate (beats/min)	99.35±12.24	112.25±14.5	108.65±16.85	0.2

Values are mean ± SD

Table 2: Separation anxiety score and sedation score of patients in the three groups

Score	*Midazolam Group*		*Diazepam Group*		*Placebo Group*	
	SAS† (%)	SS* (%)	SAS (%)	SS (%)	SAS (%)	SS (%)
1	6 (30)	5 (25)	5 (25)	5 (25)	0	0
2	11 (55)	1 (5)	11 (55)	0 (0)	4 (20)	0
3	2 (10)	7 (35)	2 (10)	7 (35)	5 (25)	3 (15)
4	1 (5)	7 (35)	2 (10)	8 (40)	11 (55)	17 (85)
Total	20 (100)	20 (100)	20 (100)	20 (100)	20 (100)	20 (100)

† SAS: Separation anxiety score;
* SS: Sedation score

difference between midazolam and diazepam groups was not statistically significant (p=0.6).

Discussion

It is a common practice to administer pre-medicant in children before anesthesia to decrease anxiety and emotional responses and to facilitate anesthesia induction[5]. Among drugs used for this purpose, benzodiazepines are considered as the safest and most effective agents[6]. Although they are commonly used, however, the best route for their administration is still in controversy. Oral and sublingual administration requires the patient cooperation. Intramuscular application produces pain and discomfort and is not currently recommended. Therefore, rectal route of administration is the most favorable one due to its ease of administration, and has effective, fast and reliable absorption in children[7]. Holms et al conducted a study on 60 children scheduled for elective surgery to compare the effectiveness of rectal diazepam (0.75 mg/kg) and midazolam (0.4 mg/kg) as an anxiolytic agent at pre-anesthesia period[8]. The results of their study showed that after 15 min following administration of midazolam or diazepam, 84 and 80% of children had no anxiety at the time of separation from their parents.

In another study by Roelofse et al on pediatric candidates of tooth extraction, the anxiolytic and hemodynamic effect of rectal midazolam (0.35 mg/kg) and diazepam (0.7 mg/kg) was evaluated[9]. They showed that, in children receiving rectal midazolam there is a higher rate of anesthesia mask acceptance and a lower level of anxiety as compared to those treated with rectal diazepam. In addition, although hemodynamic changes were greater for rectal midazolam than diazepam, but the existing difference was not statistically significant.

In another study by Jensen et al on ninety pediatric patients aged 1.5-3.5 years as candidates of dentistry operations, efficacy of rectal midazolam (0.3 mg/kg) and diazepam (0.7 mg/kg) for induction of sedation, treatment acceptance, and agitation were evaluated[10]. In this regard, it was found out that both drugs could induce an acceptable level of sedation in children. However, at the end of operation, children of diazepam group had a higher rate of agitation.

Ebru et al conducted a study on forty children aged 1-8 years as candidates of urogenital surgery to evaluate the efficacy of rectal diazepam and midazolam on hemodynamic status, sedation, and separation anxiety and post-operative pain[11]. In this study, rectal diazepam and midazolam were used at a dose of 0.5 mg/kg in combination with atropine (0.02 mg/kg) 20 min before surgery. Their results showed that midazolam is more effective in lowering anxiety at the time of separation from parents and is more sedative than rectal diazepam.

In our study, we tried to find a dose of diazepam and midazolam that could have the

least side-effects and the greatest efficacy as an anesthetic premedicant in children. It was found out that after 20 min, 85% of children receiving 0.3 mg/kg of rectal midazolam separated from their parents with no signs of anxiety and apprehension. This difference in results as compared to Holms' study (with a dose of 0.4 mg/kg) can be attributed to lower dose of the drug (0.3 mg/kg) used in our study. For the same reason, the appropriate time for evaluation was 20 min in our study. Furthermore, after 20 min, 80% of children receiving rectal diazepam (0.5 mg/kg) as a premedicant separated from their parents with no anxiety and fear that was similar to Holms study. On the other hand, in Holms study 67% of patients of midazolam group and 70% of patients from diazepam group had an acceptable level of sedation on arrival to operation room[8]. This level was 65% for midazolam and 60% for diazepam groups in our study in opposition to 15% for placebo group (Table 3) and the existing difference was statistically significant.

In our study, both diazepam and midazolam were effective in reducing anxiety at the time of separation from parents and there was no statistically significant difference between the efficacies of these drugs.

On the other hand, we did not find any clinically significant changes in cardiovascular parameters such as heart rate, or systolic and diastolic blood pressures in the patients following administration of rectal diazepam (0.3 mg/kg) or rectal midazolam (0.5 mg/kg) during periopeative period. It is noteworthy that due to lack of rectal preparation of midazolam at the time of this study, we used its injectable preparation through a rectal applicator and this may interpret the observed differences for sedative effects and time to reach an acceptable level of sedation. The reason for partial beneficial effect of these drugs can be attributed to other factors including their stimulatory effect and mucosal irritation at application site. Other confounding factors in our study may be unpleasant and unfamiliar condition of our operating room, patients not being accompanied by their parents up to operating table and noise due to patients' transportation out of the operating room.

Conclusion

Rectal midazolam (0.3 mg/kg) and diazepam (0.5 mg/kg) as an anesthetic premedicant are capable of inducing sedation and reducing anxiety at periopeative period in pediatric patients with no noticeable hemodynamic and respiratory changes.

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