



# Comparing the Sedative Effects of Intranasal Dexmedetomidine, Midazolam, and Ketamine in Outpatient Pediatric Surgeries: A Randomized Clinical Trial

Simin Azemati<sup>1</sup>, MD;  Maryam Keihani<sup>2</sup>, MD; Mohammad Ali Sahmeddini<sup>1</sup>, MD;  Fatemeh Kanaani Nejad<sup>1</sup>, MD; Laleh Dehghanpisheh<sup>1</sup>, MD; Mohammad Bagher Khosravi<sup>1</sup>, MD; Naeimehossadat Asmarian<sup>1</sup>, PhD

<sup>1</sup>Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; <sup>2</sup>Hazrat Zeinab Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

## Correspondence:

Mohammad Ali Sahmeddini, MD;  
Department of Anesthesiology, Nemazee Hospital, Nemazee Sq., Zand Blvd.,  
Postal code: 71936-13311, Shiraz, Iran  
Tel: +98 71 36474270  
Email: sahmeddini@sums.ac.ir  
Received: 14 June 2023  
Revised: 12 August 2023  
Accepted: 01 September 2023

## What's Known

- The pharmacological approach is one of the most effective methods for the management of pre-operative anxiety in pediatric patients.
- Midazolam, dexmedetomidine, and ketamine are the most popular premedications that have different potencies and side effects.

## What's New

- The preferred premedication for pediatric patients has not yet been determined.
- Based on the result of the dynamic evaluation in this study, it was observed that intranasal ketamine had the fastest and intranasal dexmedetomidine had the most potent sedative effect.

## Abstract

**Background:** The management of preoperative anxiety in pediatric patients, as well as its implications, has remained challenging for anesthesiologists. In this study, we compared the safety and efficacy of intranasal dexmedetomidine, midazolam, and ketamine as surgical premedication in children.

**Methods:** This double-blinded randomized clinical trial was conducted at two tertiary hospitals in January 2014, on 90 children aged between 2-7 years old. The participants' American Society of Anesthesiologists (ASA) physical status was I or II, and they were scheduled for elective unilateral inguinal herniorrhaphy. Using the block randomization method, the patients were randomly assigned to three groups, each receiving intranasal dexmedetomidine (2 µg/Kg), midazolam (0.2 mg/Kg), and ketamine (8 mg/Kg) 60 min before induction of anesthesia. Anxiety and sedation state were evaluated before drug administration, and then every 10 min for the next 50 min. Parental separation anxiety, mask acceptance, postoperative agitation, pain, nausea, and vomiting were also recorded and compared between these groups. All the statistical analyses were performed using SPSS software (version 21.0).  $P < 0.05$  was considered statistically significant.

**Results:** Ketamine indicated the strongest sedative effect 10, 20, and 30 min after administration of premedication ( $P < 0.001$ ,  $P = 0.03$ ,  $P = 0.01$ , respectively). However, dexmedetomidine was more effective than other drugs after 40 and 50 min ( $P < 0.001$ ). Other variables indicated no statistically significant difference.

**Conclusion:** In case of emergencies, intranasal ketamine, with the shortest time of action, could be administered. Intranasal dexmedetomidine, which was revealed to be the most potent drug in this study, could be administered 40-50 min before elective pediatric surgeries.

**Trial registration number:** IRCT2013081614372N1.

Please cite this article as: Azemati S, Keihani M, Sahmeddini MA, Kanaani Nejad F, Dehghanpisheh L, Khosravi MB, Asmarian N. Comparing the Sedative Effects of Intranasal Dexmedetomidine, Midazolam, and Ketamine in Outpatient Pediatric Surgeries: A Randomized Clinical Trial. *Iran J Med Sci.* 2024;49(7):421-429. doi: 10.30476/ijms.2023.99122.3118.

**Keywords** • Preanesthetic medication • Hypnotics and sedatives • Anti-anxiety agents

## Introduction

Preoperative anxiety is a major concern in pediatric surgery and anesthesiology. Some studies reported that up to 75% of children

experienced preoperative anxiety.<sup>1</sup> In pediatric patients, preoperative anxiety might result in aggressive reactions, increased agitation, behavioral changes, and postoperative pain. Anesthetists attempt to alleviate this discomfort and ensure a smooth induction of anesthesia.<sup>2</sup>

Multiple medications, including midazolam, dexmedetomidine, and ketamine were identified as suitable for usage in reducing preoperative anxiety and ensuring smooth parental separation.<sup>3</sup> Midazolam, a Gamma-aminobutyric acid (GABA) receptor inhibitor, is the most commonly used sedative and anxiolytic medicine in children.<sup>4</sup> Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist with sedative, anxiolytic, and analgesic effects.<sup>5</sup> Ketamine is a phencyclidine derivative that induces a condition between deep sedation and general anesthesia.<sup>6</sup>

Although several randomized clinical trials (RCTs) were conducted to compare the efficacy and safety of anxiolytic premedication drugs in children, the results remained heterogeneous.<sup>7-9</sup> Therefore, a definite answer to the question of the best sedative premedication has not been achieved yet.

This study aimed to investigate the effectiveness and safety of intranasal midazolam, dexmedetomidine, and ketamine in pediatric patients. Consequently, a continuous assessment of sedation and anxiety/agitation in both preoperative and postoperative conditions was performed to have a thorough dynamic evaluation, as well as to determine the most effective premedication for the management of preoperative anxiety in pediatric patients.

## Patients and Methods

This randomized double-blind clinical trial study was registered in the Iranian Registry of Clinical Trials (IRCT2013081614372N1) and was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1392.3671). The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from the children's parents or their legal guardians before their enrollment.

### Enrollment and Eligibility

In this trial, 90 children of American Society of Anesthesiologists (ASA) Classification physical status I or II,<sup>10</sup> aged between 2-7 years, who were scheduled for elective unilateral inguinal herniorrhaphy in January 2014 at Nemazee Hospital and Ghadir Mother and Child Hospital, both affiliated with Shiraz University

of Medical Sciences (Shiraz, Iran) were enrolled. The exclusion criteria were renal or hepatic failure, upper respiratory tract infection, cardiac arrhythmia, congenital heart disease, neurological disease, mental retardation, or having known allergy or hypersensitivity reactions to dexmedetomidine, midazolam, or ketamine.

### Sample Size

A previous study by Akin and others<sup>11</sup> reported that 66.6% of the group midazolam ( $P_1$ ) and 26.6% of the group dexmedetomidine ( $P_2$ ) were calm and cooperative at the time of mask induction. Based on the below formula, as well as taking into account the test power of 80% ( $\beta=0.2$ ), the confidence interval of 95% ( $\alpha=0.05$ ), and considering the dropout rate, a sample of 30 patients in each group with a total of 90 were enrolled in the study.

$$n=(Z_{1-\alpha/2}+Z_{1-\beta})^2*[P_1(1-P_1)+P_2(1-P_2)]/(P_1-P_2)^2$$

### Study Intervention

All patients had overnight fasting and were allowed to drink clear liquid up to 2 hours before the operation. The recruited children were assigned to each group using block randomization in 10 blocks of size 9. The blocks list was extracted from [www.sealedenvelope.com](http://www.sealedenvelope.com). Patients in group D (N=30) received 2 µg/Kg of intranasal dexmedetomidine (Precedex, Pfizer Inc., USA). The dose of dexmedetomidine was modified based on a study by Yuen and others.<sup>12</sup> Group M (N=30) received 0.2 mg/Kg of intranasal midazolam (Caspian Tamin Pharmaceutical Co., Iran), and group K (N=30) was given 8 mg/Kg of intranasal ketamine (PANPHARMA GmbH., Germany) 60 min before induction of anesthesia.

The drugs were diluted with normal saline to a final dose of 2 mL, and dripped into both nostrils equally, using a 2.5 mL sequentially numbered syringe without a needle, while the child was in the recumbent position. To keep the trial double-blind, an anesthesiologist, who was not involved in the other parts of the study (data collection and assessment), prepared and administered the drugs based on a randomization list. Parents, observers, and attending anesthesiologists, were all blinded to the allocated drugs. Anesthesia was maintained using  $O_2-N_2O$ -Isofurane using a face mask and spontaneous breathing. After losing consciousness and establishing an IV access, 1.5 µg/Kg of fentanyl was administered. Intraoperative fluid infusion consisted of 5-6 mL/Kg/h lactated ringer's solution, which was continued postoperatively with dextrose 50mg/mL in NaCl 4.5 mg/mL at a rate of 3 mL/Kg/h until oral intake could be established. At the end

of the surgery, once the children had stable respiration, they were transferred to the post-anesthesia care unit (PACU). The length of the surgery and anesthesia were recorded in PACU.

**Study Assessments**

Since drug administration, baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SaO<sub>2</sub>) were continuously monitored and were recorded every 10 min.

Preoperative sedation and anxiety were the primary outcomes of this study. The mask acceptance, parental separation anxiety postoperative sedation, agitation, pain, nausea, and vomiting were secondary outcomes of this study.

**Preoperative Sedation and Anxiety**

We used a modified observer’s assessment of the sedation tool, whose validity and reliability were confirmed previously,<sup>13</sup> and it ranged from 0 (unconscious) to 6 (alert). The anxiety scale was obtained from a previous study on pediatric premedication,<sup>11</sup> which ranged from 1 (calm) to 4 (most anxious). Anxiety and sedation state were evaluated before drug administration, then every 10 min for the next 50 min.

**Parental Separation Anxiety**

Anxiety scale<sup>11</sup> was used to assess the parental separation anxiety 45-60 min after drug administration when the patients were transferred to the operating theater.

**Mask Acceptance Scale**

A three-point scale, adopted from previous studies,<sup>11, 14</sup> was used to assess the degree of

mask acceptance. The evaluation process was performed by an anesthetist who was blinded to group randomization. In the mask acceptance scale (MAS), the scores of 1 and 2 were considered satisfactory, and 3 was considered unsatisfactory mask acceptance.

**The Postoperative Agitation**

The postoperative agitation was assessed every 15 min by a three-point scale, adapted from the study of Akin and others,<sup>11</sup> ranging from 1 (calm children) to 3 (children who were thrashing and did not calm down by verbal instructions).

Table 1 presents detailed information on the scales that are used in this study to assess the patient’s status.

The postoperative pain was assessed using the modified objective pain scale (OPS) every 15 min. This scale was validated for children by previous studies.<sup>15, 16</sup> Following surgery, those patients with an OPS of 5 or above received intravenous paracetamol at a dose of 15 mg/Kg.

The number of cases of preoperative and postoperative nausea and vomiting were documented. In case of nausea and vomiting, intravenous ondansetron at a dose of 0.15 mg/Kg was administered.

**Statistical Analysis**

All the statistical analyses were performed using SPSS software, version 21.0 (Armonk, NY: IBM Corp., Chicago, IL). Non-parametric variables were analyzed by the Kruskal-Wallis test. Then, the Dunn test was applied for *post hoc* pairwise comparison when a significant result was obtained.

Hemodynamic variables (SBP, DBP, and HR)

Table 1: Scales for evaluation of preoperative and postoperative conditions		
Scale	Patient’s status	Score
Sedation	Appears alert and awake, and responds readily to names spoken in a normal tone	6
	Appears asleep but responds readily to names spoken in a normal tone	5
	Lethargic response to name spoken in normal tone	4
	Responds only after a name is called loudly or repeatedly	3
	Response only after mild prodding or shaking	2
	Does not respond to mild prodding or shaking	1
	Does not respond to noxious stimulus	0
Anxiety	Crying or resisting	4
	Anxious and could not be reassured	3
	Anxious but could be reassured	2
	Calm and cooperative	1
MAS	Combative, crying	3
	Moderate fear of the mask, cooperative with reassurance	2
	Calm, cooperative, or asleep	1
Agitation	Combative, disoriented, thrashing	3
	Restless or crying but calms to verbal instructions	2
	Calm, easily arousals, follows commands	1

were analyzed by ANOVA test, and when it was significant, the Tukey *post hoc* test was applied to make the pairwise comparisons between the three groups. Categorical data were analyzed by the Chi square test or Fisher's exact test.  $P \leq 0.05$  was considered statistically significant.

## Results

This study included 90 patients who were randomly assigned to one of the three groups: M, D, and K. A flow diagram illustrating patient recruitment is shown in figure 1. Table 2 shows the characteristics of the recruited cases in each group.

### The Preoperative Condition

**Preoperative Sedation:** During the dynamic assessment of the sedation state among the three groups, it was revealed that in the first 30 min after administration of premedication, the most effective drug was ketamine ( $P < 0.001$ ,  $P = 0.03$ ,  $P < 0.001$ , respectively) in 10, 20, and

30 min after drug administration.

However, dexmedetomidine was more effective than other drugs 40 and 50 min after drug administration ( $P < 0.001$  for both; table 3).

**Preoperative Anxiety:** There was no significant difference in preoperative anxiety among groups (table 3).

**Parental Separation Anxiety:** 45-60 min after drug administration, 22 children (73.3%) in group D, 24 (80%) in group K, and 26 (86.7%) in group M were calm or apprehensive but could be reassured and had satisfactory parental separation ( $P = 0.53$ ).

**Mask Acceptance:** 18 patients (60%) in group M, 12 (40%) in Group D, and 14 (46.7%) in group K demonstrated satisfactory mask acceptance (scale of 1 or 2). There was no statistically significant difference in mask acceptance between groups ( $P = 0.32$ ).

**Hemodynamic Variables:** There were significant group and time effects on SBP ( $P < 0.001$ ) and a significant group×time interaction ( $P < 0.001$ ).

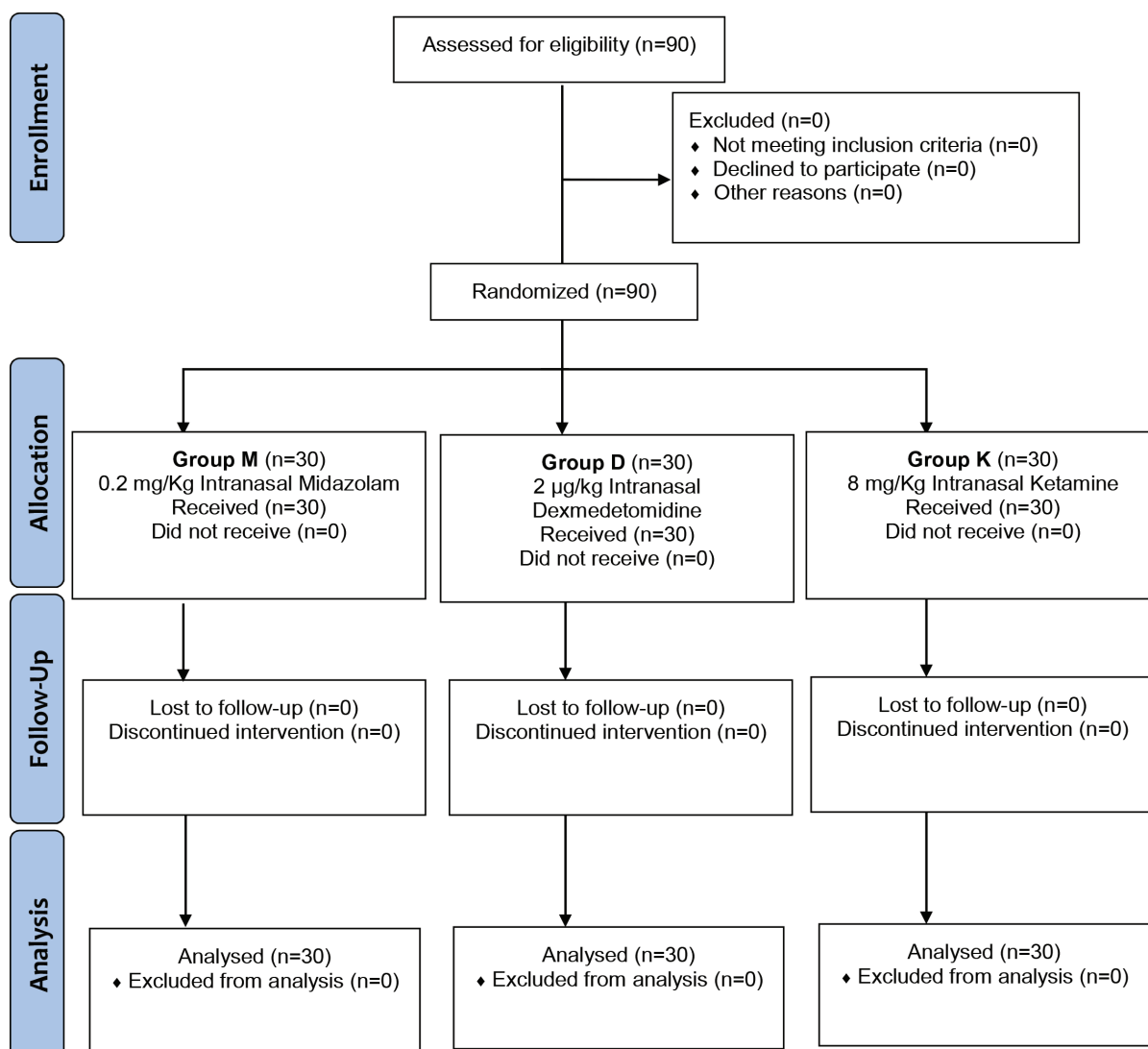


Figure 1: This figure represents the CONSORT flow diagram of the study.

**Table 2: Patient's preoperative and operative characteristics data**

Demographic data	Group M (n=30)	Group D (n=30)	Group K (n=30)	P value*
Age (year); median (IQR)	3.75 (2.5-5)	3.25 (2.4-5.1)	3 (2.4-4.7)	0.80
Sex, n (%)	Male	21 (70)	19 (63)	0.92
	Female	11 (37)	9 (30)	
Weight (Kg, mean±SD)	14.67±2.93	13.97±3.08	13.87±2.76	0.51
Duration of surgery (min, mean±SD)	16.96±10	15.96±8.21	16.92±7.81	0.30
Duration of anesthesia (min, mean±SD)	29.73±19.13	27.9±13.06	29.70±12.18	0.60

M: Midazolam; D: Dexmedetomidine; K: Ketamine; \*Based on the result of the Kruskal-Wallis test for Age, Chi square test for Sex, ANOVA test for weight, duration of surgery, and duration of anesthesia. P<0.05 was considered statistically significant.

**Table 3: Preoperative sedation and anxiety in three groups of study**

	Sedation				Anxiety			
	Group M	Group D	Group K	P value	Group M	Group D	Group K	P value
Baseline	6 (6-6)	6 (6-6)	6 (6-6)	0.35	2 (1-2)	2 (1-2)	2 (1.75-4)	0.17
10 min	6 (6-6)	6 (6-6)	5 (4-6) <sup>D, M</sup>	<0.001*	1 (1-1) <sup>D</sup>	1 (1-1) <sup>M</sup>	1 (1-2)	0.01
20 min	6 (5-6) <sup>K</sup>	5.5 (3.756)	4.5 (4-6) <sup>M</sup>	0.03	1 (1-1)	1 (1-1)	1 (1-1)	0.06
30 min	6 (5-6) <sup>D, K</sup>	5 (2-6)	4 (3-6)	<0.001*	1 (1-1)	1 (1-1)	1 (1-1)	0.51
40 min	6 (5-6) <sup>D, K</sup>	3.5 (2-6)	4 (2-6)	<0.001*	1 (1-1)	1 (1-1)	1 (1-1)	0.71
50 min	6 (5-6) <sup>D, K</sup>	3 (2-6)	5 (2.75-6)	<0.001*	1 (1-1)	1 (1-1)	1 (1-1)	>0.999

M: Midazolam; D: Dexmedetomidine; K: Ketamine; Values are presented as median (IQR). The data were analyzed using the Kruskal-Wallis test. The Dunn test was applied for *post hoc* pairwise comparison when a significant result was obtained. \*Statistically significant based on Bonferroni Correlation (P<0.01).

**Table 4: Postoperative agitation and sedation in the three studied groups**

	Postoperative agitation				Postoperative sedation			
	Group M	Group D	Group K	P value	Group M	Group D	Group K	P value
Baseline	1 (1-2)	1 (1-2)	1 (1-2)	0.97	3 (2-5)	3 (2-5)	3 (2-5)	0.64
15 min	2 (1-2)	1 (1-2)	1 (1-2)	0.38	5 (4.75-6)	6 (3.75-6)	5 (3-6)	0.43
30 min	1 (1-2) <sup>D</sup>	1 (1-1) <sup>M</sup>	1 (1-2)	0.04	6 (6-6)	6 (5-6)	6 (4.75-6)	0.19
45 min	1 (1-1)	1 (1-1)	1 (1-1)	0.85	6 (6-6)	6 (6-6)	6 (6-6)	0.47
60 min	1 (1-1)	1 (1-1)	1 (1-1)	0.71	6 (6-6)	6 (6-6)	6 (6-6)	>0.999

M: Midazolam; D: Dexmedetomidine; K: Ketamine; Values are presented as median (IQR). Analyzed by the Kruskal-Wallis test; \*Statistically significant based on Benferroni Correlation (P<0.001).

Therefore, the ANOVA+Tukey *post hoc* test was performed. From 10 to 50 min after premedication in group D, SBP was lower than groups M and K (P=0.01). SBP was reduced by 18% in group D and 3% in groups M and K, respectively.

There were significant group and time effects on DBP and HR (P<0.001, P<0.001, respectively) and a significant group×time interaction (P<0.001). Thus, the ANOVA+Tukey *post hoc* test was performed. HR and DBP of group D were significantly lower than groups M and K (P=0.01). HR was reduced by 14%, 4%, and 2% in groups D, M, and K, respectively. We found no hypoxemia (SaO<sub>2</sub><95 %) before, and during the operation in the operating room or after the operation in the PACU.

**Preoperative Nausea and Vomiting:**

Group K had higher preoperative nausea and vomiting following intranasal drug administration (P<0.001). Eight patients (26.6 %) in group K and 1 (3.3 %) in group M experienced nausea and vomiting. No patient in group D had these complications.

**The Postoperative Condition**

**Postoperative Sedation:** There was no statistically significant difference between baseline postoperative sedation and 15, 30, 45, and 60 min after awakening (P=0.64, P=0.43, P=0.19, P=0.47, and P>0.999, respectively). All the patients in the three groups had a sedation score of 3 at baseline and then leveled up to 5 or 6 in 15 min (table 4).

**Postoperative Agitation:** Based on the Bonferroni correlation, there was no significant difference in postoperative agitation in PACU between groups (table 4).

**Postoperative Pain Scale:** There was no statistically significant difference in postoperative pain among patients during the first hour after surgery (P=0.27). The patients with OPS of 5 or higher who received paracetamol were 10 (33.3%) in the M group, 5 (16.7 %) in the D group, and 5 (18.5 %) in the K group (P=0.27).

**Postoperative Nausea and Vomiting:**

There were 2 (6.7%) patients in group D, 2 (6.7%) in group M, and 4 (15.4%) in group K with

postoperative nausea and vomiting. There was no statistically significant difference in number of patients with postoperative nausea and vomiting among the three studied groups ( $P=0.47$ ).

## Discussion

The present study investigated the efficacy and safety of intranasal midazolam, ketamine, and dexmedetomidine. The findings indicated that ketamine had a significantly more sedative effect than others in the first 30 min after administration. However, patients who received dexmedetomidine had the lowest sedative state 40-50 min after the drug administration.

Many factors, including age, ASA status, preoperative pain, school experience, and parental stress, were associated with preoperative anxiety. Therefore, we set strict inclusion criteria in this study to equalize the cases and eliminate biases as much as possible.<sup>1</sup>

In the present study, the dosage of intranasal midazolam, dexmedetomidine, and ketamine was based on the safety and efficacy approval of previous studies.<sup>12, 17, 18</sup>

Among all the possible drug administration methods, the intranasal route is a noninvasive and simple method with high bioavailability. Absorption of intranasal drugs occurs directly into the systemic circulation. The absorption and bioavailability of medicines delivered intranasally were comparable to those of IV administration. Therefore, the selection of the intranasal route for administering premedication to children was reasonable.<sup>19</sup> Recent studies on different routes of midazolam administration indicated that the intranasal route was not only more effective but also more acceptable to pediatric patients.<sup>20</sup>

Several randomized clinical trials compared the effect of different intranasal sedative drugs among pediatric patients. Surendar and others conducted an RCT and compared the efficacy of intranasal midazolam, dexmedetomidine, and ketamine, 30 min after administration of the drug. They reported that all three drugs had the same sufficient sedative effects.<sup>21</sup> Besides, Elshafeey and others conducted a continuous evaluation of the sedation state every 10 min among intranasal dexmedetomidine and ketamine groups. They claimed that 10 min after administration, both groups experienced proper sedative effects.<sup>22</sup>

Despite these findings, the present study indicated that intranasal midazolam, dexmedetomidine, and ketamine premedication had obvious differences in efficacy and time of action. Ketamine was the fastest drug to sedate children (10 min after administration),

and it was also the most effective drug in the first 30 min. Dexmedetomidine was the most effective premedication 40 and 50 min after drug administration. The lowest median of the preoperative sedation state was recorded in group D, 50 min after administration. Moreover, Shereef and others reported that 30 min after drug administration, nebulized dexmedetomidine was more sedative than nebulized midazolam and ketamine,<sup>23</sup> which was compatible with the findings of the present study. In another study on different timing of intranasal dexmedetomidine administration as pediatric premedication, the researchers evaluated the efficacy of dexmedetomidine administration 10, 20, and 30 min before surgery. They indicated that only children who received dexmedetomidine 30 min prior to surgery had a satisfactory sedation state.<sup>24</sup>

The present study investigated the anxiety state every 10 min to 50 min after drug administration. Throughout the whole trial, the three medications had an equivalent effect on anxiety control, except for the first 10 min following drug administration, when patients in the ketamine group were more anxious. In another study by Akin and others, it was confirmed that intranasal midazolam and dexmedetomidine had the same effect on children's anxiety.<sup>11</sup>

Anxiety control should lead to better parental separation and more satisfactory mask acceptance among pediatric patients. In this study, as the anxiety of all patients in the three groups decreased to a median of 1, satisfactory parental separation and mask acceptance were observed in all cases, with no statistically significant differences.

Contrary to the findings of the present study, Shereef and others compared the nebulized midazolam, dexmedetomidine, and ketamine and claimed that patients in the group dexmedetomidine had more statistically significant satisfactory separation and mask acceptance than patients in the midazolam and ketamine groups.<sup>23</sup>

During the postoperative care in the present research, there was no difference in sedation and agitation among groups. Concerning the assessment of postoperative pain, although the number of patients with OPS>5 in the midazolam group was two times more than in the other groups, no statistically significant differences were observed.

In this study, the safety of these drugs was assessed by measuring HR, SBP, and DBP changes, as well as recording preoperative and postoperative nausea and vomiting. The dexmedetomidine group had a 14% reduction in HR, an 18% reduction in SBP, and a 24%

reduction in DBP. These findings were statistically more than the midazolam and ketamine groups. However, these changes in blood pressure and HR were not clinically significant, and no active management was required. Therefore, dexmedetomidine could be considered a safe premedication in pediatric patients.

Similar to the findings of the present study, a previous study reported statistically significant HR and blood pressure reduction after drug administration in the dexmedetomidine group. In a systematic review conducted on the use of dexmedetomidine as premedication in pediatric patients, it was reported that children who received dexmedetomidine had significantly lower heart rates than others.<sup>25</sup>

Concerning the evaluation of preoperative nausea and vomiting, more patients in the ketamine group (26.9%) had this complication than the midazolam group (3.3%). No patient in the dexmedetomidine group experienced preoperative nausea and vomiting. Narendra and others found that 16% of children who received intranasal midazolam and 10% of children who received intranasal ketamine experienced preoperative nausea and vomiting.<sup>26</sup>

In the present research, there was no difference in postoperative nausea and vomiting. None of the patients in the three studied groups experienced hypoxemia.

As the main limitation of the study, the small sample size and sampling method, which led to the enrollment of children who only underwent herniorrhaphy, increased the feasibility of study completion and also restricted the generalizability of the findings or could lead to bias.

## Conclusion

The effects of midazolam, dexmedetomidine, and ketamine on children aged 2-7 years old demonstrated that ketamine had the fastest and dexmedetomidine had the most effective sedative effect. Therefore, ketamine could be the preferred premedication in emergent procedures. Moreover, when there is no time limitation, dexmedetomidine could be the preferred premedication. Further evaluations with larger sample sizes and different sampling methods are required to confirm the best premedication for pediatric sedation.

## Authors' Contribution

All authors had substantial contributions to the conception and design of the work and the acquisition, analysis, and interpretation of data for the work, drafting the work and reviewing it

critically for important intellectual content, and final approval of the version to be published. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

## Acknowledgment

This study was supported by the Research Committee of Shiraz University of Medical Sciences (Grant number: CT-P-92-5311).

## Data Sharing Policy

Generated and analyzed data supporting the result of this study are available from the corresponding author upon reasonable request.

## Conflict of Interest

MohammadAli Sahmeddini and Naeimehossadat Asmariyan, as the Editorial Board Members, were not involved in any stage of handling this manuscript. A team of independent experts was formed by the Editorial Board to review the article without their knowledge.

## References

- 1 Getahun AB, Endalew NS, Mersha AT, Admass BA. Magnitude and Factors Associated with Preoperative Anxiety Among Pediatric Patients: Cross-Sectional Study. *Pediatric Health Med Ther.* 2020;11:485-94. doi: 10.2147/PHMT.S288077. PubMed PMID: 33364873; PubMed Central PMCID: PMC7751437.
- 2 Britteon P, Cullum N, Sutton M. Association between psychological health and wound complications after surgery. *Br J Surg.* 2017;104:769-76. doi: 10.1002/bjs.10474. PubMed PMID: 28195304.
- 3 Dave NM. Premedication and Induction of Anaesthesia in paediatric patients. *Indian J Anaesth.* 2019;63:713-20. doi: 10.4103/ija.IJA\_491\_19. PubMed PMID: 31571684; PubMed Central PMCID: PMC6761781.
- 4 Almenrader N, Passariello M, Coccetti B, Haiberger R, Pietropaoli P. Premedication in children: a comparison of oral midazolam and oral clonidine. *Paediatr Anaesth.* 2007;17:1143-9. doi: 10.1111/j.1460-9592.2007.02332.x. PubMed PMID: 17986032.
- 5 Phan H, Nahata MC. Clinical uses of dexmedetomidine in pediatric patients. *Paediatr Drugs.* 2008;10:49-69. doi: 10.2165/00148581-200810010-00006.

- PubMed PMID: 18162008.
- 6 Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesth Prog.* 1999;46:10-20. PubMed PMID: 10551055; PubMed Central PMCID: PMCPMC2148883.
  - 7 Abdelaziz HMM, Bakr RH, Kasem AA. Effect of intranasal dexmedetomidine or intranasal midazolam on prevention of emergence agitation in pediatric strabismus surgery: a randomized controlled study. *Egyptian journal of anaesthesia.* 2016;32:285-91. doi: 10.1016/j.egja.2015.11.009.
  - 8 Oriby ME. Comparison of Intranasal Dexmedetomidine and Oral Ketamine Versus Intranasal Midazolam Premedication for Children Undergoing Dental Rehabilitation. *Anesth Pain Med.* 2019;9:e85227. doi: 10.5812/aapm.85227. PubMed PMID: 30881910; PubMed Central PMCID: PMCPMC6412317.
  - 9 Bd V, Goyal S, Sharma A, Kothari N, Kaloria N, Sethi P, et al. Comparison of intranasal dexmedetomidine-midazolam, dexmedetomidine-ketamine, and midazolam-ketamine for premedication in paediatric patients: a double-blinded randomized trial. *Anaesthesiol Intensive Ther.* 2023;55:103-8. doi: 10.5114/ait.2023.129276. PubMed PMID: 37409840; PubMed Central PMCID: PMCPMC10415598.
  - 10 Doyle DJ, Hendrix JM, Garmon EH. American Society of Anesthesiologists Classification. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Joseph Maxwell Hendrix declares no relevant financial relationships with ineligible companies. Disclosure: Emily Garmon declares no relevant financial relationships with ineligible companies. 2023. PubMed PMID: 28722969.
  - 11 Akin A, Bayram A, Esmoğlu A, Tosun Z, Aksu R, Altuntas R, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Paediatr Anaesth.* 2012;22:871-6. doi: 10.1111/j.1460-9592.2012.03802.x. PubMed PMID: 22268591.
  - 12 Yuen VM, Hui TW, Irwin MG, Yao TJ, Chan L, Wong GL, et al. A randomised comparison of two intranasal dexmedetomidine doses for premedication in children. *Anaesthesia.* 2012;67:1210-6. doi: 10.1111/j.1365-2044.2012.07309.x. PubMed PMID: 22950484.
  - 13 Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol.* 1990;10:244-51. PubMed PMID: 2286697.
  - 14 Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Paediatr Anaesth.* 2002;12:685-9. doi: 10.1046/j.1460-9592.2002.00918.x. PubMed PMID: 12472704.
  - 15 Shamim F, Ullah H, Khan FA. Postoperative pain assessment using four behavioral scales in Pakistani children undergoing elective surgery. *Saudi J Anaesth.* 2015;9:174-8. doi: 10.4103/1658-354X.152874. PubMed PMID: 25829906; PubMed Central PMCID: PMCPMC4374223.
  - 16 Wilson GA, Doyle E. Validation of three paediatric pain scores for use by parents. *Anaesthesia.* 1996;51:1005-7. doi: 10.1111/j.1365-2044.1996.tb14991.x. PubMed PMID: 8943588.
  - 17 Hosseini Jahromi SA, Hosseini Valami SM, Adeli N, Yazdi Z. Comparison of the effects of intranasal midazolam versus different doses of intranasal ketamine on reducing preoperative pediatric anxiety: a prospective randomized clinical trial. *J Anesth.* 2012;26:878-82. doi: 10.1007/s00540-012-1422-6. PubMed PMID: 22688444.
  - 18 Tsze DS, Steele DW, Machan JT, Akhlaghi F, Linakis JG. Intranasal ketamine for procedural sedation in pediatric laceration repair: a preliminary report. *Pediatr Emerg Care.* 2012;28:767-70. doi: 10.1097/PEC.0b013e3182624935. PubMed PMID: 22858745.
  - 19 Chapter 3 - The Spectrum of Pain and Anxiety Control. In: Malamed SF, editor. *Sedation (Sixth Edition)*: Mosby; 2018. p. 14-22. doi: 10.1016/B978-0-323-40053-4.00003-2.
  - 20 Mayel M, Nejad MA, Khabaz MS, Bazrafshani MS, Mohajeri E. Intranasal midazolam sedation as an effective sedation route in pediatric patients for radiologic imaging in the emergency ward: A single-blind randomized trial. *Turk J Emerg Med.* 2020;20:168-74. doi: 10.4103/2452-2473.297461. PubMed PMID: 33089024; PubMed Central PMCID: PMCPMC7549517.
  - 21 Surendar MN, Pandey RK, Saksena AK, Kumar R, Chandra G. A comparative evaluation of intranasal dexmedetomidine, midazolam and ketamine for their sedative and analgesic properties: a triple blind randomized study. *J Clin Pediatr Dent.* 2014;38:255-61. doi: 10.17796/jcpd.38.3.l828585807482966. PubMed PMID: 25095322.
  - 22 Elshafeey AEAM, Youssef GFK, Elsalam EHA, Saleh M, Mahrose R. Comparative study between intranasal dexmedetomidine



- and intranasal ketamine as a premedication for anxiolysis and sedation before pediatric general anesthesia. *Ain-Shams Journal of Anesthesiology*. 2020;12:1-8. doi: 10.1186/s42077-020-00104-8.
- 23 Shereef KM, Chaitali B, Swapnadeep S, Gauri M. Role of nebulised dexmedetomidine, midazolam or ketamine as premedication in preschool children undergoing general anaesthesia-A prospective, double-blind, randomised study. *Indian J Anaesth*. 2022;66:S200-S6. doi: 10.4103/ija.ija\_931\_21. PubMed PMID: 35874483; PubMed Central PMCID: PMC4255070.
  - 24 Monteiro M, Cristiani F. Effect on the behaviour of dexmedetomidine as anaesthetic premedication in the paediatric population: a prospective observational study. *Rev Esp Anesthesiol Reanim (Engl Ed)*. 2021;68:179-82. doi: 10.1016/j.redar.2020.05.020. PubMed PMID: 32883525.
  - 25 Peng K, Wu SR, Ji FH, Li J. Premedication with dexmedetomidine in pediatric patients: a systematic review and meta-analysis. *Clinics (Sao Paulo)*. 2014;69:777-86. doi: 10.6061/clinics/2014(11)12. PubMed PMID: 25518037; PubMed Central PMCID: PMC4255070.
  - 26 Narendra PL, Naphade RW, Nallamilli S, Mohd S. A comparison of intranasal ketamine and intranasal midazolam for pediatric premedication. *Anesth Essays Res*. 2015;9:213-8. doi: 10.4103/0259-1162.154051. PubMed PMID: 26417129; PubMed Central PMCID: PMC4563959.