J Anesth (2012) 26:878–882
DOI 10.1007/s00540-012-1422-6

ORIGINAL ARTICLE

Comparison of the effects of intranasal midazolam versus different doses of intranasal ketamine on reducing preoperative pediatric anxiety: a prospective randomized clinical trial

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Received: 10 September 2011 / Accepted: 21 May 2012 / Published online: 12 June 2012

Abstract
Purpose To compare the effects of intranasal midazolam versus different doses of intranasal ketamine on reducing preoperative pediatric anxiety.
Methods The participants of this double-blinded clinical trial study consisted of 120 children aged between 2 and 8 years. They were chosen for elective surgery and randomly assigned to four equal groups. For reducing preoperative anxiety, in the first group midazolam 0.2 mg/kg, in the second group (K1) ketamine 0.5 mg/kg, in the third group (K2) ketamine 3 mg/kg, and in the fourth group normal saline 1 drop/5 kg were administered intranasally. After 15 min, severity of anxiety was assessed with the modified Yale preoperative anxiety score (m-Yale PAS), and level of sedation was evaluated by the Ramsay Sedation Scale before intravenous catheterization. All data were transferred to SPSS-10 software and analyzed statistically with ANOVA, Kruskal–Wallis, and Mann–Whitney tests. A p value < 0.05 was considered meaningful.

The clinical trial registration number is IRCT201104236254N1.

Results The mean of m-Yale PAS in midazolam group was significantly lower than the other three groups ($p < 0.05$). Regarding this score, there was no significant statistical difference between K2 and normal saline groups ($p = 0.944$), but the differences between K1 and K2 ($p = 0.034$) and also between K1 and normal saline ($p = 0.049$) groups were significant statistically. The Ramsay Sedation Scale in the midazolam group was significantly higher than the other three groups ($p < 0.05$). By this scale, there was no significant statistical difference between (K2) and normal saline groups ($p = 0.940$). The differences between (K1) and normal saline ($p = 0.045$) and also between (K1) and (K2) groups ($p = 0.009$) were significant statistically.
Conclusion Intranasal midazolam was more effective than low- or high-dose intranasal ketamine in reducing preoperative pediatric anxiety. The lower dose of ketamine reduced preoperative anxiety more than a higher dose of ketamine, which may be clinically insignificant.

Keywords Ketamine · Midazolam · Pediatric preoperative anxiety · Sedation

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Introduction

The most important factors that determine postoperative outcome are incisional pain, nausea and vomiting, preoperative anxiety, and discomfort from intravenous injection [1]. Preoperative anxiety in children is a common phenomenon that has been associated with a number of negative behaviors such as agitation, talking too much, clinging to parents, becoming combative, crying or yelling, spontaneous urination, and the need for physical restraint during anesthetic induction [2]. Children with a high level of preoperative anxiety are more likely to exhibit signs of

postoperative emergence delirium [3] and to have a more painful, slower, and more complicated recovery process [4]. Preoperative anxiety has also been associated with the display of some postoperative maladaptive behaviors, including postoperative pain, sleeping disturbances, parent–child conflict, and separation anxiety. As a result, it is important from physiological as well as psychosocial aspects to decrease preoperative anxiety [2, 5].

In this regard, intranasal midazolam has some advantages. Because of high mucosal vascularity, the intranasal route offers rapid and virtually complete absorption into the systemic circulation. As midazolam has high hepatic clearance, avoidance of hepatic first-pass metabolism offers greater systemic bioavailability by the intranasal route. It has a faster onset than the oral or rectal route. Also, recovery from anesthesia is not affected [6]. In one study it was determined that intranasal administration of midazolam 0.2 mg/kg requires less patient cooperation and elicits a rapid response, although the production of a burning sensation is unpleasant [7].

Ketamine is a phencyclidine anesthetic agent that provides analgesic activity at subanesthetic doses. It is an *N*-methyl-D-aspartate receptor antagonist with opioid-receptor activity. Ketamine is highly lipid soluble and is rapidly absorbed after intravenous, intramuscular, and intranasal administration. It is an excellent analgesic, sedative, and amnesic agent that can be given by the intravenous, intramuscular, intranasal, or oral route. The bioavailability via oral administration is 20–30 %, and through the intranasal route it is approximately 40–50 % [8, 9].

In the study reported here, we hypothesized that administration of intranasal midazolam and intranasal ketamine would reduce preoperative anxiety by their properties of producing sedation. We also tested the hypothesis that different doses of intranasal ketamine would produce different levels of sedation.

Considering these aspects, we compared the effects of intranasal midazolam versus two doses of intranasal ketamine to determine the best medication for reducing preoperative pediatric anxiety.

Materials and methods

This study was performed after obtaining the permission of the institution's human subjects committee and having the informed consent of the parents of the participants in the pediatrics hospital in Qazvin, Iran. In this randomized, double-blinded, controlled clinical study, 120 children between the ages of 2 and 8 years, American Society of Anesthesiologist (ASA) grade I and scheduled for elective surgery, were assigned to four equal groups (by using colored cards).

This study was powered on the basis of previous results showing 50 % incidence of anxiety in the control group. A sample size of 30 patients in each group was calculated to detect a decrease in the incidence of anxiety to 15 % with $\alpha = 0.05$ and $\beta = 0.2$.

Those patients with a positive history of cardiovascular disease, convulsion, upper respiratory tract infection or allergic rhinitis, consumers of sedative or antihistamine drugs, and patients with nasal anatomical deformities were excluded from this study (Fig. 1).

Children came to the operation room with their parents. For reducing patient anxiety, in the first group midazolam (0.2 mg/kg), in the second group (K1) ketamine (0.5 mg/kg), in the third group (K2) ketamine (3 mg/kg), and in the fourth group normal saline (1 drop/5 kg) were administered intranasally by one trained researcher. After administration of premedication, vital signs (heart rate and blood pressure) and arterial oxygen saturation were monitored by cardiovascular monitoring and pulse oximetry.

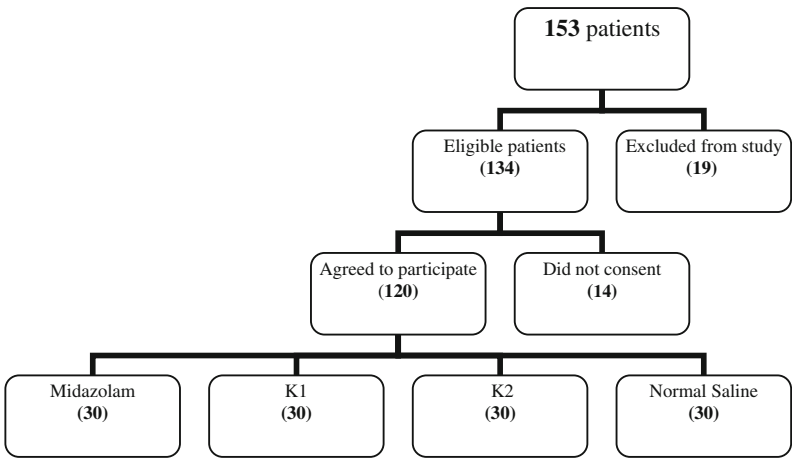

Fig. 1 Flow diagram of study participants: *K1*, low-dose ketamine (0.5 mg/kg); *K2*, high-dose ketamine (3 mg/kg)

After 15 min, the children were separated from their parents. Before intravenous catheterization, severity of anxiety was assessed with the modified Yale preoperative anxiety score (m-Yale PAS), and the level of sedation was evaluated with the Ramsay Sedation Scale (RSS) by an anesthesia provider who did not know which medication was administered to the children.

In m-Yale PAS, anxiety was assessed based on their activities (1–4), emotional expression (1–4), vocalization (1–6), state of arousal (1–4), and interaction with family members (1–4). The minimum score is 5 (minimum anxiety) and the maximum is 22, which indicates severe anxiety [1, 3, 10].

The Ramsay Sedation Scale defines the conscious state from level 1 (the patient is anxious, agitated, or restless) through the continuum of sedation to level 6 (the patient is completely unresponsive) [11]. It was evaluated as follows:

Scale 1: Patient is anxious and agitated or restless, or both
Scale 2: Patient is cooperative, oriented and tranquil
Scale 3: Patient responds to commands
Scale 4: Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
Scale 5: Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
Scale 6: Patient exhibits no response.

Premedication, induction, and maintenance of anesthesia were the same in all patients. All data were transferred to SPSS-10 software and analyzed statistically with analysis of variance (ANOVA), Kruskal–Wallis, and Mann–Whitney tests. The continuous variables were submitted to the Kolmogorov–Smirnov test to verify normal distribution. Continuous data (demographic data and m-Yale PAS) were reported as mean ± SD and were analyzed by analysis of variance for multiple comparisons. Tukey's post hoc test was used for intergroup comparison. Categorical data (in Ramsay Sedation Scale) were reported as number (percentages) and were analyzed by Kruskal–Wallis test. If there was a distinction, the Mann–Whitney *U* test was used for intergroup comparisons. $p < 0.05$ was considered meaningful.

Results

The study groups were comparable with respect to age, sex, and weight (Table 1).

During the entire 15 min of the study, systolic and diastolic blood pressure remained stable. Pulse rate was in the range of 80–120 beats/min with no episode of bradycardia. Oxygen saturation remained in the range of 94–100 % without oxygen administration.

In comparison of the anxiolytic effect of midazolam with various doses of ketamine and normal saline, it was shown that the mean m-Yale PAS in the midazolam group was lower than in the other three groups. According to statistical analysis, there were significant differences between midazolam and K1 ($p = 0.006$), between midazolam and K2 ($p = 0.000$), and between midazolam and normal saline groups ($p = 0.000$).

Also, there were significant statistical differences between K1 and K2 ($p = 0.034$) and K1 versus normal saline groups ($p = 0.049$), but the difference between normal saline and K2 groups was not statistically significant ($p = 0.944$) (Fig. 2).

The Ramsay Sedation Scale in the midazolam group was significantly higher than in the three other groups. The Mann–Whitney *U* test showed that there were significant statistical differences between K1 and normal saline groups and also between the K1 and K2 groups, but this difference was not significant statistically between the K2 and normal saline groups (Table 2).

Discussion

In our study, the anxiolytic and sedative effects of intranasal midazolam were compared with various doses of intranasal ketamine and normal saline as placebo. There were no significant statistical differences among the four groups regarding their age, sex, and weight; thus, all groups were comparable with each other. It was determined that intranasal midazolam led to better sedation than intranasal ketamine. Low-dose intranasal ketamine produced more sedation than high-dose intranasal ketamine but less than

Table 1 Patient demographic characteristics

Variable	Groups				*p* value
	Midazolam ($n = 30$)	K1 ($n = 30$)	K2 ($n = 30$)	Normal saline ($n = 30$)	
Age (years)	4.1 ± 1.4	4.9 ± 1.8	5.1 ± 1.5	4.3 ± 1.4	0.09
Weight (kg)	15.5 ± 4.1	16.6 ± 4.8	17 ± 4.5	17.6 ± 3.6	0.3
Sex					
Male	13	16	15	14	
Female	17	14	15	16	0.1

Values are expressed as number or mean ± standard deviation

n number of patients, *K1* low-dose ketamine (0.5 mg/kg), *K2* high-dose ketamine (3 mg/kg)

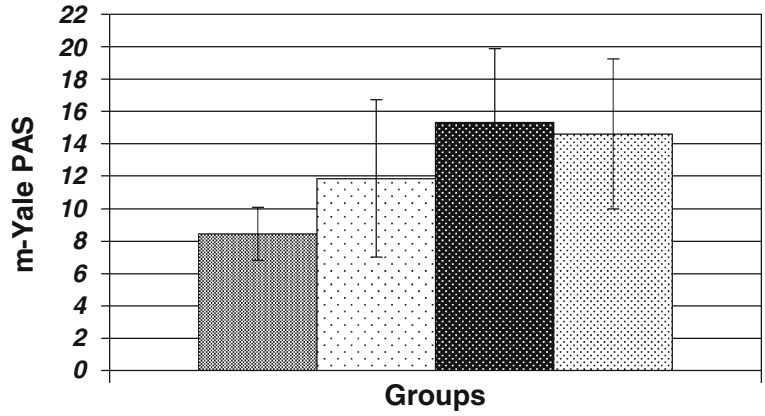

Fig. 2 Modified Yale preoperative anxiety score (m-Yale PAS) in four groups. Values are expressed as mean (±SD)

Table 2 Comparison of Ramsay Sedation Scale in the four groups

Score	Groups				*p* value	
	M ($n = 30$)	K1 ($n = 30$)	K2 ($n = 30$)	NS ($n = 30$)		
1	9	13	21	19	M–K1	0.001
2	8	11	8	8	M–K2	0.000
3	6	4	0	3	M–NS	0.000
4	4	1	1	0	K1–K2	0.009
5	3	1	0	0	K1–NS	0.045
6	0	0	0	0	K2–NS	0.940
Median (range)	2 (1–5)	2 (1–5)	1 (1–4)	1 (1–3)		

K1 low-dose ketamine (0.5 mg/kg), *K2* high-dose ketamine (3 mg/kg), *M* Midazolam, *NS* normal saline, *n* number of patients

intranasal midazolam. In response to the lower score of anxiety and higher score of sedation in midazolam and low-dose ketamine (K1) groups, children in these two groups separated more easily from their parents than did the other children.

There are different methods of drug administration, such as oral, nasal, rectal, intramuscular, and intravenous injection, for reducing preoperative anxiety. When choosing the optimal routes for sedation of pediatric patients, several factors are under consideration: ease of use, reliable administration, minimal adverse effects, the patient's age, and history of underlying illness [12]. Some drug administration requires a needle injection, which may be painful, anxiety provoking, pose a risk for contaminated needle-stick injury, and time consuming for staff, who must be trained in proper injection technique. By contrast, intranasal delivery of medication is relatively painless, inexpensive, and easy to administer with minimal training [13]. Thus, intranasal administration of sedative drugs may be an appropriate technique for pediatric age group.

Midazolam has been used for preoperative sedation by the intravenous (IV), intramuscular (IM), rectal, oral, and sublingual routes, but each has its own advantages and disadvantages. The intramuscular route is painful. Rectal administration is associated with unpredictable absorption and discomfort to the child. The oral route has low bioavailability because of the high first-pass metabolism of midazolam. Bitter taste is also a limiting factor and causes rejection as well as low compliance. The sublingual route is more beneficial in this regard. However, for desirable effect, the drug must be held under the tongue for at least 30 s, which requires a degree of cooperation that is difficult to achieve in preschool children [6].

Ketamine is an excellent analgesic and amnesic agent, but several adverse effects of ketamine have been reported, including increased salivary and bronchial secretions, nausea, vomiting, noise intolerance, confusion, blurred vision, difficulty in concentration, vertigo, and emergence reactions [14]. Factors that affect the incidence of emergence reactions are age, dose, gender, psychological susceptibility, and concurrent drug consumption. Children do not report as high an incidence of unpleasant emergence reactions as do adult patients. Larger doses and rapid administration of large doses seem to predispose patients to a higher incidence of adverse effects [8].

In some studies, it was shown that ketamine is superior to midazolam. Gharde et al. evaluated the efficacy of intranasal midazolam (0.2 mg/kg) versus intranasal ketamine (10 mg/kg) and their mixture (midazolam 0.1 mg/kg–ketamine 7.5 mg/kg). They concluded that, for producing sedation, intranasal ketamine was better than intranasal midazolam and that the combination of the two was better than midazolam alone but provides no benefit as compared with ketamine alone [9]. Gautam et al. compared intranasal midazolam versus intranasal ketamine as premedication in pediatric surgical procedure. They found that intranasal ketamine (5 mg/kg) was more effective than intranasal midazolam (0.2 mg/kg) regarding to the separation of the child from the parents. In response of the child to intravenous line insertion, the sedative effect of intranasal midazolam and ketamine was equal [15].

In comparison to the foregoing studies, in our study it was determined that intranasal midazolam was more effective than intranasal ketamine (0.5 and 3 mg/kg) for reducing preoperative anxiety and providing sedation in pediatric patients. It was interesting that by increasing the dose of intranasal ketamine, the children developed less sedation than those who received a lower dose of ketamine. Huge et al. determined a linear dose–response relationship for the psychedelic effects of ketamine. They compared two different doses of intranasal ketamine (0.2 vs. 0.4 mg/kg) and showed that pain relief and the resultant sedative effects occurred after intranasal ketamine administration in both groups but that a higher dose of ketamine (0.4 mg/kg) elicited significantly more side effects [14]. The result of this study may be a good explanation for the lack of the dose–response relationship of intranasal ketamine in our study. Our results demonstrated, in comparison to a higher dose of intranasal ketamine (3 mg/kg), a dosage as low as 0.5 mg/kg intranasal ketamine might be suitable for achieving an adequate therapeutic action (sedation and anxiolysis) combined with lesser side effects, because, on the basis of some studies, there is a dose–response correlation between ketamine and its side effects [8].

Also, Abrams et al. compared four different intranasal medications for sedation before dental procedures: midazolam 0.4 mg/kg, ketamine 3 mg/kg, sufentanil 1.5 μg/kg, and sufentanil 1 μg/kg. They concluded that midazolam and sufentanil at the lower dose (1 μg/kg) were most effective and had the fewest complications [13].

The limitation of our study is that it would have been of more clinical value to explore the benefits of combining intranasal midazolam and intranasal ketamine to reduce pediatric preoperative anxiety and decrease the incidence of ketamine-related side effects.

In conclusion, this study showed intranasal midazolam (0.2 mg/kg) would be superior in terms of anxiolysis and sedation. Low-dose intranasal ketamine (0.5 mg/kg) produced more sedation than high-dose intranasal ketamine (3 mg/kg), which may be clinically insignificant.

Acknowledgments The authors thank Nahid Hosseini Jahromi and Mohammad Mehravaran for their valuable help in this study. We are also grateful to those parents who gave permission to provide their children as examples in this study.

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