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Research Paper

Oral Ketamine or Nasal Midazolam for Sedation in Pediatric Upper Gastrointestinal Endoscopy

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ABSTRACT

Background: There is no agreement on the route of administration and the drug of choice for providing adequate sedation for pediatric invasive procedures.

Objectives: We compared the utility, safety, and sedation effects of intranasal midazolam and oral ketamine.

Materials & Methods: This double-blind clinical trial was performed on 100 children aged 2 to 14 years who were candidates for upper gastrointestinal (GI) endoscopy. Patients were randomly assigned to two groups: ketamine (4 mg/kg orally) and midazolam (0.1 mg/kg intranasal). Sedation score, fear levels, children's behavior at the time of separation from parents, and vital signs were recorded.

Results: Higher systolic blood pressure was seen in children who received ketamine (P=0.012) and lower arterial oxygen saturation in the midazolam group (P=0.023). Also, the level of sedation showed no significant difference between the groups.

Conclusion: Based on the results, administering oral ketamine or intranasal midazolam before endoscopy induced a similar sedation score in children. Also, both methods could be safe and non-invasive modalities for sedation.

Keywords: Ketamine, Midazolam, Conscious sedation, Endoscopy, Gastrointestinal

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Highlights

- Both oral ketamine and nasal midazolam are non-invasive anesthetic methods for children.
- There was a slight decrease in arterial O_2 saturation in the midazolam group and higher systolic blood pressure in the ketamine group.
- No significant differences were observed regarding sedation score, recovery time, cooperation during separation from parents, and fear level.
- Both methods can be used safely during upper gastrointestinal endoscopy in children.

Introduction

Young children may not understand the necessity of invasive procedures due to a lack of mental maturity. Also, the natural fear of injection and separation from parents can exacerbate this situation [1-4]. Different levels of sedation can be applied to children before invasive procedures. The European Society for pediatric gastroenterology, hepatology, and nutrition (ESPGHAN) recommends general anesthesia (GA) or deep sedation for pediatric gastrointestinal (GI) endoscopy [1]. However, some medical centers may not have access to anesthesiologists, and some parents may not have consent due to the possible complications and the long period until discharge.

On the other hand, there are a limited number of safe sedative medications for children [5-8]. The selective drugs should have a rapid onset, provide adequate sedation, have few side effects, and not threaten respiration and hemodynamics [9-10]. Midazolam is a sedative, hypnotic, amnestic, anxiolytic, and anticonvulsant agent [9, 11, 12]. It is a safe medication for short procedures in the pediatric group due to its 6–15 min distribution half-life and an elimination half-life of 1.5–2 h [10]. It can be administered through several routes, including oral, intravenous, muscular, buccal, nasal, and rectal [3, 13]. Blister taste and nasal irritation are the most common side effects of intranasal midazolam [13, 14]. Its use may be limited because of side effects, including mild respiratory depression leading to apnea [10]. Moreover, oral ketamine is a safe rapid-onset drug with sedative, analgesic, and amnestic effects [9, 15-17]. It is recommended to use ketamine cautiously due to its side effects, such as delirium, aspiration, excitation, stridor, laryngospasm, and post-sedation agitation [2, 17, 18].

To the best of our knowledge, the efficacy and safety of oral ketamine and nasal midazolam have not been compared through the time of pediatric upper GI endoscopy. Both drugs are prescribed without any invasive injections and without inducing additional anxiety. Because of no agreement on the route and drug of choice to provide adequate and safe sedation in pediatric invasive procedures, we conducted a study to compare the utility, safety, and sedation effects of intranasal midazolam and oral ketamine during upper gastrointestinal endoscopy in children.

Materials and Methods

This randomized double-blinded clinical trial was performed on 100 children who were candidates for upper gastrointestinal endoscopy and whose parents did not consent to GA. They were referred to 17-Shahrivar Hospital, Rasht city, Iran, from January 2014 to January 2015.

The exclusion criteria were as follows: a history of allergy to benzodiazepines and ketamine and the appearance of endoscopy-related complications such as gastrointestinal bleeding or excessive procedure prolongation. After obtaining written informed consent, the eligible children were randomly assigned to two groups, including those who received oral ketamine (+placebo) and intranasal midazolam (+placebo). The patients were fasting for solid or non-clear liquids for 8 hours preoperatively. In the first group, 4 mg/kg oral ketamine (Rotex Medica Company, Germany) in combination with 0.5 mL/kg USP suspension (the United States of pharmacopoeia) was prescribed. Also, normal saline was dropped into the nasal cavity as the placebo. In another group, midazolam (0.1 mg/kg, intranasal) (Daroopakhsh Company, made in Iran) was administered in each nostril and slowly divided equally, drop by drop. Cooperated children over 2 years old were asked to stick out their tongues to abstain from swallowing the drug inside the nose until complete drug absorption, and the USP suspension was also prescribed

as the placebo. The USP suspension was provided as a mixture of sucrose and water at 85%. Prescribing these drugs was done in parents' arms to minimize patients' stress 30 minutes before endoscopy.

Although the onset time of the sedation effect of intranasal midazolam is 10-15 min, and the duration of its effect is 60 minutes, oral ketamine effects appear between 20-30 min after prescription. Endoscopy was performed 30 min after drug and placebo administration for each patient. The fact that the onset of oral ketamine sedative effect is later than intranasal midazolam justifies the time of endoscopy in our study. For this purpose, if the patient is receiving ketamine, the onset of its sedative effect has occurred. The sedative effects of intranasal midazolam continue for up to 60 min, so half an hour after the administration was the logical time for endoscopy.

In this double-blind study, the endoscopist or the person who recorded the data and the parents or patients were unaware of the medications prescribed. A single experienced nurse, unaware of the groups assigned, administered both nasal and oral solutions. Only one nurse in the endoscopy ward was involved in the grouping and type of prescription drugs in patients.

Variables including sex, age, height, sedation score, fear levels, cooperation and behavior of children at the time of separation from parents, arterial oxygen saturation by digital pulse oximetry, and vital signs were recorded before, during, and after the procedure. A child's blood pressure status is evaluated based on age and sex, and the standard height percentile [19]. Furthermore, the time to being completely conscious after the procedure and complications, including nausea and vomiting, seizure, laryngospasm, stridor, and unconsciousness (confusion, delirium, etc.), were recorded. The severity of impatience at the time of separation from parents was scored as follows: 1 (no fear, good cooperation, or asleep), 2 (slight fear or cry, relaxed by ensuring), 3 (moderate fear or crying, no relaxed by ensuring), or 4 (crying needed to another person to keep the child). The fear scale was also labeled as none, mild, moderate, or severe. Ramsay scale [20] was used to assess sedation level as 1 (patient awake and anxious, agitated, or restless), 2 (patient awake and cooperative, oriented and tranquil, 3 (patient asleep, responsive to commands), 4 (patient asleep, with brisk response to stimuli (light and noise), 5 (patient asleep, with response only to pain), or 6 (patient with no response to any stimuli [light, noise, or pain]). The recovery time and recall of unpleasant experiences in >6 years old children, 1 hour after the procedure, were recorded and compared (1: recall in detail, 2: relative recall, 3: amnesia). Due to the possibility of midazolam-induced respiratory depression or postoperative seizure due to ketamine, we prepared flumazenil and diazepam vials before the procedure.

Nasal oxygenation was also considered when oxygen desaturation occurred. In cases of severe vomiting, ondansetron was prescribed. Also, labetalol was available for probable hypertension crises. In those with hypotension, normal saline was administered. Resuscitation equipment was ready as routine.

For statistical analysis, the results were presented as Mean±SD for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using the Chi-square or Fisher exact test. Quantitative variables were also compared with the t-test, analyses of variance (ANOVA), the Mann-Whitney U test, or the Kruskal Wallis test. The change in study parameters after the procedure was examined using the paired t-test or Wilcoxon test. The SPSS software, version 22.0 for windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. $P<0.05$ were considered statistically significant.

Results

In this study, 103 children were assessed for eligibility, and after excluding 3 children, 100 patients in the two groups of ketamine and midazolam were compared (Figure 1). Most patients in both groups were girls, indicating 26(52%) in the ketamine and 28(56%) in the midazolam group. There was no significant difference regarding the demographic characteristics such as sex (P=0.841) and mean age between the two groups receiving ketamine or midazolam (7.52±2.69 years vs 7.54±3.12 years, respectively, P=0.880). Comparing hemodynamic parameters before, during, and after the procedure, data showed statistically significant lower arterial oxygen saturation during (98.14±2.41% vs 96.65±4.05%, respectively, P=0.023) and after the procedure (98.02±2.98% vs 96.86±3.48%, respectively, P=0.01) in children who received intranasal midazolam, rather than who received oral ketamine. Also, higher systolic blood pressure (based on child age and height percentile) was seen in children medicated with ketamine (111.53±12.38, 101.86±12.53, P=0.012) (Table 1). It is worth noting that blood pressure in ketamine recipients never exceeded stage 1 of hypertension.

Table 1. Comparing the hemodynamic status between ketamine and midazolam groups

Parameters	Time of Assessment	Mean±SD		P
		Ketamine	Midazolam	
SBP (Systolic blood pressure)	Before endoscopy	109.80±15.41	101.76±12.44	0.055
	After endoscopy	111.53±12.38	101.76±12.53	0.012
DBP (Diastolic blood pressure)	Before endoscopy	67.76±13.92	60.59±11.52	0.088
	After endoscopy	65.71±11.90	61.76±12.76	0.085
PR (Pulse rate)	Before endoscopy	115.39±18.92	116.98±22.79	0.705
	Within endoscopy	135.90±19.35	141.20±28.28	0.279
	After endoscopy	105.59±11.04	107.39±17.10	0.313
O_2 saturation	Before endoscopy	99.55±1.96	98.90±1.63	0.063
	Within endoscopy	98.14±2.41	96.65±4.05	0.023
	After endoscopy	98.02±2.98	96.86±3.48	0.019

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Table 2. Impatience, fear, and level of sedation in ketamine and midazolam groups

Parameters	Items	No. (%)		P
		Ketamine	Midazolam	
Impatience at the time of separation from parents	Excellent	38 75)	42(84)	0.262
	Good	11(22)	5(10)	
	Partially good	1(2)	2(4)	
	Poor	0(0)	1(2)	
Fear	Without fear	37(74)	41(82)	0.413
	Mild fear	8(16)	4(8)	
	Moderate fear	5(10)	4(8)	
	Severe fear	0(0)	1(2)	
Ramsay score	Awake and anxious	10(20)	12(24)	0.490
	Awake and cooperative	16(32)	21(42)	
	Asleep, responsive	24(48)	17(34)	
	Asleep, with brisk response to stimuli	0(0)	0(0)	
	Asleep, with a response only to pain	0(0)	0(0)	
	No response to any stimuli	0(0)	0(0)	

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Table 3. Comparing the cooperation at the time of separation from parents based on age groups between two groups

Age	Variables	Score	No. (%)				P	
			Ketamine		Midazolam		Intra-group	Inter-group
2-5 (y)	Cooperation score	Excellent	11	68.8	11	68.8	0.696	
		Good	4	25.0	2	12.5		
		Fair	1	6.2	2	12.5		
		Poor	0	0.0	1	6.2		
		Total	16	100	16	100		
6-9 (y)	Cooperation score	Excellent	18	81.8	18	88.2	0.679	0.262
		Good	4	18.2	3	11.8		
		Total	22	100	21	100		
0-14 (y)	Cooperation score	Excellent	9	75.0	13	100	0.156	
		Good	3	25.0	0	0.0		
		Total	12	100	13	100		

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Table 4. Comparing the sedation score based on age groups between two groups

Age Group	Variables	Sedation Score	No. (%)		P	
			Ketamine	Midazolam	Intra-group	Inter-group
2-5 (y)	Sedation level	Awake and anxious	7(43.8)	6(37.5)	0.169	
		Awake and cooperative	3(18.8)	8(50)		
		Asleep, responsive	6(37.5)	2(12.5)		
		Total	16(100.0)	16(100.0)		
6-9 (y)		Awake and anxious	3(13.6)	5(23.8)	0.614	0.445
		Awake and cooperative	9(40.9)	8(38.1)		
		Asleep, responsive	10(45.5)	8(38.1)		
		Total	22(100)	21(100)		
10-14 (y)		Awake and anxious	0(0.0)	1(7.7)	0.447	
		Awake and cooperative	4(33.3)	5(38.5)		
		Asleep, responsive	8(66.7)	7(53.8)		
		Total	12(100.0)	13(100.0)		

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Table 5. Side effects in ketamine and midazolam groups

Figures	No. (%)		P
	Ketamine	Midazolam	
Nausea	4(8)	2(4)	0.687
Vomiting	3(6)	2(4)	0.999
Seizure	0(0)	0(0)	-
Apnea	0(0)	0(0)	-
Laryngospasm	0(0)	0(0)	-
Hypertension	7(14)	0(0)	0.012
Dizziness	8(16)	0(0)	0.006
Diplopia	2(4)	0(0)	0.425
Nystagmus	3(6)	0(0)	0.117
Tipsiness	1(2)	0(0)	0.999
Loosened extremities	6(12)	0(0)	0.027
Blurred vision	1(2)	0(0)	0.999
Headache	1(2)	0(0)	0.999

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As Table 2 shows, 75% and 84% of children who received ketamine and midazolam had respectively excellent cooperation during the procedure, and no significant difference was noted (P=0.262). The lack of fear was observed in 74% and 82% of patients in the two groups, respectively (P=0.413). Comparing the level of sedation according to the Ramsay score showed no significant difference in children who received ketamine vs midazolam (P=0.490).

There was no significant relationship between the groups regarding cooperation at the time of separation from parents and age (P=0.262). However, the highest level of cooperation was seen in children aged 10 to 14 years compared to younger children (respectively, 88.0% vs 68.8%, P<0.0001) (Table 3).

As shown in Table 4, comparing the sedation score between the groups showed no inter-group difference between the three age subgroups (P=0.445). The sedation score was significantly better in the group aged 10 to 14 years compared with the lower ages (P=0.010). The sedation score status was not different in the two groups regarding sex (P=0.490).

Side effects, including hypertension, dizziness, and loosening of extremities, were shown only in the ketamine group but not in the midazolam group (P=0.012, P=0.006, and P=0.027, respectively). Some complications, including nausea, nystagmus, mild vomiting, diplopia, blurred vision, and headache, were more common in the ketamine group than in the midazolam group, with no statistically significant difference (Table 5). Laryngospasm, apnea, and seizure did not occur in any group.

In this study, drug-induced hypertension was mild and resolved without any treatment after the procedure. Decreased O_2 saturation was quickly corrected with nasal oxygenation. Sublingual ondansetron was administered in cases of persistent nausea/vomiting that continued after the procedure. There were no cases of drug-induced hypotension that required the administration of normal saline.

On the other hand, 44.1% of children aged >6 years receiving ketamine remembered the procedure in detail, while remembering the procedure was revealed in 58.8% of those who received midazolam without any difference (P=0.114). There was no significant difference in terms of the mean length of recovery time between the two groups (P=0.474), but in a few patients in the ketamine group, recovery time was prolonged up to 90 minutes.

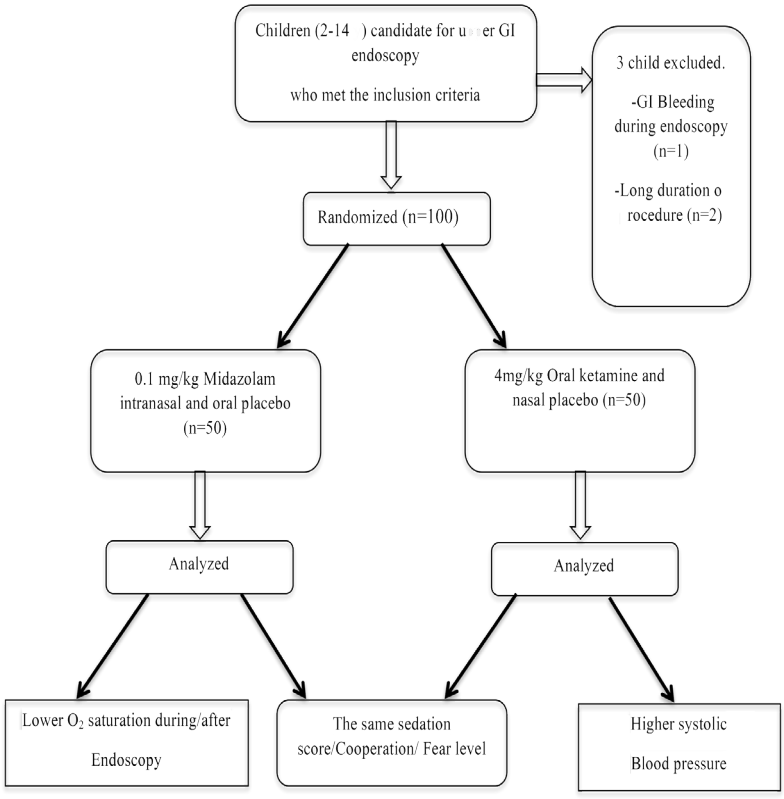

Figure 1. Patient selection and treatment process

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Discussion

In the current study, we compared the safety and effectiveness of the two sedative drugs: oral ketamine and nasal midazolam. Regarding efficacy and hemodynamic stability, a slight decrease in arterial oxygen saturation was revealed in the midazolam group but not in the ketamine group.

Midazolam is one of the most commonly used agent in children with hypnotic, sedative, amnesic, anticonvulsant, and anxiolytic effects before diagnostic procedures, despite concerns about respiratory depression [22, 23]. Consistent with the present study, Lane et al. found no severe respiratory depression by intranasal midazolam [24]. Also, Miqdady et al. found a mild decrease in oxygen saturation in children who received midazolam [25].

We did not find any significant decrease in O_2 saturation in children who received ketamine. As noted, ketamine can maintain airway reflexes during sedation, which may induce minimal side effects on the respiratory system [26]. Although it can also be accompanied by an increased risk of laryngospasm [2, 27-29], this complication did not occur during the current study.

Ketamine is a dissociative agent with a rapid onset of action that induces profound sedation, analgesia, and amnesia, with a short duration of action (15-30 min) which is adequate for routine diagnostic endoscopy, allowing fast recovery [26]. It induces functional dissociation between the limbic and the cortical systems. Impaired sensory recognition of painful stimuli impacts this cataleptic state, resulting in memory-inducing, a condition known as “dissociative anesthesia” [27]. In the present study, no significant difference was seen in remembering the detail of the procedure between the two groups, despite the expected difference between groups in terms of recalling the procedure. Viana et al. assessed the occurrence of amnesia after a dental procedure which was slightly higher in the oral midazolam group than in intranasal midazolam and a combination of oral ketamine / midazolam [30].

Overall, no significant difference was found in other parameters, including the severity of impatience at the time of separation from parents, sedation score, level of fear, and the presence of restlessness and agitation during the procedure between the two groups. Consistent with our study, Khoshrang et al. revealed no significant difference between the sedation score of children who

received intranasal Midazolam vs intranasal Ketamine [3]. Akçay et al. showed better sedation scores in children who received the combination of intra-nasal ketamine and midazolam than in children who received these drugs alone [31]. Rubinstein et al. found that the level of sedation during the procedure in children treated with ketamine was not significantly different from those treated with midazolam which was consistent with the current study. However, failure to achieve adequate sedation was more common in the ketamine group [15]. Recovery time in the previous research was longer in the intranasal ketamine group than in children who received intranasal midazolam, contrary to our study [3]. However, the method of ketamine administration was different in the two studies.

Regarding complications, our results showed that dizziness, nystagmus, diplopia, and loosening extremities were more common in children who received ketamine, consistent with some other studies [17, 26]. However, the difference in the results is justifiable, according to the different doses and administration methods.

Conclusion

Either oral ketamine or intranasal midazolam before endoscopy is a safe and non-invasive method that induces sedation, and regardless of the slight differences in blood pressure and oxygen saturation, they had no superiority to each other in terms of sedation score, fear, or impatience at the time of separation from parents. In conclusion, ketamine might be preferred to midazolam regarding respiratory and O_2 saturation stability, while midazolam can be preferred concerning drug side effects and maintaining blood pressure.

Ethical Considerations

Compliance with ethical guidelines

All study procedures followed the ethical guidelines of the Declaration of Helsinki 2013. The study protocol was approved by the Ethics Committee of the Vice-Chancellor of Research at Guilan University of Medical Sciences (Code: 1930309905, Date: 2014/9/6) and registered at IRCT (CODE: IRCT 2014111419936N1) (Date: 2014/12/12).

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Authors contributions

Conceptualization and investigation: Shohreh Maleknejad, Seyyedeh Azade Hoseini Nouri, Afshin Safaei-Asl, and Farnoush Farrzi; Methodology: Abtin Heidarzadeh and Afagh Hasanzadeh Rad; Data analysis: Abtin Heidarzadeh; Original draft: Shohreh Maleknejad and Seyyedeh Azade Hoseini Nouri; Writing, review, and editing: Seyyedeh Azade Hoseini Nouri, Afagh Hasanzadeh Rad, Shohreh Maleknejad, and Afshin Safaei; Supervision: Shohreh Maleknejad.

Conflict of interest

The authors declared no competing interests.

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