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# Comparison of the Efficacy and Side Effects of Intravenous and Intramuscular Injection of Ketamine for Children Requiring Sedation: A Randomized Double-Blind Clinical Trial Study

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## *Abstract*

### *Background*

Ketamine is an antagonist receptor of N-methyl-D-aspartate (NMDA), and phencyclidine derivate sedative agent. Thus the aim of this study was to evaluate the effect of intravenous (IV) and intramuscular (IM) injection of Ketamine for sedation procedure of children.

### *Materials and Methods*

In this randomized clinical trial the patients, 1-6 year-old children referred to Emergency Department of Ahvaz Golestan and Imam Khomeini Hospitals, Ahvaz city, Iran, were divided randomly into two groups (IV and IM groups). Patients in the IV group received ketamine with dose of 1.5 mg/kg intravenously and the patients in the IM group received ketamine with dose of 4 mg/kg intramuscularly. Then efficacy and side effects in both groups were performed every 5 minutes for the first for the first 15 minutes.

### *Results*

222 patients with indication for sedation were enrolled. Results showed that in 1$^{st}$ min, most of the patients that received IM ketamine were in level 1 of sedation (67.6 %, n= 73); while the majority of patients that received IV ketamine were in level 1 to 3 of sedation (28.9%, 24.6% and 26.3%, respectively) (P<0.001). Moreover, in 5$^{th}$ min, most of the patients that received IV ketamine were in level 6 of sedation (62.3%), while those who received IM ketamine were in level 5 of sedation (52.8%) (P<0.001), which was better in IV group. While in 15$^{th}$ min, we did not find significant differences between the groups (P=0.057).

### *Conclusion*

The results of this study showed the beneficial effects of IV ketamine in making better sedation levels in pediatric patients for different purpose (medical and para-clinical procedures).

***Key Words:*** Children, Efficacy, Emergency Department, Sedation, Ketamine.

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## 1- INTRODUCTION

Up to 80% of children have anxiety and stress before surgical and medical interventions (1, 2), which can decrease the quality of medical procedures. On the other hand, the best way to decrease children's anxiety is sedation, which helps children to bear painful and unpleasant procedures, but sedation has several side-effects such as an imbalance in hemodynamic status especially in children in emergency departments (ED) (2, 3). Ketamine is an antagonist receptor of N-methyl-D-aspartate (NMDA), and phencyclidine derivate sedative agent (4-6), which is an appropriate choice for short and painful procedures in children due to some specific properties such as rapid onset, relatively short-term effects, and excellent sedative and analgesic effects with low risk of emergence phenomena and complications (7-13).

There are two different methods for ketamine administration including intravenous (IV), and intramuscular (IM) that have been performed in several studies in order to diagnose the best way to do this procedure with lower incidence rate of side effects (9, 14-16). Despite the different studies on this issue, the superiority of either IV or IM application of the drug is still under debate. Based on these studies, choosing the route of administration depends on different factors including ED facilities, patient characteristics and comfort, and physician's experience and preference, drug's complications and side effects, and onset and duration of drug action (15-17). To the best of our knowledge, there is not enough prospective study about this issue; however, the obtained results were antitheses, therefore, this study was designed to evaluate and compare clinical efficacy and side effects of IV and IM injection of Ketamine for sedation procedure of children.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This is a prospective double-blind clinical trial. Children requiring sedation presented to ED at Ahvaz Golestan and Imam Khomeini Hospitals with two separate research teams, in Ahvaz, in the southwest of Iran, from November 2016 to May 2017. This study is registered in the Iranian registry of clinical trials (IRCT2016021826630N1, http://www.irct.ir).

### 2-2. Methods

The participants were randomly allocated in two groups using a block randomization procedure with matched subjects in each block based on sex and age. The patient and the nurse did not know the type of prescription. After obtaining informed consent, eligible patients were enrolled (**Figure.1**). The baseline characteristics and complete history of drug allergy were recorded in a form for both groups before intervention.

### 2-3. Measuring tools

The blood pressure and sedation levels were recorded with an emergency physician who was not aware of the doses and the route of ketamine administration. The sedation levels were recorded with Ramsay Sedation Scale (18) in 1, 5 and 15 minutes after drug administration in both groups. Based on this scale, the sedation levels were divided to 6 different levels from anxious, agitated, restless (as level 1) to no response to light glabellar tap or loud auditory stimulus (as level 6). Moreover, the side effects of ketamine such as nausea and vomiting were measured visually, restlessness based on the child's crying that despite the efforts of parents, continued for more than 2 minutes, apnea on the basis of pulse oximetry and respiratory status and whether changes in the pattern of breathing, laryngospasm basis of pulse oximetry and the clinical

signs, seizure based on clinical manifestations, laryngotracheal secretions according to clinical symptoms, troubled dreams and the number of waking up with crying based on parents reports 24 hours after injection were recorded. The hemodynamic parameters, side effects and the efficacy findings of patients receiving IV ketamine were compared to patients receiving IM ketamine.

### 2-4. Intervention

Patients in the IV group received ketamine with dose of 1.5 mg/kg intravenously and patients in the IM group received ketamine with dose of 4 mg/kg intramuscularly.

### 2-5. Ethical consideration

The study was approved by the Ethics Committee of Ahvaz Jundishapur University (IR.AJUMS.REC.1394.431).

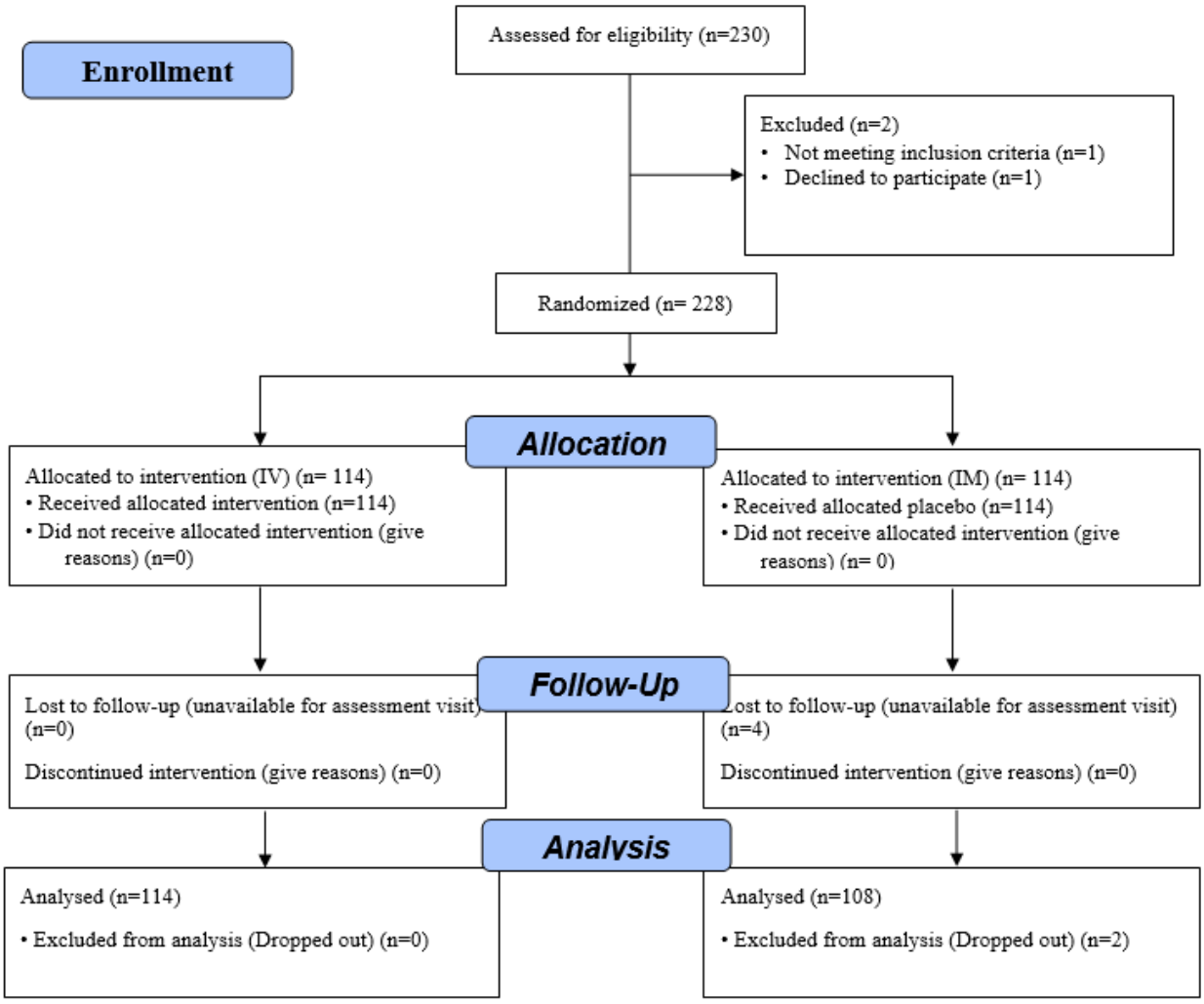


**Fig1**: Consort diagram.

### 2-6. Inclusion and exclusion criteria

### 2-6-1. Inclusion criteria

Consisted of 1-6 year-old patients referred to Emergency Department of Ahvaz Golestan and Imam Khomeini Hospitals needing sedation for medical procedures (sutures, joint relocations, dental procedures), or for any para-clinical procedures (ultrasound, CT- scan, and

MRI), and whose parent or guardian signed a consent form to participate in the study.

### 2-6-2. Exclusion criteria

Did not sign the consent form, having sensitivity to ketamine, evidence of abnormal brain findings such as hydrocephalus, microcephaly, mass and increased intracranial pressure, seizures, having the history of apnea, difficulty in breathing, airway problems, cardiovascular disorders, a history of severe brain trauma, lack of sedation with the administered dose and needing higher dose of ketamine, age below 1 year or more than 6 years, and dissatisfaction to continue participation in study. We also excluded patients with incomplete data.

### 2-7. Data Analyses

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS software version 22.0. To compare qualitative variables between groups Chi-square test was performed. The normal distribution of all studied parameters was checked with Kolmogorov-Smirnov test. Student t-test and paired t-test, Mann-Whitney and Wilcoxon were used for variables. The two tailed p-value < 0.05 was considered significant.

## 3- RESULTS

Two hundred twenty-two patients completed the study; 114 from IV group and 108 from IM group. The study flowchart is shown in **Figure.1**. The baseline characteristics of patients are listed in **Table.1**. Eight patients dropped out and finally, because of unavailability for assessment visit, and 222 patients completed the study. Results showed that the mean of systolic blood pressure (SBP) at different times was variable between two groups, in 1st min it was significantly higher in IV group (P<0.001) (**Table.2**); while it was higher in IM group in 15th min (P=0.004). Moreover, diastolic blood pressure (DBP) had the same condition, while in 1st min it was just significantly different between the groups but was higher in IV group as compared to IM group (P<0.001) (**Table.2**).

We found that administration ketamine in IV route made better sedation levels in pediatric patients. In other words, we found that in 1st min, most of the patients that received IM ketamine were in level 1 of sedation (67.6 %, n= 73), while most of the patients that received IV ketamine were in level 1 to 3 of sedation (28.9 %, 24.6 % and 26.3 %, respectively) (P<0.001) (**Table.2**). Moreover, in 5th min, most of the patients that received IV ketamine were in level 6 of sedation (62.3 %, n= 71), while the majority of patients who received IM ketamine were in level 5 of sedation (52.8 %, n= 57) (P<0.001), which was better in IV group. While in 15th min, we did not find significant differences between the groups (P=0.057) (**Table.2**). Furthermore, in terms of complications (vomiting, dysphoria and laryngotracheal secretions), we did not find significant differences (P>0.05) (**Table.2**).

**Table-1:** The characteristics of children require sedation in Emergency Department

| Variables | Group | | P-value |
|---|---|---|---|
| | IV | IM | |
| Age (year) | 2.44 ± 1.33 | 2.27 ± 1.03 | 0.283 |
| Gender (male) | 73 (64 %) | 69 (63.9 %) | 0.982 |
| Doses (mg) | 21.7 ± 6.97 | 50.17 ± 14.7 | <0.001 |

IV: Intravenous, IM: Intramuscular.

**Table-2:** Studied variables during different periods of time in both IV and IM groups

| Variables | | Group | | P-value |
|---|---|---|---|---|
| | | IV | IM | |
| SBP (mmHg) | Before intervention | 88.46 ± 11.6 | 86.8 ± 10.6 | 0.269 |
| | 1th min | 103.37 ± 16.16 | 91.66 ± 12.87 | <0.001 |
| | 5th min | 98.81 ± 13.75 | 101.99 ± 13.16 | 0.081 |
| | 15th min | 93.72 ± 12.58 | 98.33 ± 11 | 0.004 |
| DBP (mmHg) | Before intervention | 57.71 ± 10.64 | 55.27 ± 9.14 | 0.069 |
| | 1th min | 71.07 ± 14.1 | 58.12 ± 10.23 | <0.001 |
| | 5th min | 66.49 ± 12.08 | 65.41 ± 11.19 | 0.493 |
| | 15th min | 62.32 ± 11.46 | 62.68 ± 10.21 | 0.805 |
| Time of sedation (s) | | 54.82 ± 24.85 | 174.43 ± 46.6 | <0.001 |
| Sedation levels in 1th min | Level 1 | 33 (28.9 %) | 73 (67.6 %) | <0.001 |
| | Level 2 | 28 (24.6 %) | 32 (29.6 %) | |
| | Level 3 | 30 (26.3 %) | 2 (1.9 %) | |
| | Level 4 | 19 (16.7 %) | 0 | |
| | Level 5 | 4 (3.5 %) | 1 (0.9 %) | |
| Sedation levels in 5th min | Level 2 | 0 | 1 (0.9 %) | <0.001 |
| | Level 3 | 0 | 2 (1.9 %) | |
| | Level 4 | 5 (4.4 %) | 27 (25 %) | |
| | Level 5 | 38 (33.3 %) | 57 (52.8%) | |
| | Level 6 | 71 (62.3 %) | 21 (19.4 %) | |
| Sedation levels in 15th min | Level 1 | 0 | 2 (1.9 %) | 0.057 |
| | Level 2 | 1 (0.9 %) | 1 (0.9 %) | |
| | Level 3 | 2 (1.8 %) | 2 (1.9 %) | |
| | Level 4 | 6 (5.3 %) | 11 (10.2%) | |
| | Level 5 | 77 (68.1 %) | 52 (48.1 %) | |
| | Level 6 | 27 (23.9 %) | 40 (37 %) | |
| Vomiting | | 5 (4.4 %) | 3 (2.8 %) | 0.52 |
| Dysphoria | | 10 (8.8 %) | 6 (5.6 %) | 0.354 |
| Laryngotracheal secretions | | 8 (7 %) | 7 (6.5 %) | 0.874 |

IV: Intravenous; IM: Intramuscular; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Sedation levels: level 1: Anxious, agitated, restless, Level 2: Cooperative, oriented, tranquil, Level 3: Responsive to commands only, Level 4: Brisk response to light glabella tap or loud auditory stimulus, Level 5: Sluggish response to light glabella tap or loud auditory stimulus, Level 6: No response to light glabella tap or loud auditory stimulus.

## 4- DISCUSSION

This study evaluated and compared clinical efficacy and side effects of IV and IM injection of Ketamine for sedation procedure of children. We found that administration of ketamine in IV route made better sedation levels in pediatric patients in short periods of time, without causing serious complications. In the study performed by Rezazadeh et al. it was shown that efficacy and safety of IV and IM methods of ketamine usage in the pediatric procedural sedation were widely similar, but the intravenously administration of the ketamine can be proposed as the preferable mode (19). Ramaswamy et al. showed that time from drug injection to discharge was shorter in the IV compared to IM ketamine group, both overall and for the short-suture group. However, time from triage to discharge was similar (16). In another study performed by Gharavifard et al. it was shown that although the sedative and analgesic effects of IM and IV ketamine are not significantly different, duration of effect and onset of action are more desirable in the IV group for suturing, fracture reduction, and foreign body removal. Meanwhile, the IM method can lead to lesser need of rescue doses (20). The results of these studies were similar to

ours. While a study performed by Roback et al. showed that ketamine 4 mg/kg IM was more effective than 1 mg/kg IV in pediatric sedation for orthopedic procedures but demonstrated significantly longer recovery times and more vomiting (14). These differences in both efficacy and rate of complications in was in contrast to our study, which may be due to studied population with different demographic features (such as age and gender) with different indication for sedation, different dosage in IV group and different race. According to the meta-analysis study done by Green et al., administrating high IV doses of the ketamine (initial dose≥2.5mg/kg and a total dose 5mg/ kg), the IM method of ketamine injection and the increasing age can be proposed as the predictors of the emesis. The peak age is 12 years old. It was also concluded in their study that a low level of IM ketamine and high doses of the IV ketamine might result in patients' recovery agitation (21, 22).

Different adverse effects can occur by combining ketamine with other drugs, for example, the occurrence of oxygen desaturation is more frequent when midazolam was added to IV ketamine than applying ketamine alone (23, 24). Ketamine stimulates oral secretions, and there is no consensus on whether co-administration of an anticholinergic is essential, with evidence from observational studies and RCTs to support both sides of the argument (12, 17, 25).

### 4-1. Limitations of the study

The study had several limitations such as short follow- up duration, and small sample size.

## 5- CONCLUSION

The results of this study showed the beneficial effects of IV ketamine in making better sedation levels in pediatric patients for different purpose (medical and para-clinical procedures), and significantly leads to make better sedation levels without serious complications in the short term.

## 6- CONFLICT OF INTEREST: None.

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