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Original Article

Comparing the Sedative Effect of Oral Midazolam versus Oral Ketamine on Children Aged 1-7 Years in Need of Radiologic Procedures

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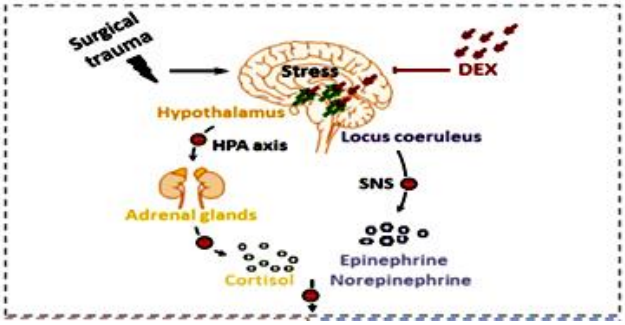
ABSTRACT

Sedation is one of the most important criteria for eliciting the cooperation of young patients. The purpose of this study was to compare the sedative effect of oral administration of ketamine and midazolam in children admitted to an emergency department in Zahedan. In this double-blind clinical trial, children were placed in grades one and two according to the ASA status classification system. Then, they were randomized into two groups of 50 individuals each. One group received 0.5mg/kg midazolam and the other received 5 mg/kg ketamine. The medication was administered orally in both groups. The scores of children's sedation and separation from their parents were recorded, and the obtained data were analyzed in SPSS using Chi-square test and independent t-test. The mean heart rate of patients before the intervention in the two groups had a slight difference, which was not statistically significant (P = 0.159). But after the intervention, this mean was significantly different in the two groups (P = 0.018). The mean scores of sedations and separation from the parent were not significantly different at 10, 20, and 30 minutes after medication in the two groups before and after the intervention. The mean length of hospitalization after sedation in the two groups differed significantly (p = 0.007) in the ketamine group (28.62 minutes) and the midazolam group (34.04 minutes). In the ketamine group, the mean heart rate decreased less after the intervention and the length of hospital stay was shorter compared with the midazolam group. Also, the percentage of children who showed earlier onset of sedation (20 minutes after taking the drug) was higher [in the ketamine group]. Therefore, ketamine seems more desirable for treatment and radiographic procedures in the emergency department.

GRAPHICAL ABSTRACT



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Introduction

Performing diagnostic and therapeutic measures is associated with many problems and lack of cooperation in children [1]. Accordingly, one may refer to children's pain, anxiety, and lack of understanding the need for diagnostic procedures, which in itself cause fear and avoidance of necessary diagnostic and therapeutic procedures [2]. Other reasons for this lack of cooperation include fear of the hospital environment, confrontation with unfamiliar nurses, exposure to diagnostic devices, and separation from parents [3]. Clinicians have always been seeking appropriate sedation methods with the most effectiveness and the least complications for children [٤] (Figure 1).

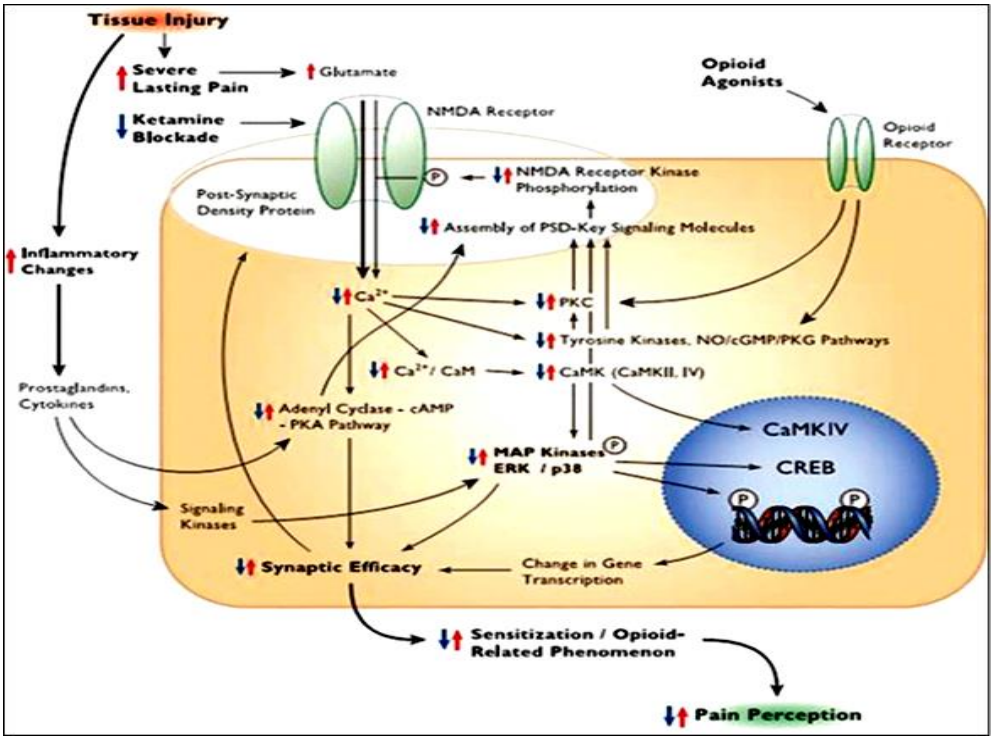

Figure 1: Effect of a combination of oral midazolam and low-dose ketamine on anxiety, pain, swelling [٥]

The purpose of these methods is to calm children without reducing their consciousness so that they can respond to verbal and physical stimuli and their respiratory function remains intact. Therefore, determining the sedative drug, appropriate dose, and method of administration should be such that the child at once is calmed and suffers the least amount of side effects [6-8]. Among the recommended drugs, midazolam and ketamine are most often used to sedate children [9]. Midazolam is a short-acting, water-soluble benzodiazepine that has mild side effects, i.e. nausea, vomiting, agitation, and brings about short-term forgetfulness and pain relief; it helps control movements and dispel anxiety; it also has a rapid onset of action, a short duration of sedation, as well as muscle relaxant and anticonvulsant effects [10-12] (Figure 2).

Figure 2: Prehospital ketamine administration dosing

Midazolam is most commonly administered orally [13-16]. Used orally, intravenously, and intramuscularly to sedate children, ketamine is a phencyclidine derivative with sedative and analgesic properties and with side effects such as hallucination, delirium, feeling of separation, nausea, and vomiting [17]. According to some studies, oral administration of both midazolam and ketamine induces sedation in children within 20 minutes and has similar clinical effects [18]. In

the study by Heshmati *et al*. (2009), different doses of ketamine were compared and in the group that received ketamine, the children were easily separated from their parents and the anesthesia process was ideal with no specific complications such as respiratory depression, tachycardia, or hypoxia. Another study showed that sedation induced by taking ketamine orally in children receiving radiation therapy even with more radiation therapy had a similar therapeutic effect compared with sedation in children who received ketamine intramuscularly and received less radiation therapy; furthermore, oral administration of this drug was associated with a longer sedation than the case caused by intramuscular injection [19-21].

In the study by Alderson *et al*. (1994), 40 children aged 1-6 years were divided into two groups for dental procedures; one group received 0.5 mg/kg midazolam and the other received 5 mg/kg ketamine. It was found that 10% of children in the midazolam group and 20% in the ketamine group cried when they were separated from their parents. The discharge time in the midazolam group was 20 minutes earlier than in the other group [22]. Funk *et al*. (2000) observed that children's anxiety and [fear of] separation decreased by 70% and 51% in the group receiving oral midazolam and ketamine [respectively], but dizziness and nausea were higher in the oral ketamine group [23]. In a double-blind study by Younge *et al*. (2001), 59 children aged 1-7 years who needed wound healing with local anesthetic injections and had an anxiety score above 1 were divided into two groups, in which one group received ketamine at a dose of 10 mg/kg and the second group received midazolam at a dose of 0.7 mg/kg. Resistance to local anesthetic injection and the onset time of achieving a sedation score less than 4 were [respectively] lower and faster in the ketamine group (Figure 3) [24-26].

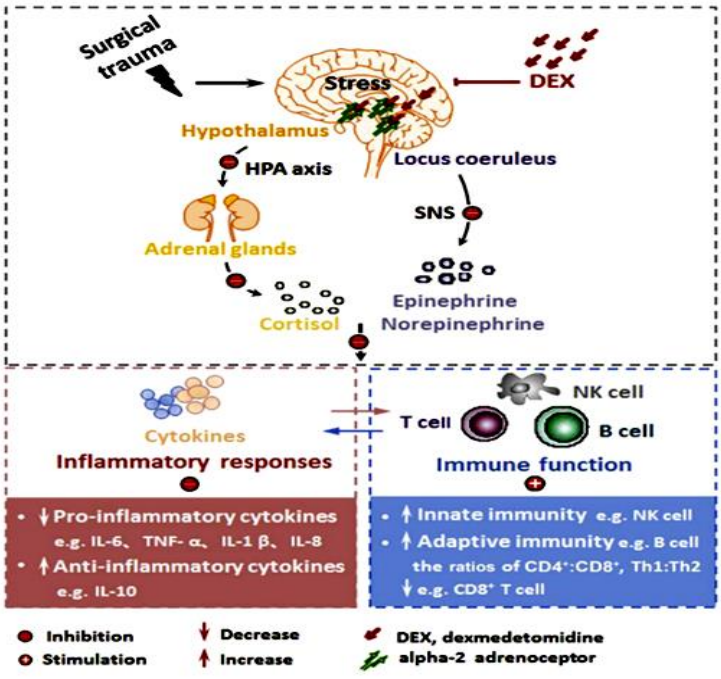

Figure 3: What's New for Pediatrics? A Narrative Review

Besides, agitation and vomiting were associated with midazolam and ketamine, respectively [27-29]. In the study by Damel *et al*. (2008), 20 children aged 2-6 years were divided into two groups; one group was given 0.5 mg/kg oral midazolam and the other group was given 5 mg/kg oral ketamine. Heart rate, respiratory rate, and oxygen saturation were recorded in the normal range. Both groups were under good sedation at 30 minutes, yet the midazolam group experienced a higher reduction in anxiety and better answered the questions than did the ketamine group [30-33]. The present research was conducted due to the fact that different studies have reported varying results and since there is a shortage of studies in Iran to compare the effectiveness of oral administration of midazolam and ketamine and their side effects in

children who need radiologic diagnostic procedures, and finally considering that intravenous sedation is usually applied for small radiologic procedures. The purpose of this study was to determine and compare the sedative effect of oral midazolam and ketamine in children aged 1-7 years who required radiologic procedures and had been admitted to the emergency department. To this end, we explored the relationship between separation from parent, length of hospital stays, time required for the onset of sedation, and the degree of sedation in children orally receiving midazolam or ketamine.

Material and Methods

Study design and setting

The study protocol was approved by the Ethics Committee of Zahedan University of Medical Sciences (ethical code: IR.ZAUMS.REC.1397.109). This is a double-blind, randomized clinical trial. The study population was selected among children aged 1-7 years with a status classification system (ASA) grade of one or two who needed a diagnostic imaging procedure at the emergency department of Khatam al-Anbia Hospital in Zahedan (2018-2019). Based on similar studies [4,9], 50 people in each group were randomly selected using a permutation test. However, this number was increased to 55 people in order to improve the accuracy of the results and to consider the possibility of sample attrition. The eligibility criteria included children aged 1-7 years who needed a diagnostic imaging procedure. On the other hand, the exclusion criteria were children with comorbidities such as seizure, cardiovascular and respiratory diseases, and active respiratory infection, diseases of the nervous system such as autism and ADHD, history of drug allergy to sedatives, children receiving other sedatives, the use of antibiotics such as erythromycin which could impair metabolism, needing more than 60 minutes for the imaging procedure, and parents' unwillingness

Procedure

Data were collected based on a questionnaire, examination, and the results of [medical] devices. First, the purpose of the study and its conditions were explained to the parents. The written consent was then obtained from those who agreed to cooperate and their children both met the inclusion criteria and were in grades one or two according to the ASA status classification system (Table 1).

Table 1: The written consent was then obtained from those who agreed to cooperate and their children both met the inclusion criteria and were in grades one or two according to the ASA status classification system

ASA1	No organic, physiological, biochemical, or psychological disorders
ASA2	Moderate to mild systemic disorders such as controlled diabetes and seizure
ASA3	Severe systemic disorders such as uncontrolled diabetes and seizures and other underlying diseases
ASA4	Life-threatening systemic disorders
ASA5	Low chance of survival

Next, the children were randomly divided into two groups of 50 each. The oral form of the two drugs was not available but it was possible to orally administer their intravenous form. In one group, children received 0.5 mg/kg oral midazolam (using midazolam 5 mg/ml ampoule), and the second group were administered 5 mg/kg oral ketamine (using 50 mg/10 ml ampoule). Additionally, both groups were given 20 cc of cherry juice (by the glass) to improve the taste of the medicine [34-36]. Prior to administering the two drugs, the necessary equipment (suction, oxygen mask, oxygen, oral airway, intubation devices (endotracheal intubation)) and antagonist drugs were prepared. Afterward, heart rate, respiratory rate, oxygen saturation level (O2sat), blood pressure, weight, and the level of consciousness of all patients were recorded by the emergency medicine assistant [37]. Then, sedation was prescribed, and a questionnaire was given to the pharmacy staff, who were given the necessary training to alternately deliver one of the two drugs (A = midazolam; B = ketamine) according to patient's

weight. Without informing the emergency medicine assistant, they poured the drug into the juice and delivered it to the patient.

Then, they recorded the A or B code on the questionnaire and gave it to the emergency medicine assistant to complete. Parents were advised not to give any other food to their child during the process, and the patients were monitored in the children's room. After the drug was administered, 10, 20, and 30 minutes later, the level of sedation in each group was measured using a 5-point scale (Table 1); thus, a score of 3 suggested "comfortable", 4 suggested "drowsy", and 5 suggested "asleep". The score of separation of children from parents (Table 2) was measured based on a 4-point scale, so scores 1 and 2 suggested an acceptable level. After showing a satisfactory level of drowsiness, the children were separated from their parents and sent to their related unit for imaging operations [38]. After the imaging procedure, they were returned to the emergency department and the duration of the imaging procedure and the child's condition (in terms of the level of consciousness and other factors) were re-examined. Finally, we analyzed patients' information which was recorded in the questionnaire.

Table 2: Children's sedation score

Sedation	Score
1	Agitated - The patient cries or turns to his/her parents
2	Conscious - The patient is alert but does not turn to his/her parents, may complain but does not cry
3	Comfortable - The patient sits or leans comfortably and opens his/her eyes spontaneously
4	Drowsy - The patient sits or leans comfortably with closed eyes and responds to stimuli
5	Asleep - The patient's eyes are closed but he/she cannot respond to stimuli

American Society of Anesthesiologists (ASA) classification system for patients requiring sedation for therapeutic and diagnostic procedures (procedural sedation).

Table 3: Children's score of separation from parents

1	**Separates happily**
2	Separates without crying
3	Separates while crying
4	Separates by force

Statistical analysis

Data were analyzed in SPSS-22 using chi-squared test and independent t-test. Mean and standard deviation were used for quantitative data and frequency and percentage were used for qualitative data. Values less than 0.05 were considered statistically significant.

Results and Discussion

This study was performed on 100 children in need of radiologic procedures admitted to the emergency department of Khatam al-Anbia Hospital in Zahedan (2018-2019). Two patients in the ketamine group and three others in the midazolam group declined to take the drug or did not take it completely and were, consequently, excluded from the study. Therefore, a total of 48 patients in the ketamine group and 47 patients in the midazolam group were finally assessed. The results of Table 4 reveal that the mean age of patients was 3.99 years with a standard deviation of 0.71, and the mean weight of patients was 14.07 [kg] with a standard deviation of 4.01. The minimum age of patients was 1 year and their maximum age was 7 years. Also, the weight of patients ranged between 6 and 28 [kg].

Table 4: Descriptive indicators for patients' age

Variable	Mean	SD	Median	Minimum	Maximum
Age	3.99	1.71	4	1	7
Weight	14.07	4.01	14	6	28

Table 5 clarified that the percentage and frequency of both genders were almost equal.

Table 5: Frequency distribution and percentage of patients' gender

Gender	Number	Percentage
Female	50	52.6
Male	45	47.4
Total	95	100

According to Table 6, the mean length of patients' hospital stay was 31.33 [minutes] with a standard deviation of 9.86. Also, the minimum and maximum length of hospital stay was 10 and 60 minutes.

Table 6: Descriptive indicators for the length of patients' hospital stay when sedation was over (minutes)

Variable	Mean	SD	Median	Minimum	Maximum
Age	31.33	9.86	30	10	60

Table 7 shows that patients' heart rate, respiratory rate, and arterial blood oxygen decreased after the intervention [39].

Table 7: Descriptive indicators of patient's heart rate, respiratory rate, and arterial blood oxygen before and after the intervention

Variable	Indicator	Mean	SD	Median	Minimum	Maximum
Heart rate	Before intervention	111.6	11.68	112.5	86	134
	After intervention	107.81	11.17	110	75	138
Respiratory rate	Before intervention	17.61	6.53	15	12	27
	After intervention	14.98	4.06	13	10	26
Arterial oxygen saturation	Before intervention	97.85	2.28	98.5	90	100
	After intervention	96.89	2.14	98	90	100

Table 8: Frequency distribution of patients' scores of sedations and separation after receiving the injections

Variable		Indicator	Frequency	Percentage
Sedation score	Agitated	10 minutes after injection	44	44.3
		20 minutes after injection	10	10.5
		30 minutes after injection	8	8.4
	Consciousness	10 minutes after injection	32	33.7
		20 minutes after injection	20	21.1
		30 minutes after injection	2	2.1
	Comfortable	10 minutes after injection	19	20
		20 minutes after injection	34	35.8
		30 minutes after injection	15	15.8
	Drowsy	10 minutes after injection	0	0
		20 minutes after injection	30	31.6
		30 minutes after injection	39	41.1
	Asleep	10 minutes after injection	0	0
		20 minutes after injection	1	1.1
		30 minutes after injection	31	32.6
Separation score	Separates happily	10 minutes after injection	6	6.3
		20 minutes after injection	15	15.8
		30 minutes after injection	32	33.7
	Separates without crying	10 minutes after injection	16	16.8
		20 minutes after injection	42	44.2
		30 minutes after injection	47	49.5
	Separates while crying	10 minutes after injection	32	33.7
		20 minutes after injection	35	36.8
		30 minutes after injection	12	12.6
	Separates by force	10 minutes after injection	41	43.2
		20 minutes after injection	3	3.2
		30 minutes after injection	4	4.2

Table 9: Frequency distribution of patients' age and weight in the two groups

Variable	Indicator	Mean	SD	Frequency	Significance level
Age* Group	Ketamine	3.84	1.72	48	0.33
	Midazolam	4.15	1.7		
Age* Group	Ketamine	13.54	3.69	48	0.21
	Midazolam	14.4	4.46		
Length of hospitalization * Group	Ketamine	28.62	7.35	48	0.007
	Midazolam	34.04	11.3		

The results of independent t-test showed that the mean age and weight in the two groups were slightly but not significantly different; however, the two groups differed significantly in terms of the mean length of hospitalization.

Table 10: Frequency distribution of heart rate, respiratory rate, and arterial blood oxygen in the two groups before and after the intervention

Variable		Mean		SD		Number	Significance level	
		Before intervention	After intervention	Before intervention	After intervention		Before intervention	After intervention
Heart rate* Group	Ketamine	113.3	110.46	11.72	9.61	48	0.159	0.018
	Midazolam	110	105.13	11.44	11.87			
Respiratory rate* Group	Ketamine	15.83	14.52	3.4	3.24	48	0.099	0.25
	Midazolam	19.38	15.47	14.3	4.63			
Arterial blood oxygen*Group	Ketamine	97.79	97.06	2.76	2.39	48	0.793	0.47
	Midazolam	97.91	96.74	1.66	1.83			

The results of independent t-test confirmed that the mean heart rate in the two groups was significantly different, yet the mean respiratory rate and the mean arterial blood oxygen level were slightly but not significantly different in the two groups [40].

Table 11 indicates no statistically significant difference in the sedation score [of the two groups] 10, 20 and 30 minutes after drug administration.

Table 11: Frequency distribution of patients' sedation in the two groups

Variable		**Indicator**	**Quiet**		**Agitated**		**Total**		**Significance level**
			Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Sedation score	Ketamine	10 minutes after injection	9	18.75	39	81.25	48	100	0.75
		20 minutes after injection	35	72.91	13	27.08	48	100	0.34
		30 minutes after injection	43	89.58	5	10.41	48	100	0.97
	Midazolam	10 minutes after injection	10	21.27	37	78.72	47	100	0.75
		20 minutes after injection	30	63.82	17	36.17	47	100	0.34
		30 minutes after injection	42	89.26	5	10.63	47	100	0.97

The results of Table 12 show no statistically significant difference in the separation score of patients [in the two groups] 10, 20, and 30 minutes after drug administration.

Table 12: Frequency distribution of patients' separation [from their parents] in the two groups

Minute/Group			Separation distribution		Total	Significance level
			Score: 1 &2	Score:3,4&5		
After 10 minutes	Ketamine	Frequency	35	13	48	0.35
		Percentage	72.91	27.08	100	
	Midazolam	Frequency	38	9	47	
		Percentage	80.85	19.14	100	
After 20 minutes	Ketamine	Frequency	18	30	48	0.61
		Percentage	0.05	62.5	100	
	Midazolam	Frequency	20	27	47	
		Percentage	42.55	57.44	100	
After 30 minutes	Ketamine	Frequency	6	42	48	0.25
		Percentage	12.5	87.5	100	
	Midazolam	Frequency	10	37	47	
		Percentage	21.27	87.72	100	

Patient management techniques based on traditional behaviors such as cuddling and verbal communication have been used in the past to engage children in medical procedures, but they are not effective enough in agitated and traumatic children. Among multiple methods for drug administration, we chose oral administration because it is more easily accepted by children and their parents and, as evidence supports, it allows the drug to be absorbed quickly and at a high rate [10]. Similar to some other studies, we used cherry juice to remove the bitter taste of the drugs [10]. No placebo was used in this study, because similar studies on dental and surgical patients have reported the effectiveness of both midazolam and ketamine compared with placebo. In this study, we compared the effectiveness of these two drugs [10].

The mean age of patients in our study was 4 years. The frequency distribution of patients' age in the two groups exhibited an almost equal mean age and no statistically significant difference. We also observed a consistent frequency distribution in both genders.

The mean weight of patients was 14.07 kg with a standard deviation of 4.10. The mean weight was 13.54 kg in the ketamine group and 14.6 kg in the midazolam group, indicating no significant difference but a consistent distribution of demographic variables in the two groups and their similar population. The mean length of hospital stay after sedation was 31.33 minutes with a standard deviation of 9.86. More specifically, this mean was 28.62 minutes in the ketamine group and 34.04 minutes in the midazolam group, suggesting a significant variation (P = 0.007).

The mean heart rate of ketamine group before the intervention was 113.3 with a standard deviation of 11.72; after the intervention, it was 110.46 with a standard deviation of 9.61 (Tables 9). This mean before the intervention in the midazolam group was 110 with a standard deviation of 11.44; after the intervention, it was 105.13 with a standard deviation of 11.87. The results of independent t-test displayed no significant difference in the heart rate of patients in the two groups before the intervention. However, a statistically significant difference occurred in this regard between the two groups after the intervention (P = 0.018).

Furthermore, in line with the findings of other researchers, we noted that the mean heart rate of patients in the midazolam group decreased after the intervention, which is probably due to the better sedative effects of midazolam in relieving children's anxiety [11].

The mean respiratory rate of the ketamine group before the intervention was 15.83 with a standard deviation of 3.4, but it decreased to 14.52 with a standard deviation of 3.24 after the intervention. In the midazolam group, this mean was 19.38 with a standard deviation of 14.3 before the intervention, but it dropped to 15.47

with a standard deviation of 4.63 after the intervention. The mean respiratory rate of patients decreased in both groups after the intervention, which could be related to the sedative effect of drugs in mitigating patients' anxiety. Meanwhile, no statistically significant difference occurred between the two groups in this regard. According to Table 10, the sedation rate at 20 minutes was 72.91% in the ketamine group and 63.82% in the midazolam group, indicating a slightly but not significantly higher rate in the ketamine group. After 30 minutes, the sedation rate was 89.58% in the ketamine group and 89.36% in the midazolam group, which were not significantly different. Quick sedation is desirable in the emergency, and we noted that the onset of efficacy was at 20 minutes in the ketamine group and at 30 minutes in the midazolam group, indicating the superiority of ketamine in this regard. This is in good agreement with the findings of Young et al. and Yeganeh *et al*. [9].

According to Table 11, which shows the separation score of children from their parents, the rate of good sedation in the ketamine group was 62.5% and 87.5% at 20 and 30 minutes, respectively; in the midazolam group, it was 57.44% and 78.72% at 20 and 30 minutes, respectively. While the ketamine group had better results in this case, the difference was not statistically significant, which is in agreement with the findings of Heshmati *et al*. [15].

Limitations

The most important limitation of this study concerned the initial unwillingness of families in letting their child be given the two related drugs. Yet, they finally granted their approval after being enlightened about the effect of this medication in reducing the child's anxiety and discomfort. Other limitations of this study were the refusal of some children to take the medication and also unavailability of the oral form of the two drugs.

Conclusion

Although the statistical results did not suggest a significant difference, and both groups had the same sedation score at 30 minutes, the percentage of children who showed an earlier onset of sedation (20 minutes after taking the drug) was greater in the ketamine group. Therefore, ketamine seems more desirable for doing therapeutic and radiologic procedures in the emergency department. Additionally, compared with the midazolam group, the ketamine group had a shorter hospital stay when sedation was over. Thus, this length was 28.62 minutes in the ketamine group and 34.04 minutes in the midazolam group, demonstrating a significant difference (P = 0.007).

Also, the mean heart rate differed significantly in the two groups after the intervention. It could be concluded that ketamine is more appropriate for sedation as it is not associated with cardiac depression, which has been reported in other studies.

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Future research

It is necessary to conduct further studies with larger sample sizes to investigate administering the right sedative for traumatic children who are admitted to the emergency department. It is also rewarding to use ketamine and midazolam in non-emergency situations where there is enough time to sedate the patient or in emergency departments that are not very crowded.

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Authors' contributions

All authors have contributed significantly and met criteria for authorship. All the authors read and approved the final copy of the manuscript.

Conflict of Interest

We have no conflicts of interest to disclose.

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