The injection rate of intravenous midazolam significantly influences the occurrence of paradoxical reaction in pediatric patients

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Background: Paradoxical reactions to benzodiazepines including restlessness, anxiety and sometimes violent behavior sometimes occur. Most of the known predicting factors of disinhibitory reactions such as age, gender, genetic or the psychological background are not modifiable. This study was conducted to evaluate the effect of rate of midazolam administration, as a controllable factor, on the occurrence of paradoxical reaction to midazolam (PRM) in pediatric patients. **Materials and Methods:** In a randomized, double-blind clinical trial 98 American Society of Anesthesiologists physical status I, II, aged from 6 months to 6 years, and undergoing elective surgery, were enrolled in the study. Patients were randomly allocated to receive midazolam 0.1 mg/kg as a 0.1% solution at an injection rate of 0.2 ml/s or 1 ml/s. The occurrence of PRM was compared between the two groups with Chi-square test. **Results:** The occurrence of PRM in the rapid injection group was significantly higher than the slow injection group (20.4% vs. 4.1%, P < 0.05, relative risk CI: 95% 6.03 (1.24–29.4)). **Conclusion:** Slow intravenous administration of midazolam significantly reduces the occurrence of paradoxical reactions and should be respected in premedication of pediatric patients.

Key words: Administration rate, midazolam, paradoxical reaction, premedication

INTRODUCTION

Benzodiazepines are administered to pediatric patients preoperatively to provide anxiolysis, amnesia, and sedation.[1-5] However, patients sometimes show paradoxical reaction to benzodiazepines and become restlessness, anxious or even aggressive.[6-10] Paradoxical reaction following midazolam administration is an unpleasant experience for the children and makes their parents and the operating room personnel worrisome. Most earlier studies focused on the treatment of paradoxical reaction to midazolam (PRM), while the recommended medications including the flumazenil, physostigmine, haloperidol, larger doses of benzodiazepines and ketamine have several potential adverse effects,[11-15] and reported to be only partially effective.[5,9] Thus, an important element of our practice should be to try to reduce the occurrence of paradoxical reactions. Noteworthy, we cannot make an intervention on most of the suggested predicting factors of paradoxical reaction such as age, gender, genetic[10,16] or the psychological background[17,18] of the patients. Thus, it would be reasonable to focus on the profile of administered medications that is potentially modifiable.

It has been suggested that higher doses of benzodiazepines are correlated with more occurrence of disinhibitory reactions.[9,19] Another factor known to influence some drug reactions is the speed of intravenous administration.[20] However, the impact of this factor on the occurrence of PRM has not been studied before. This study was conducted to compare two rates of midazolam administration (0.2 ml/s vs. 1 ml/s of 0.1% solution) on the occurrence of PRM in pediatric patients.

MATERIALS AND METHODS

Study design and participants

This randomized double-blind clinical trial was approved by the Research Ethics Committee of Hormozgan University and written informed consent was obtained from the parents of all patients. Between June 2008 and February 2009, a total of 98 American Society of Anesthesiologists physical status I, II patients, aged from 6 months to 6 years, and undergoing elective surgery, were enrolled in the study. Patients with a history of psychological disorders, mental retardation, previous surgical procedures, receiving sedative or herbal medications and those who had preoperative

pain were not included in the study.

The sample size was calculated based on the estimation equation of sample size for two ratios, with estimated incidence of PRM in slow and rapid injection groups as 5% and 30%, respectively. Based on 0.9 power to detect a significant difference and α level of 0.05, 45 patients in each group was estimated to be appropriate. Additional four patients were added to compensate for possible dropouts.

Procedures

Patients were randomly allocated to receive midazolam (Dormicum®; Roche, Brussels, Belgium) 0.1 mg/kg as 0.1% solution in distilled water at an injection rate of either 0.2 ml/s (rapid injection group) or 1 ml/s (slow injection group). Block randomization with a block size of 4 was considered to assign an equal number of individuals to each group. The drug was administered by one anesthetist in the calm environment of premedication room while the children were left free in a sitting or supine position or even in the arm of their parents. Midazolam was infused manually using a chronometer. All children had intravenous access before transfer to the operating room. Nurses in our pediatric ward usually use most easily accessible veins in the children's hand or forearm. Angiocatheter number 22 was most often used for intravenous access. The interval between intravenous line insertion in the ward and admission to the operating room was at least 2 h. Before midazolam administration, the anesthetist recorded a calmness score using a 5-point Likert scale (4= spontaneously calm, 3= calmed after reassurance, 2= crying, 1= agitated with violent crying, 0= uncontrollable, inconsolable, and

needing restraint).[21]

After approximately 1 min of midazolam administration, the children were transported to the nearby operating room while one parent attended the children. A single anesthetist who was blinded to the nature of assignments observed the patients for 10 min for the occurrence of paradoxical reactions. He was not present in the premedication room and was blinded to the allocations as well as children's baseline calmness scores. The diagnosis of PRM was made based on the observation of a sudden occurrence of restlessness, agitation, anxiety, inconsolable crying or aggressive behavior after a transient sedative state.[8] Induction of general anesthesia was performed after 10 min of assessment and earlier in the case of PRM. During the preinduction period, vital signs as well as oxygen saturation of patients were monitored continuously. Age, weight, sex and the occurrence of PRM were recorded in children. The study design has been summarized in Figure 1.

Statistical analysis

Data are presented as means (standard deviation) or percentages, as appropriate. Baseline characteristics and outcome measures of the two groups were analyzed with Student's *t*-test for continuous data and Chi-square test for categorical analysis. Calmness scale was presented as median and interquartile range and analyzed with Mann–Whitney U-test. All comparisons were two-tailed. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 16.0 software (SPSS, Inc., Chicago, IL, USA).
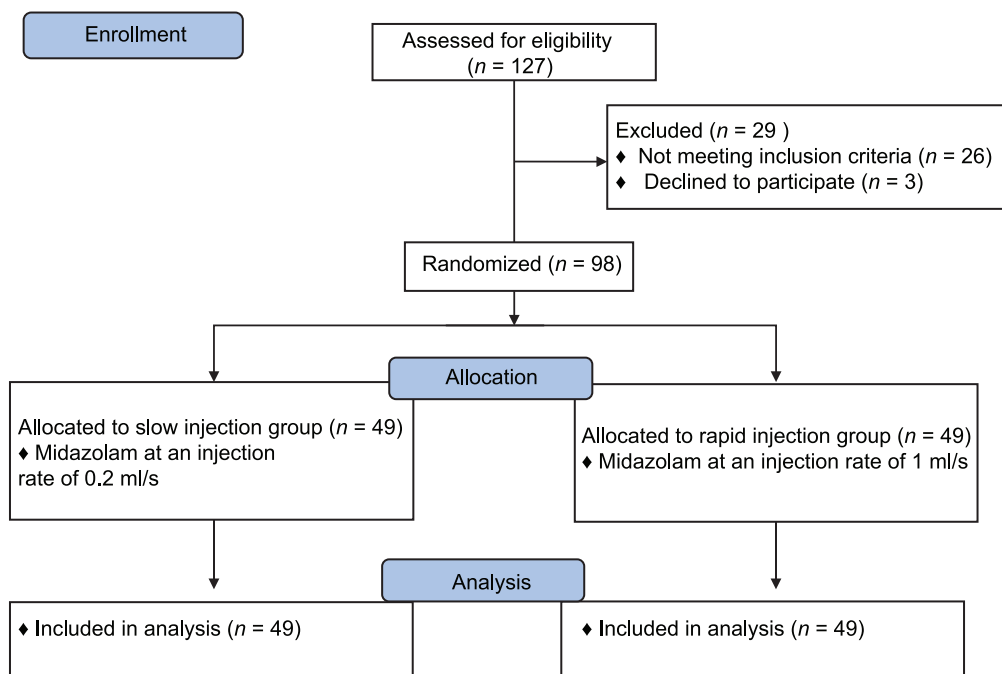

Figure 1: The consort flow diagram of the study

RESULTS

The study population included 76 boys and 22 girls with the average age of 28 ± 16 months. The most common site of surgery was lower abdomen, followed by ear, nose, and throat. The two groups were comparable respecting the baseline characteristics and calmness scores [Tables 1 and 2].

The incidence of PRM in the rapid injection group was significantly greater than the slow injection group (20.4% vs. 4.1%, P = 0.02). The relative risk was 6.03 (95% CI, 1.24, 29.4). The incidence of PRM in the first quartile of age (14 months) was 4/27 (14.8%), in the second quartile (15-24 months) was 5/22 (22.7%) and in the third quartile (25-40 months) was 3/22 (12%). None of the 24 children older than 40 months experienced PRM (P = 0.02). None of the patients experienced hypoxia, bradycardia or severe hypotension during the assessment period.

DISCUSSION

The reported occurrence of paradoxical reactions to benzodiazepines largely varies from <1% to >50% in patients with personality disorders.[22-24] The incidence of PRM in the slow injection arm of this study is comparable to earlier reports in pediatric patients.[14,17] The difference in the reported incidences may be due to different baseline characteristics of the study populations, administered benzodiazepine and its dosage, route of administration and finally the definition and time spent to assess the reaction. In this study, the diagnosis of PRM was confirmed by the

Table 1: Demographic data and baseline characteristics of patients

	Slow injection (*n*=49)	Rapid injection (*n*=49)	*P*
Male sex *n* (%)	42 (85.7)	34 (69.4)	0.08*
Age (month)	29.2 (18.1)	27.7 (15.6)	0.70**
Weight (kg)	11.4 (3.5)	11.6 (3.2)	0.79**
Site of operation			
Extremities	5 (10.2)	7 (14.2)	0.86*
Lower abdomen	22 (44.9)	21 (42.8)	
Upper abdomen	6 (12.2)	8 (16.3)	
Ear, nose and throat	16 (32.6)	12 (24.4)	
Thoracic	0 (0)	1 (2.0)	

*Chi-square test; **Two-sample *t*-test

Table 2: The dose and the consequences of midazolam administration in the two groups

	Slow injection (*n*=49)	Rapid injection (*n*=49)	*P*
Administered dose (mg)	1.15 (0.35)	1.16 (0.32)	0.87*
Baseline calmness score (median, IQR)	4,1	4,1	0.73**
Paradoxical agitation *n* (%)	2 (4.1)	10 (20.4)	0.02¥

*Two-sample *t*-test; **Mann-Whitney U-test; ¥Chi-square test. IQR=Interquartile range

familiar explained clinical picture and ruling out other causes of agitation, including hypoxia, hypotension and pain. Moreover, because no other drug was administered during the evaluation period, the possibility of reaction to other drugs is excluded.

Given that paradoxical reactions to benzodiazepines are mostly uncharacteristic, defining diagnostic criteria would be difficult. The diagnosis usually relies on the subjective judgment of the clinician when significant deviation from predicted normal behavior encountered. DeMascio and Shades proposed the following definition for "behavioral toxicity" following medication use. "Behavioral toxicity is a phrase used to denote those pharmacological reactions of a drug that, when administered within the dose range in which it has been found to possess clinical utility produce-through mechanisms not immediately specifiable-alterations in perceptual and cognitive functions, psychomotor performance, motivation, mood, interpersonal relationships or intrapsychic processes of an individual to the degree that they interfere with, or limit the capacity of the individual to function within his setting or constitute a hazard to his physical well-being."[25] Although this definition accurately describes paradoxical reactions, strict behavioral and clinical points at which these reactions occur could not be defined. Thus, the diagnostic criterion is a source of ambiguity in all studies targeting this medical condition. In this study, we defined PRM as restlessness, agitation, anxiety or aggressive behavior after a sedative state. We believe this sequence of events (i.e. sedation, followed by sudden onset of paradoxical reaction after administration of a potent sedative agent) is unlikely to be a normal behavioral reaction.

The state of anxiety of children when entering the operating room influences their following responses to sedative modalities. One of the factors that may affect the calmness of children and possibly the incidence of paradoxical reaction to sedative medications is their earlier experience of the operating room environment. In this study, we included those children who came for the first time to the operating room, whereas one parent attended the children, thus excluding this possible confounding factor. Moreover, our patients were similarly calm in the premedication room.

The mechanism of paradoxical reactions to benzodiazepines is not fully understood. Benzodiazepines bind to gamma-amino-butyric acid ($GABA_A$) receptors, causing increased influx of chloride ions into the neuron, inhibiting depolarization, resulting in sedation of the patient. The most likely theory for paradoxical reactions states that the inhibitory action of benzodiazepines may cause a loss of cortical control in some patients, leading to excitement, aggression, and even psychosis.[8] Pediatric patients

demonstrate limited capability to concentrate on the external social cues that lead to appropriate behavior, make them more prone to disinhibitory reactions. Some authors have attributed these reactions to serotonin imbalance[26] and central cholinergic system[9] in susceptible subjects.

Previous studies have shown that the disinhibitory reactions more commonly occur with the administration of midazolam[10] and alprazolam[23] among benzodiazepines. These drugs are rapidly excreted and the metabolite of midazolam, alpha1-hydroxymidazolam, contributes to only 10% of biological activity of midazolam. The involvement of high-dose, high-potency, and short half-life benzodiazepines in most reported disinhibitory reactions suggests the role of rapidly fluctuating plasma levels of benzodiazepines in the occurrence of these reactions[9,19] The findings of this study indicate the role of rapid drug administration in the occurrence of PRM, which supports this so-called "rebound insomnia" hypothesis.[27] This phenomenon occurs when benzodiazepines with short plasma half-lives are abruptly withdrawn.

In general, multiple factors modulate the pharmacogenomics of midazolam including receptor affinity, occupancy, reserves, imbalance in stimulation of different receptors in different areas of the brain, and receptor pathology. All of these factors should be taken into account when evaluating for PRM. Thirty years ago Biggio and Costa described a new class of ligands.[28] The beta-carboline derivatives decrease GABAergic transmission and demonstrate the contrary effects anticipated. Activation of benzodiazepine receptors may induce a wide range of responses from sedation to behavioral hyperactivity. We propose that different infusion rates may produce unlike concentrations of midazolam at the effect sites and subsequent induction of dissimilar receptors in the brain. This will induce contrasting clinical effects. Another support for this explanation may be derived from the theory of differing effects of centrally active drugs such as anesthetics on the Central nervous system inhibitory and excitatory neurotransmitter systems depending on their concentration in the brain.[29] For instance, it is known that etomidate has both pro- and anti-convulsant effects on EEG. Clinical findings demonstrate that the dose and rate of etomidate administration determine, which of its contrasting effects on the seizure threshold will occur in a particular clinical setting.[30]

Study limitations

The validity and reliability of the calmness scale used for measuring behavior in the preoperative phase have not been evaluated in a separate study. However, in this study only one investigator used the scale, and so inter-observer variability could not be a concern. Another limitation was the subjective diagnosis of PRM. To the best of our knowledge, no definite diagnostic criteria for PRM are available. To enhance accuracy, only one anesthesiologist who was experienced in the field of pediatric anesthesia reported the incidence of PRM after exclusion of other potential causes of agitation. Finally, we did not evaluate the family history of patients for psychological problems or personality disorders. As psychological background is one of the predicting factors of paradoxical reaction, considering this issue in planning for future studies is warranted.

The conclusion for clinical practice would be the slow incremental administration of benzodiazepines with the lowest dose sufficient for sedation. This strategy may reduce the incidence of unexpected disinhibitory effects of benzodiazepines. However, since PRM is usually unpredictable, the anesthetist should be prepared for the prompt treatment of unwanted reactions, especially when midazolam is used for younger children. Further molecular biotechnology studies are warranted to elucidate the association of PRM with receptor occupation in different routes, doses and rates of midazolam administration.

AUTHORS' CONTRIBUTIONS

AM proposed the hypothesis of study, provided assistance in the design of the study and carried out all clinical assessments. SHT provided assistance in the design of the study and statistical analysis. MM designed the study protocol and prepared the manuscript. All authors have read and approved the content of the manuscript.

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