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Comparing the Hemodynamic Stability, Anti-Anxiety, and Sedation Effects of Intranasal Midazolam and Ketamine as Premedication in Pediatric Hernia Repair Surgery

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Abstract

Background: Fear and anxiety before entering the operating room are significant issues in pediatric anesthesia. Given that the venipuncture process is accompanied by separation anxiety, and the ease of use of intranasal premedication versus intravenous, rectal, or intramuscular methods, and considering the risk of aspiration during oral delivery in children, the purpose of this study was to compare and contrast the anti-anxiety and sedation effects of intranasal midazolam and intranasal ketamine as a premedication in pediatric hernia repair surgery.

Methods: This was a double-blind randomized clinical trial involving 36 participants aged 1 to 6 years who underwent hernia repair surgery in Bu Ali Hospital between 2020 and 2021. The child was transferred to the operating room after 30 minutes of evaluating the effects of the drug and recording the related data. In the operating room, data from an electrocardiogram device, arterial oxygen saturation level, and blood pressure were all checked. At 5 minute intervals, the patient's hemodynamics were checked and recorded. The time from the beginning to the end of anesthesia was recorded.

Results: This study included 36 patients (18 in each group). The average age and weight of the patients were 37.71 ± 21.73 months (range = 1-72 months) and 14.60 ± 4.26 kg (range = 6.5-25 kg), respectively. Independent t-tests showed no significant difference between the two groups. Heart rate and blood pressure were measured in two groups (ketamine and Midazolam) but no significant difference was observed among the three stages (before premedication, before anesthesia, and after intubation) (P>0.05). The relationship between qualitative outcomes was analyzed using Chi-square test but no significant difference was observed.

Conclusion: the current study showed that there is no statistically significant difference between intranasal ketamine and midazolam in terms of effectiveness and side effects.

Key Words: Anti-Anxiety, Hemodynamic Stability, Intranasal, Ketamine, Midazolam, Pediatric Hernia Repair Surgery, Premedication, Sedation.

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1- INTRODUCTION

Fear and anxiety about the operating room and surgery are important issues in pediatric anesthesia (1). Anxiety can cause aggressive reactions, increase the child's restlessness, lack of cooperation with anesthesiologists, and even challenge postoperative pain control. In addition to behavioral manifestations, preoperative anxiety activates the human stress response, that increases serum cortisol, epinephrine, and natural killer cell activity, as well as changes in vital signs such as blood pressure, heart rate, and respiratory rate, among others.(2, 3) To reduce preoperative anxiety in children, a multi-factorial approach involving the use of sedative drugs, the presence of parents in the operating room, playing with the child, creating a friendly environment, and appropriate pain control is required (4).

Currently, the most common method is to administer appropriate drugs before entering the operating room. However, premedication in the pediatric age group creates a difficult situation because the child and parents both experience anxiety. As a result, a drug that reduces separation anxiety while also providing adequate sedation and analgesia, less respiratory distress, and no complications after surgery is an ideal drug for children. Similarly, the ideal method of administration should require less cooperation, be harmless, and less unpleasant, so that parents are less concerned (2, 5). Benzodiazepines such as midazolam, opioids such as fentanyl and sufentanil, phencyclidine derivatives such as ketamine, short-acting barbiturates such as pentobarbital, and alpha 2 receptor agonists such as clonidine are among the most common of these drugs, each with its own set of advantages and disadvantages with various delivery methods such as intravenous, intramuscular, oral, rectal, sublingual, and nasal.(6) Because of the extensive network of intranasal vessels, instilling medical drops into the nose (intranasal) is the most effective method to increase the drug's bioavailability more than other methods. Using intranasal drops is advocated due to the direct absorption of the drug into the systemic circulation, the non-occurrence of drug destruction caused by the digestive system and the first pass effect from the liver, as well as the non-occurrence of absorption by the lung.(2) Midazolam is a water-soluble benzodiazepine with a short duration of action that induces amnesia and reduces anxiety.(7, 8) Ketamine is a phencyclidine derivative that maintains upper airway muscle tone and respiratory movement and causes sedation and analgesia by weakening the N-methyl D-aspartate (NMDA) receptor (2).

A hernia is an abnormal protrusion of tissue or an organ, such as the intestine, from the normal cavity wall.(9) It usually occurs in the abdominal area, particularly in the groin.(10) the other kinds of hernia including: hiatal , incisional and umbilical.(11) Hernia repair is the oldest and most commonly used type of hernia surgery.(12) The surgeon makes a long incision directly over the hernia and then uses surgical instruments to open the incision sufficiently to allow access to the hernia.(13) The displaced tissues or organs are then returned to their proper location, and the hernia sac is removed (14).

Considering the risk of aspiration during the operation following oral delivery in children, adversity of venipuncture process, intramuscular, and rectal administration in one hand, and the ease of use of intranasal premedication, on the other hand, made us compare and contrast the hemodynamic stability, anti-anxiety and sedation effects of intranasal midazolam and intranasal ketamine as premedication in pediatric hernia repair surgery.

2- MATERIALS AND METHODS

2-1. Design and Participants:

The current study is a double-blind randomized clinical trial involving 36 participants aged between 1 to 6 years who underwent hernia repair surgery in Bu Ali Hospital between April 8, 2020, and November 12, 2021.

2-1-1. Inclusion and exclusion criteria

Patients who met the following criteria were included in this study: 1) age range of 1 to 6 years, 2) physical status 1 or 2 according to the American Society of Anesthesiology (ASA PA), 3) those having an informed parental consent to participate in the study, 4) patients with no history of using sedative or analgesic drugs in the previous 24 hours, 5) patients with normal liver function tests, 6) patients with no psychological diseases, and 7) no food or drug allergies.

Patients were excluded from this study if they had any of the following conditions:

1) An allergy to any of drugs used in premedication or during surgery,

2) A hemodynamic disturbance,

3) Respiratory problems during surgery or irritable upper airway disorders such as a common cold, or

4) A lack of consent from their parents.

2-2. Procedure

2-2-1. Preoperative Preparation

The anesthesiologist separately explained participation procedures and potential side effects to the parents, and an informed written consent was obtained from the parents. Using Random Allocation software, the selected samples were randomly assigned into two groups in the form of six blocks with six participants. The project manager was told how to divide the samples into blocks, but the person evaluating the results was not informed. Age, gender, race, and weight were among the demographic factors recorded in their files. All participants were admitted to the hospital the night before the operation, were consulted by an anesthesiologist, and NPO from 00:00 with no medication.

2-2-2. Premedication and surgical procedure

The participants were split into two groups of 18 people. 30 minutes before the procedure, one group was given intranasal midazolam ($0/5_{mg/kg}$) and the other group was given intranasal ketamine ($5_{mg/kg}$) with no waste of medicine. The level of sedation, behavioral assessment, heart rate, potential complications, ease of separation from parents, and satisfaction were all recorded after separation from parents. The child was transferred to the operating room 30 minutes after administration, evaluating the effects of the drug and recording the related data. In the operating room, data from an electrocardiogram, arterial oxygen saturation level, and blood pressure were all checked. At 5-minute intervals, the patient's hemodynamics were checked and recorded. The time from the beginning to the end of anesthesia was recorded. The ease with which the child was separated from his or her parents was recorded as three levels 1: arguing and struggling, 2: anxious, 3: calm, and 4: sleeping. The level of anxiety-relieving effect was classified as 1: anxious and fearful behavior, 2: whining and crying, 3 calm behavior, and 4 friendly behavior. Sedation was classified as 1: fully conscious, 2: awake, 3: confused, and 4: sleepy. Parents' satisfaction with premedication was classified as 1: awful, 2: bad, 3: average, and 4: good. Heart rate was recorded before premedication, before anesthesia, and after intubation. In the operating and recovery rooms, possible side effects such as nausea and vomiting were recorded. The amount of recovery time in the recovery room was recorded as 1: short (less than 30 minutes), 2: medium

(30 to 60 minutes), and 3: long (more than 60 minutes). If analgesia was required in the recovery room, intravenous pethidine ($0.5_{mg/kg}$) was administered.

2-2-3. Anesthesia method

Induction was performed by atropine ($0.02_{mcg/kg}$), fentanyl ($2_{\mu g/kg}$) and propofol ($3_{mg/kg}$). After administering intravenous Atra ($0.5_{mg/kg}$) for muscle relaxation, intubation was performed. Anesthesia was maintained with a sevoflurane mac, 50% N2O, 50% O2, and a flow of $2_{L/min}$. After the operation, atropine ($0.02_{mg/kg}$) and neostigmine ($0.05_{mg/kg}$) were administered to reverse muscle relaxation. The amount of anesthetic given to each group was the same.

2-4. Data analysis

SPSS version 24 was used to analyze the data (IBM, USA). Percentage, mean and standard deviation, median, and range of changes were used to describe the variables. Chi-Square tests, Fisher's exact test, and Mann-Whitney tests were used to compare variables influencing treatment outcomes to assess the adequacy of random allocation and compliance with inclusion and exclusion criteria based on the nature of the variable. Mann-Whitney and Chi-Square tests were used to compare results between groups, and McNemar and Will-Coxon tests were used to compare results before and after the treatment.

3- RESULTS

3-1. Demographic characteristics

This study included 36 patients (18 in each group). The average age of the patients was 37.71 ± 21.73 months (range = 1-72 months) (P value = 0.25) and their average weight was 14.60 ± 4.26 kg (range = 6.5-25 kg) (P value < 0.001).

Table 1 displays the patients' demographic characteristics.

Table-1: Demographic characteristics of the patients

Variables		Midazolam	Ketamine	P-value
Age *		39.39 ± 22.92	37.78 ± 19.43	0.529
Weight *		14.73 ± 4.90	14.47 ± 3.65	0.380
Gender **	Male	12 (66.67%)	10 (55.56%)	0.468
	Female	6 (33.33%)	8 (44.44%)	

* Mean ± Standard deviation, ** Frequency (Percentage)

3-2. Cardiac and hemodynamic evaluation

The relationship between heart rate and blood pressure was studied in two groups (ketamine and Midazolam) but there was no significant difference among the three stages (before premedication, before anesthesia, and, after intubation) (**Table 2**) (P>0.05).

Table-2: Heart rate and blood pressure before premedication, before anesthesia and, after intubation in the ketamine and midazolam group

Variables			Midazolam	Ketamine	P-value
Heart Rate *		Before premedication	110.33 ± 16.67	103.11 ± 12.08	0.073
		Before anesthesia	109.28 ± 12.34	111.39 ± 14.12	0.822
		After intubation	116.39 ± 13.03	117.89 ± 14.13	0.777
Blood pressure *	Before premedication	Systole	100.00 ± 9.02	92.56 ± 11.01	0.341
		Diastole	61.89 ± 8.66	63.11 ± 12.24	0.713

	Before anesthesia	Systole	95.39 ± 9.74	95.00 ± 12.72	0.468
		Diastole	61.39 ± 9.64	64.50 ± 13.62	0.506
	After intubation	Systole	103.94 ± 8.53	96.17 ± 25.26	0.250
		Diastole	62.39 ± 7.30	65.00 ± 12.59	0.424

* Mean ± Standard deviation

3-3. Anxiety level and reaction to separation

At the assessment of the anxiety level, the group that received midazolam displayed a friendlier attitude than the group that received ketamine. On the other end of the spectrum, the anxious and fearful behavior in the midazolam group was lower, and the ease of separation from parents, as well as the level of anxiety, were higher in the ketamine group than in the midazolam group. However, these differences were not statistically significant (**Table 3**) (P-value > 0.05).

Table-3: Sedation level, anxiety level, and reaction to separation in the ketamine and midazolam groups

Variables		Midazolam	Ketamine	P-value
Sedation *	Fully conscious	2 (11.1%)	1 (5.6%)	0.549
	Awake	5 (27.8%)	6 (33.3%)	
	Confused	5 (27.8%)	8 (44.4%)	
	Sleepy	6 (33.3%)	3 (16.7%)	
Anxiety level *	Anxious and fearful	0 (0%)	2 (11.1%)	0.277
	Whining and crying	6 (33.3%)	6 (33.3%)	
	Calm	8 (44.4%)	9 (50%)	
	Friendly behavior	4 (22.2%)	1 (5.6%)	
Reaction to separation *	Arguing and struggling	0 (0%)	0 (0%)	0.942
	Anxious	7 (38.9%)	8 (44.4%)	
	Calm	10 (55.6%)	9 (50%)	
	Sleepy	1 (5.6%)	1 (5.6%)	

* Frequency (Percentage)

The patient's recovery time, parental satisfaction with the method, postoperative nausea and vomiting, and ASA SCORE were all evaluated after the surgical procedure, but no significant difference was found (**Table 4**) (P>0.05).

Table-4: Post-operative parameters in the ketamine and midazolam groups

Variables		Midazolam	Ketamine	P-value
Recovery time *	Less than 30	9 (50%)	13 (72.2%)	0.057
	30 to 60	9 (50%)	3 (16.7%)	
	More than 60	0 (0%)	2 (11.1%)	
Parental satisfaction *	Awful	1 (5.6%)	1 (5.6%)	0.480
	Poor	8 (44.4%)	4 (22.2%)	
	Average	5 (27.8%)	9 (50%)	
	Good	4 (22.2%)	4 (22.2%)	
Post-surgical Nausea	Yes	0 (0%)	1 (5.6%)	0.310

Vomiting *	No	18 (100%)	17 (94.4%)	
ASA score *	1	14 (77.8%)	14 (77.8%)	1.000
	2	4 (22.2%)	4 (22.2%)	

* Frequency number (Percentage)

4- DISCUSSION

The purpose of this study was to compare the sedation effects of midazolam and intranasal (IN) ketamine in the premedication of pediatric hernia repair surgery. There was no significant difference between the two groups in terms of sedation, anti-anxiety effects, or recovery time in this study. Pediatric surgery requires the use of stress-reduction techniques such as premedication due to the unique conditions of the age spectrum, including emotional issues such as separation from parents and fear of surgery. There was no discernible difference in heart rate or blood pressure between the two groups during the premedication phase of surgery. Various drugs and routes of administration have been tested to find the best premedication for children. Premedication is chosen for its safety, rapid onset, and effectiveness in anxiety reduction and facilitating anesthesia induction. Previous studies comparing oral and intranasal routes of administration of premedication have found that the intranasal route is more acceptable to children and has higher bioavailability than the oral route. Dexmedetomidine, ketamine, and midazolam are the most commonly used premedications today (15, 16).

Midazolam has been used as a pediatric premedication in a variety of settings for a long time. While the intranasal route is considered a quick, non-invasive method with favorable pharmacokinetics, its main drawbacks are nasal irritation during administration and negative postoperative behavioral changes (17, 18). Because of its sedative and analgesic properties, ketamine is commonly used as an oral premedication in children. However, its use as a premedication option has been limited due to adverse postoperative side effects such as salivation, nausea, vomiting, and psychological complications (15).

Garcia-Velasco et al. investigated the safety and efficacy of IN midazolam and ketamine as premedications, and their findings were promising.(19) Khatavkar SS et al. investigated the benefits of combining IN midazolam with ketamine versus midazolam for sedation in pediatric patients and discovered that combining IN midazolam with ketamine produced better results.(20) Our study did not look into the combination of two premedications.(21) Our findings, like those of Narendra, showed that intranasal use of midazolam and ketamine as premedication in children did not result in a significant difference in the sedation scale between the two groups. However, Narendra's study revealed that midazolam was associated with fewer side effects, which contradicted the findings of the current study. In addition, contrary to the findings of this study, Bahetwar et al. discovered that using ketamine IN was associated with a higher success rate than using midazolam (22).

According to Khoshrang et al., the recovery time in group K (ketamine) was significantly longer than in group M (midazolam), which was consistent with our findings. However, no significant difference in sedation was observed between K & M groups (23).

The current study's findings revealed that there was no significant difference in heart rate or blood pressure between the two groups. However, Khusrang et al.'s study

reported that midazolam had fewer side effects.

They found that sialorrhea and tachycardia were very common in the ketamine group, which contradicted our findings. Given that different groups of children of different races, ages, and genders, with diverse background problems and many cultural differences, were investigated in all of these studies via unequal doses of medications on one hand and the non-uniformity of the surgeries performed on the other, the results of all studies cannot be definitively confirmed or rejected, and reaching a definite result requires multicenter studies with larger sample sizes.

5- CONCLUSION

The current study showed that there is no statistically significant difference between intranasal ketamine and midazolam in terms of effectiveness and side effects.

5-1. Ethical considerations

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences and the National Ethics Committee of Iran with a registration code of IRCT20210904 and it was carried out following the principles of the Helsinki Declaration.

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