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Comparison of Intramuscular Dexmedetomidine with Intramuscular Ketamine in Children undergoing CT Imaging: A Double-Blind Clinical Trial

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Abstract

Background

Computed tomography (CT) scan is one of the most frequent tests among children in which they should be completely calm and immobilized for a correct patient test. In this study, we aimed to investigate the effects of intramuscular dexmedetomidine (DEX) with intramuscular ketamine in children undergoing CT imaging.

Materials and Methods

This double-blind clinical trial study was conducted in Golestan and Imam Khomeini hospitals of Ahvaz, Iran, in 2017 and 2018. In the first and second groups, intramuscular ketamine and intramuscular DEX were injected with doses of 4 mg/kg and 3 µg/kg, respectively. The objective of the drug injection was to reach the patient at a level of sedation of 4. During the entire period of sedation, heart rate and blood pressure were measured and recorded at the start of the study as well as after 5, 10, 15, 20, 25, 35, 45, and 55 minutes.

Results

In this study, 94 children needing sedation in CT-scan were included. The mean age of the children was 3.87 ± 1.70 years old and 54.3% of them were girls. Mean time of onset of sedation in ketamine group (8.82 ± 3.86 minutes) was significantly lower compared to that of the DEX group (20.46 ± 10.9 minutes) ($p < 0.001$). In addition, the mean duration of sedation effect in ketamine group was significantly lower than that of the DEX group ($p = 0.002$). There was no significant difference in the mean discharge time in the two groups. In the ketamine group, 8 cases had side effects, however, no side effects were observed in the DEX group ($p = 0.006$).

Conclusion

Based on the results, although DEX has a slower onset of effect and a longer duration of effect compared to ketamine, due to its lower side effects, it can be an appropriate alternative to commonly used sedative medications.

Key Words: Computed Tomography, Dexmedetomidine, Pain management, Sedation, Ketamine.

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1- INTRODUCTION

Computed tomography (CT) scan is one of the most frequent tests among children in which they should be completely calm and immobilized for a correct patient test. This is not possible in pediatric patients and requires intervention and sedation (1). In recent years, various methods have been tested for sedation of children, including antihistamines and anesthetics such as ketamine, propofol, midazolam, etomidate, and chloral hydrate (2). Most children do not receive enough medication due to concerns about the sedation side effects of medications, and this issue causes them not to be sufficiently motionless, leading to unsatisfactory diagnostic evaluations (3). Ideal sedation for children in the emergency room must contain features such as the fast onset of effect, short duration of effect, lack of effect on breathing and hemodynamics, lack of need for advanced airway and intubation, low side effects, and quick and trouble free recovery (4).

Ketamine is one of the most important drugs prescribed for children's sedation, and is one of the Phencyclidine (PCP) derivatives that has been widely used for sedation since 1970 (5). Due to its deep analgesic effects and minimal respiratory depression (hypoventilation), this drug has low and predictable side effects (5, 6). Previous studies have shown that ketamine is along with complications such as restlessness, transient tachypnea, laryngospasm, nausea and vomiting, nightmares, increased intraocular pressure (IOP), and increased intracranial pressure (ICP) (6-8). Dexmedetomidine (DEX) is one of the most commonly used drugs as a substitution for common sedatives, which is an alpha 2-adrenoceptor selective agonist with high specificity (9). DEX was approved by the Food and Drug Administration (FDA) in 1999 for use as sedative, antidepressant, anesthetic, soporific, and analgesic until 24 h after surgery (10). This drug, in its use as an adjuvant in general anesthesia with a central sympatholytic effects, contributes to stabilization of the hemodynamic state of the patient and has a strong anesthetic and analgesic effect (11), which reduces the need for opioids and their subsequent complications (12), and diminishes stress response, in addition to improving the quality of recovery (13). Considering the fact that adequate studies have not been accomplished regarding the position of DEX in relieving acute pain and sedation of children in emergency, the present study aimed to evaluate the effect of intramuscular DEX in comparison with intramuscular ketamine in the sedation of children undergoing CT- scan.

2- MATERIALS AND METHODS

2-1. Study design

This double-blind clinical trial study was conducted between 2017 and 2018 to compare the level of sedation of intramuscular ketamine and intramuscular DEX among children undergoing CT- scan admitted to Golestan and Imam Khomeini hospitals affiliated to Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran.

2-2. Ethics

This study was carried out according to the Declaration of Helsinki (DoH) ethics for research on human subjects and after obtaining permission from the ethics committee of AJUMS, as well as registering the clinical trial code (IR.AJUMS.REC.1396.1143).

2-3. Inclusion and exclusion criteria

The study inclusion criteria were children aged 2 to 8 years old with Glasgow Coma Scale (GCS) = 15, who had no loss of consciousness and needed CT scan imaging, and had informed consent to participate in the study. Similarly, the

study exclusion criteria included prognosis of difficult airway, history of drug allergy, history of adverse response to the drugs used in the present study, presence of hemodynamic instability, respiratory diseases of upper and lower active airways, cardiovascular disease (CVD), taking digoxin and beta-blocker, liver and kidney diseases, altered level of consciousness (defined as GCS < 15), history of disease with increasing ICP, American Society of Anesthesiologists (ASA) score greater than 2, and lack of parental consent for participation of the patient in the study.

2-4. Interventions

Sampling was performed using simple randomization method and the subjects were divided into two groups of ketamine and DEX based on random permutation. For patients in the first and second groups, intramuscular ketamine and intramuscular DEX were injected by expert emergency medicine specialist with dosages of 4 mg/kg and 3 µg/kg, respectively. The objective of injection of the drug was to reach the patient at a level of sedation of 4 based on Ramsay Sedation Scale (RSS) used to measure sedation levels. The time to reach this level of sedation was considered as the time of onset of effect of the drug. The goal was to reach the RSS score of 4 for the CT- scan, graded as an appropriate sedation (AS) level (25). Score 1-3 and 5-6 were regarded as under sedation (US), and over-sedation (OS), respectively. Moreover, returning to the second Ramsay level was considered to calculate the duration of effect of the drug. During the study, for children who did not reach the desired sedation level with a certain dose of intramuscular prescription, another dose of the same drug was injected at half the initial dose, and the interval between two injections was 10 minutes. In case of the lack of response and failure to enter the required level of sedation after 30 minutes from the last dose, intravenous ketamine was prescribed at 1 mg/kg rate. The cases of the need for ketamine injection were regarded as a failure of sedation.

2-5. Outcome

During the entire period of sedation, heart rate and blood pressure were measured and recorded at the start of the study as well as after 5, 10, 15, 20, 25, 35, 45, and 55 minutes. Furthermore, the duration of the onset of the sedation effect, the intramuscular dosage received, the duration of effect of the sedation, the maximum level of sedation in terms of RSS, the frequency of failures in sedation and the need for intravenous ketamine administration, the duration of discharge, and drug side effects such as hypotension, hypertension, hypoxemia, vomiting, bradycardia, tachycardia, emergency phenomena, etc. were also fully recorded.
After taking the medication, the patients were placed in the supine position and oxygen supplementation was prescribed for them using a mask with a rate of 4-6 Lit/min. In case of arterial hypoxemia to less than 94%, or apnea of more than 10 seconds, auxiliary ventilation was started for the patient using a face mask and a bag. During the sedation process, the level of sedation of the patient was recorded based on the modified RSS.

After performing the CT- scan, the patient continued to receive the oxygen supplementation in the same position in order to obtain the discharge criteria. The discharge criteria included: sustained vital signs, RSS score of 1 or 2, pain control, activity levels similar to before sedation, oral tolerance of fluids, presence of reliable companion, and oral and written training of post-procedure instructions.

2-6. Blinding

All injections and filling in the questionnaires were performed by another person who was present in the study and

trained to perform this task, moreover, the drugs were injected to the patient as blind and the patients were blind regarding the type of the drug injected. Furthermore, calculation of the appropriate dosage for injection was conducted by another colleague. Therefore, the patient and the project executer were not aware of the type of drug.

2-7. Statistical analysis

After collection and initial processing of data, data were recorded in SPSS software version 16.0. The Kolmogorov-Smirnov (K-S) test was exploited to examine the normality of the data distribution. To investigate the relationship between quantitative variables, T-test was used in the case of normal distribution of data, however, in the case of abnormal distribution, the Mann-Whitney-U statistical test was employed. Furthermore, the relationship between qualitative variables was assessed using Chi-square and Fisher's exact test. Besides, Pearson or Spearman tests were utilized to check the relationship between variables. In all cases, p-value of less than 0.05 was considered to be statistically significant.

3- RESULTS

3-1. Baseline data

In this study, 94 children who needed sedation in the CT- scan were enrolled and 7 patients were excluded from the study for various reasons (such as declined to participate or not meeting inclusion criteria) (**Figure.1**). The mean ages of children participating in the study were 3.87 ± 1.82 years (2-8 years), and 3.70 ± 1.58 years (2-7 years), respectively in the ketamine and DEX groups (**Table.1**). In the ketamine and DEX groups, 25 (53.2%), and 26 (55.3%) of the participants were girls, respectively. The mean weights of the patients in the ketamine and DEX groups were 14.51 ± 3.01 kg (10-22 kg) and 13.89 ± 3.00 kg (9-21 kg), respectively (**Table 1**).

Table 1. Baseline characteristics of study groups

Variables	Dexmedetomidine group (n= 47)	Ketamine group (n= 47)	P-value
Gender, female Number (%)	26 (55.3)	25 (53.2)	0.07
Age, year, (mean ± SD), (Range)	3.70 ± 1.58 (2 - 7)	3.87 ± 1.82 (2 - 10)	0.843
Weight, kg, (mean ± SD, (Range)	13.89 ± 3 (9 - 21)	14.51 ± 11.23 (10 - 22)	0.443

SD: Standard deviation.

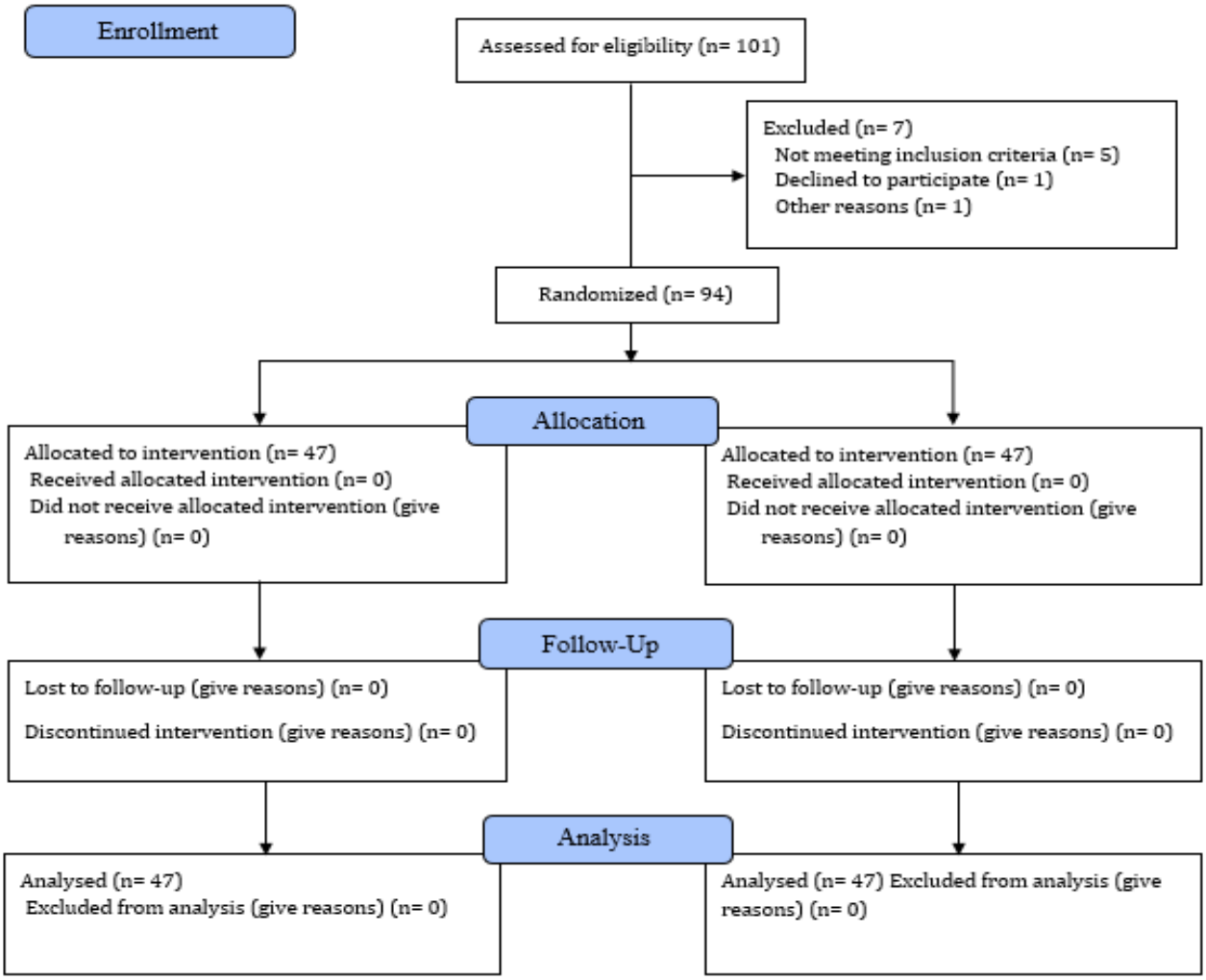

Fig.1: CONCORT flowchart.

3-2. Study outcomes

The mean time of onset of sedation was 8.82 ± 3.86 minutes (1-16 minutes), and 20.46 ± 10.90 minutes (8-45 minutes) in the ketamine and DEX groups, respectively (**Table.2**). The mean duration of effect of sedation in the ketamine and DEX groups was 26.31 ± 11.23 minutes (10-45 minutes), and 34.36 ± 12.83 minutes (10-60 minutes), respectively (p = 0.002) (**Table.2**). Moreover, the mean time of discharge in the ketamine and DEX groups was 35.40 ± 14.34 minutes (15-60 minutes), and 54.08 ± 12.62 minutes (40-90 minutes), respectively (p=0.212) (**Table.2**). The levels of sedation obtained on the basis of RSS criteria were 4 and 5 in 40 (85.1%) and 7 (14.9%) of the participants in the ketamine group, respectively. In addition, the levels of sedation in the DEX group were 4 and 5 in 41 (87.2%), and 6 (12.8%) of the subjects (p=0.765) (**Tables 2 and 3**). In the ketamine group, 8(17.0%) of the patients experienced side effects of the drug, including 4(8.5%), 2(4.3%), and 2(4.3%) cases of vomiting, tachycardia, and tachycardia-vomiting and hypoxemia, respectively. However, there was no drug side effects in the DEX group after prescription of two doses of the drug (p = 0.006). The mean heart rate at the beginning of the study and after 10 and 15 minutes was significantly higher in the

DEX group compared to the ketamine group, however, there was no significant difference between the two groups in other times (**Figure.2**). The mean arterial pressure at the beginning of the study, as well as after 5, 10, 20, 25, and 35 minutes, was higher in the ketamine group in comparison to the DEX group, but the difference between the two groups was not significant in other times (**Figure.3**).

Table 2: Secondary outcomes

Variables		Dexmedetomidine group (n= 47)	Ketamine group (n= 47)	P-value
Sedation score, Number (%)	4 score	41 (87)	40 (85)	0.765
	5 score	6 (13)	7 (15)	
Sedation onset, minute, (mean ± SD), (Range)		20.46 ± 10.90 (8 – 45)	8.82 ± 3.86 (1 – 16)	< 0.001
Duration of sedation, minute, (mean ± SD), (Range)		34.36 ± 12.83 (10 – 60)	26.31 ± 11.23 (10 – 45)	0.002
Time of discharge, minute, (mean ± SD), (Range)		54.08 ± 12.62 (40 – 90)	35.40 ± 14.34 (15 – 60)	0.212

SD: Standard deviation.

Table-3: Comparison of the success rate of sedation after each injection and the degree of sedation created in the two groups.

Variables	Sub-group	Dexmedetomidine group (n= 47)	Ketamine group (n= 47)	P-value
After onset dose, number (%)	Successful (4 score)	9 (19.1)	37 (78.7)	< 0.001
	Unsuccessful	38 (80.9)	10 (21.3)	
After second dose, number (%)	Successful (4 score)	41 (87.2)	47 (100)	0.026
	Unsuccessful	6 (12.8)	0	

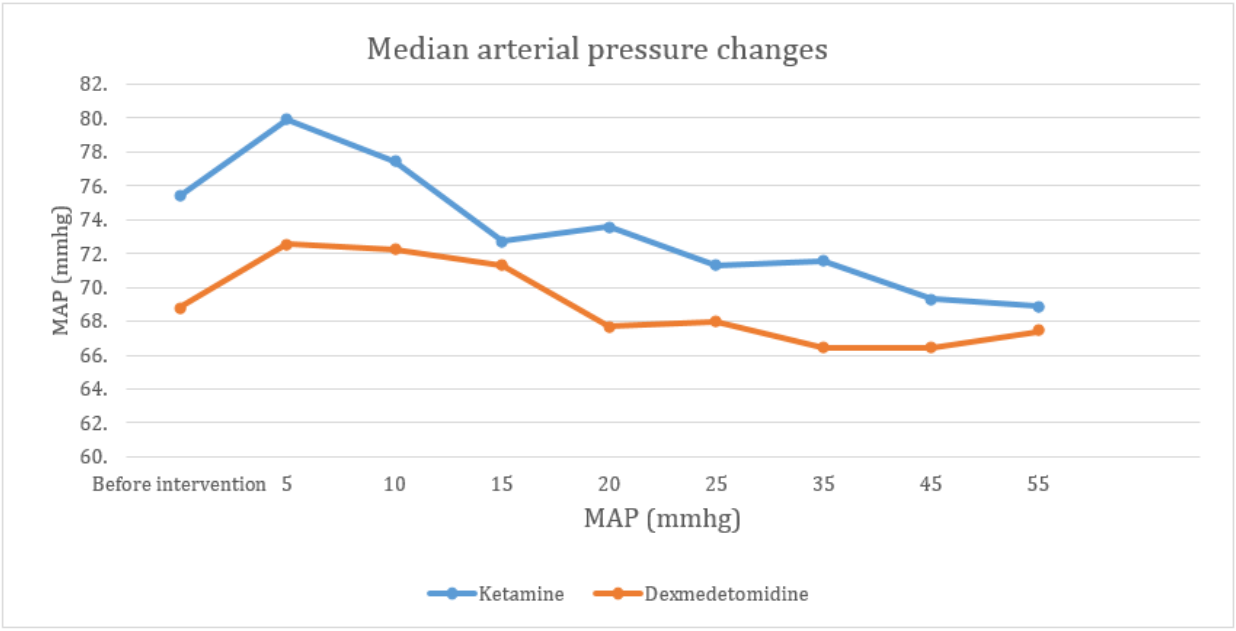

Fig.2: Median arterial pressure changes in two groups during the study.

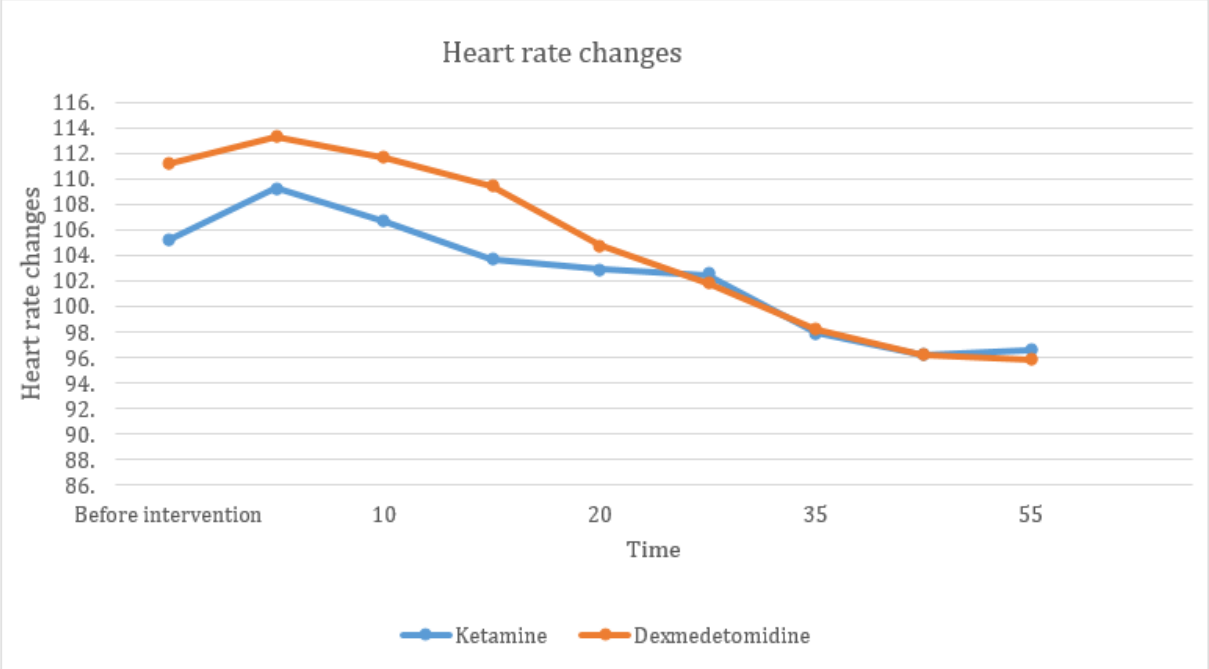

Fig.3: Heart rate changes in the two groups during the study.

4- DISCUSSION

In this study, we studied the effects of intramuscular dexmedetomidine (DEX) with intramuscular ketamine in children undergoing CT imaging. The results of this study showed that the mean time of onset of sedation in ketamine group was significantly lower compared to that of the DEX group. An ideal anesthetic should be fast-acting in terms of the onset and completion of effect, have low fat-solubility, have predictable response to it, can be easily titrated, be reliable in achieving a certain level of sedation, keep the airway tone, and have the least cardiovascular effects. Unfortunately, no such ideal material exists. Nevertheless, DEX includes some of these features. In studies on rodents and humans, it has been revealed that this drug, through its effect on α2 adrenergic receptors, causes a relatively rapid onset of sedative effects along with normal sleep and lowest respiratory depression (14). In a study conducted by Mason et al. (15) on the sedation effect of intramuscular DEX on children needing CT-scan or magnetic resonance imaging (MRI), the mean time of reaching sedation was 13.1 minutes, which is lower than that of the present study. In the study carried out by Tammam (16), the time of onset of sedation with muscular DEX was 16.8 ± 4.5 minutes, which is close to that of the current study. In addition, Koroglu et al. (17), reported slower onset of sedation with propofol, and in another study (18), they reported the onset of its effect faster than midazolam. Mason et al. (19), and Berkenbosch et al. (20) reported the mean time of reaching sufficient sedation after receiving 2 µg/kg of DEX as 8.6 and 10.3 minutes, respectively; the shorter time in these two studies in comparison to the current study may be due to intravenous injection in these studies. In a study in 2015, Mekitar et al. (21) reported the mean time of reaching sedation after intranasal administration of DEX as 13.4 minutes, which is less than the time required for sedation through the intramuscular pathway in the present study. In the study by Sarendar et al. (22), the onset of

sedation in intramuscular injection of midazolam and ketamine was lower than that of DEX. In general, it can be concluded that the time required to reach sedation with DEX is higher than that of the conventional drugs, and the intramuscular form of this drug has slower effect compared to the intravenous form. Furthermore, in the current study, the duration of effect of sedation in the ketamine group was also significantly lower in comparison to the DEX group. Moreover, the mean time of discharge in the ketamine group was lower than that of the DEX group, but the difference between the two groups was not significant (p=0.212). In the ketamine group, 78.7% of the patients responded to the first dose and the rest to the second dose, and there was no case of failure in sedation. In the DEX group, appropriate sedation was created for 19.1% and 87.2% of the patients, with the first dose and after the second dose, respectively; in addition, in 12.8% of the cases, sedation failure was observed, and the difference between the two groups was significant in this regard.

However, in a study by Mason et al. (15), all 65 children who received intramuscular DEX, were able to successfully complete the imaging study. In the studies accomplished by Koroglu et al. (22), and Mekitar et al. (21), no cases of failure in sedation with the administration of DEX were reported. In the study by Tammam (16), the rate of sedation failure following the intramuscular injection of DEX and intramuscular ketamine was 27.8% and 22.2%, respectively, which both cases were higher compared to the current study. Mahmoud et al. (23), comparing DEX and propofol for sleep study with MRI imaging, reported the success rate for DEX and propofol as respectively 88.5% and 70.0%, which are very close to the present study. In the study by Sarendar et al. (22), the highest overall success rates in the establishment of adequate sedation were 87.5%, 66.7%, and 61.9% in the DEX group, followed by ketamine group, and midazolam group, respectively. Overall, it seems that DEX has an acceptable and comparable level of efficacy and success in sedation compared to current conventional sedative medications. However, in the studies by Mason et al. (15), Heard et al. (24), Mekitar et al. (21), McVey and Tobias (25), and Tammam et al. (17), no significant complications were reported following administration of DEX. Therefore, it seems that DEX can be used as a safe and complication-free drug for sedation in children, which is considered as a great advantage of this drug over common drugs for sedation in children. Furthermore, in some studies, including the ones conducted by Tammam et al. (18), and McVey et al. (25) and Tobias et al. (26), the combination of DEX and ketamine was claimed to be a suitable method for sedation, reporting higher success rates and fewer side effects compared to these two drugs separately.

In the study by McVey and Tobias (25), it is argued that when these two drugs are combined with each other, DEX can prevent tachycardia, hypertension, salivation, and the emergency phenomena caused by ketamine, and on the other hand, ketamine can prevent bradycardia and hypotension reported following taking DEX. In addition, the supplementary benefit of this compound is that ketamine increases the speed of sedation. The recommended dosages of the drugs are also as the initial dose of 1 1 µg/kg of DEX and 1-2 mg/kg of ketamine, which can be continued with infusion of 1-2 µg/kg.1 hr and a supplementary dose of 0.5-1 mg/kg of ketamine if needed.

4-1. Limitations of the study

Our study has some limitations, one of which is the short follow-up period, and also, the small sample size.

5- CONCLUSION

Based on the results, although intramuscular DEX has a slower onset of effect and a longer duration of effect compared to ketamine, it can be an alternative to commonly used sedative medications due to its lower side effects. Moreover, it seems that the combination of ketamine and DEX can increase the effectiveness and reduce the side effects, which in this case further studies in the future are required.

6- CONFLICT OF INTEREST: None.

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