

## ORIGINAL RESEARCH

## A Randomized Clinical Trial of Intravenous and Intramuscular Ketamine for Pediatric Procedural Sedation and Analgesia

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### Abstract

**Introduction:** Ketamine is an agent broadly used for pediatric procedural sedation and analgesia in emergency departments. It has been found to be safe and with a low risk of complications. Choosing between intravenous (IV) and intramuscular (IM) injections is a matter of concern, so we did a comparison between the two methods in terms of their efficacy and rate of complications. **Methods:** This single-blind clinical trial recruited 240 children (age: three months to 15 years, weight > 5 kg), who underwent short and painful procedures at the emergency departments. They were randomly allocated to two groups of 120 patients to receive either IV or IM ketamine with of 1.5 and 4 mg/kg doses, respectively. Indications for use, dose, side effects, and efficacy of the medications as well as duration of the procedure and time to recovery were compared between the two groups. **Results:** The mean age of the IV and IM groups were  $6.5 \pm 3.6$  and  $3.05 \pm 2.6$  years, respectively ( $p < 0.001$ ). The onset of action of ketamine was  $1.7 \pm 1.1$  minutes in the IV group and  $8.6 \pm 3.1$  in the IM ones ( $p < 0.001$ ). Patients of the IV and IM groups remained in optimal sedation for  $20.6 \pm 12.0$  and  $37.2 \pm 11.8$  minutes, respectively ( $P < 0.001$ ). Time until emergency department discharge was  $65.3 \pm 36.9$  minutes in the IV group and  $72.2 \pm 14.5$  in the IM group ( $P = 0.40$ ). Ketamine had excellent and moderate efficacy in 66.7% and 32.5% of the IV group and 70.0% and 25.0% in the IM group, respectively ( $p = 0.02$ ). Totally, 60.0% of IV group patients and 40.0% of IM group experienced drug side effects ( $p = 0.21$ ). Need for rescue dose was significantly higher in IV group (26.7% vs. 10.0%;  $p < 0.001$ ). Finally, recovery was tranquil and comfortable in 88 patients (73.3%) of the IV group and 108 patients (90.0%) of the IM group ( $p = 0.06$ ). **Conclusion:** We found 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.

**Key words:** Ketamine; analgesia; sedation; injections, intramuscular; infusions, intravenous

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### Introduction:

Ketamine is an antagonist receptor of N-methyl-D-aspartate (NMDA) and phencyclidine derivative sedative agent broadly used for pediatric procedural sedation and analgesia (PSA) in emergency departments (1-3). Rapid onset, relatively short-term effects, and excellent sedative and analgesic effects make it an appropriate choice for short and painful procedures. Numerous clinical trial studies have approved ketamine as a desirable and safe medication with low risk of emergence phenomena (4-10). Several studies in this field have compared two methods of intravenous (IV) and intramuscular (IM) administration based on time until

hospital discharge and the incidence rate of side effects (6, 11-13). However, the superiority of either IV or IM application of the drug has been still under debate. Choosing the route of administration depends on available factors such as: emergency department facilities, patient characteristics and comfort, and physician's experience and preference, drug's complications and side effects, and onset and duration of drug action (12-15). Since few studies were done among Iranian population in this regard, the present study was performed to identify the preferable route for using ketamine by comparing the efficacy and side effects of the above-mentioned methods.



**Methods:****Study design and setting**

This single-blind clinical trial was conducted on three months to 15 years old children that weighted more than 5 kilograms, and required PSA for short and painful emergency procedures, who were presented to the emergency departments of Imam Reza and Hasheminejad Hospitals, Mashhad, Iran. Ethics committee of Mashhad University of Medical Sciences confirmed the study protocol and researchers were committed to the principles of the Helsinki declaration throughout the study period. Before any intervention, administered medication and its complications were thoroughly explained for their parents and informed written consent was obtained from them. This trial is registered in Iranian registry of clinical trial (IRCT) under number IRCT2014071218454N1.

**Participants**

240 children were recruited using convenience sampling. They were randomly allocated in two groups of 120 patients by using block randomization method. Subjects with a history of allergy to ketamine, severe cardiovascular diseases, thyroid disorders, head injury, central nervous system (CNS) disorders, glaucoma or acute globe injuries, history or evidence of psychosis, obstructive sleep apnea, active pulmonary diseases such as upper respiratory tract infection, tracheal stenosis or surgery, needed procedures associated with stimulation of posterior pharyngeal region, and those who were not willing to participate were excluded from the study.

**Intervention**

Sedation by ketamine was performed according to standard guidelines (14). Pulse oximetry and cardiac monitoring were constantly performed before, during, and after sedation. A nurse, blinded to the intervention, was present by the side of the patients during the whole procedure and not only recorded the routine nursing observations and evaluations, but also any abnormal conditions until the patient recovered to his/her pre-procedure state. Venipuncture was performed for all patients to ensure blindness of the nurses and physicians. The first group of patients received IV ketamine (1.5 mg/kg, Infusion by 100 milliliter normal saline; maximum dose 200 mg), and the second took an IM dose (4 mg/kg; maximum dose 200 mg). Patients with an open airway and adequate oxygen saturation, who were awake or could be easily awakened with minimal stimulation, able to drink liquids, and returned to the baseline level of consciousness were considered eligible for discharging from the emergency department.

**Outcomes**

The data regarding demographic characteristics, duration of the procedure, the medicine's onset and duration of action, efficacy, side effects, and time until emergency department discharge were gathered for all participants.

At the end of the procedure, a specialist, who was blinded to the intervention, rated the efficacy of medicine in pain management and sedation as excellent (full sedation, immobility, and analgesia during the whole procedure), moderate (slight movements due to pain without interfering in the procedure), and poor (movements associated with pain that interfered in the procedure). The patients' status was followed for at least one hour in the recovery room and the incidence of any adverse effects was recorded. Children with restlessness or hallucinations were categorized as "recovery with agitation". In the absence of any side effects, the subjects were classified as "tranquil and comfortable".

**Statistical analysis**

The sample size calculation was performed based on detection of clinically significant differences in the incidence of vomiting. In a previous study, vomiting occurred in 18.3% and 35.4% of patients in IV and IM groups, respectively (11). With considering  $\alpha = 0.05$  and 80% power, 232 patients were needed to be enrolled. The collected data were entered to SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and described by using mean and standard deviation, graphs and tables. Variables without normal distribution and ordinal ones were analyzed through Mann-Whitney U test. Chi-square test was also performed to compare qualitative variables between the two groups. For assessment of any difference between IV and IM groups related to efficacy, side effects, duration of the procedure, time to recovery and time to discharge we used generalized linear model adjusted for baseline characteristics. P values less than 0.05 were statistically considered significant.

**Results:**

The mean age of the IV and IM groups were  $6.5 \pm 3.6$  and  $3.05 \pm 2.6$  years, respectively ( $p < 0.001$ ). 80 (66.7%) and 60 (50.0%) cases were male in IV and IM groups, respectively ( $p = 0.009$ ). The mean weight of the IV and

**Table 1:** Demographic characteristics of children receiving intravenous (IV) or intramuscular (IM) ketamine

Characteristics	Group (%)		p
	IV	IM	
<b>Age (years)</b>	$6.5 \pm 3.6$	$3.05 \pm 2.6$	<0.001*
<b>Gender</b>			
Male	80 (66.7)	60 (50.0)	0.009#
Female	40 (33.3)	60 (50.0)	
<b>Weight (kg)</b>	$2.3 \pm 13$	$14.2 \pm 8.6$	<0.001*
<b>Procedure</b>			
Suturing	81(67.5)	97 (81.0)	0.34#
Fracture reduction	21(17.5)	11 (9.0)	
Foreign body removal	18 (15.0)	12 (10.0)	

Values are Number (%); \*, Based on Mann-Whitney U test; #, Based on Chi-Squared test



**Table 2:** Outcome of children receiving intravenous (IV) or intramuscular (IM) ketamine

Factor	Group		Odds ratio	95% CI	p*
	IV	IM			
<b>Efficacy</b>					
Excellent	80 (66.7)	84 (70.0)	Ref	Ref	
Moderate	39 (32.5)	30 (25.0)	1.5	0.8 - 3.0	0.24
Poor	1 (0.8)	6 (5.0)	0.4	0.05 - 3.4	0.19
<b>Need to rescue dose</b>					
No	88 (73.3)	108 (90)	Ref	Ref	
Yes	32 (26.7)	12 (10.0)	5.8	2.5 -13.6	<0.001
<b>Recovery</b>					
Tranquil and comfortable	88 (73.3)	108 (90.0)	Ref	Ref	
Brief agitation	32 (26.7)	12 (10.0)	2.0	0.9 - 4.8	0.06
<b>Side effects</b>					
No side effects	48 (40.0)	72 (60.0)	Ref	Ref	
Nausea and vomiting	40 (33.3)	18 (15.0)	1.6	0.8 - 3.5	0.21
Hallucination	16 (33.3)	12 (10.0)	1.7	0.6 - 4.2	0.30
Agitation	24 (20.0)	12 (10.0)	1.1	0.4 - 2.7	0.88
Respiratory depression	8 (6.7)	18 (15.0)	0.5	0.1 - 1.8	0.29
Total	72 (60.0)	48 (40.0)	1.5	0.8 - 2.7	0.21

Values are Number (%); \*, Based on generalized linear model adjusted for age, gender, and weight of patients; CI = confidence interval; Ref = reference category

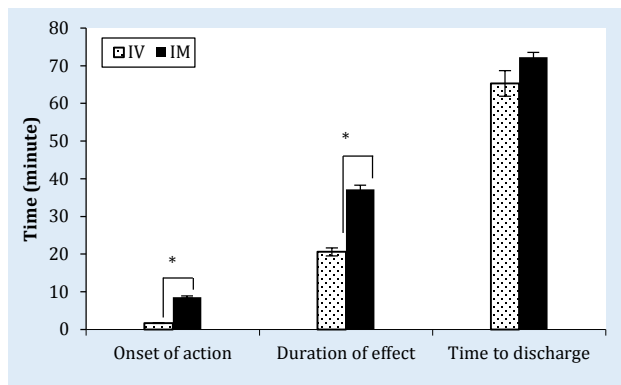
IM groups were  $22.3 \pm 13.0$  and  $14.2 \pm 8.6$  kilograms, respectively ( $p < 0.001$ ). Suturing, distal radius fracture reduction, and foreign body removal were performed for 178 (74.0%), 32 (13.5%), and 30 (12.5%) subjects, respectively (Table 1). The onset of ketamine action was  $1.7 \pm 1.1$  (range: 1 - 5) minutes in the IV group and  $8.6 \pm 3.1$  (range: 5 - 15) in the IM group ( $p < 0.001$ ). Patients of the IV and IM groups remained in optimal sedation for  $20.6 \pm 12.0$  (range: 6 - 45) and  $37.2 \pm 11.8$  (range: 15 - 60) minutes, respectively ( $p < 0.001$ ). Time until emergency department discharge was  $65.3 \pm 36.9$  minutes in the IV group and  $72.2 \pm 14.5$  minutes in the IM group ( $p = 0.40$ ) (Figure 1). Ketamine had excellent and moderate efficacy in 66.7% and 32.5% of the IV group and 70.0% and 25.0% in the IM group, respectively ( $p = 0.02$ ) (Table 2). Totally, 60.0% of IV group patients and 40.0% of IM experienced drug side effects. After adjustment for age, gender, and weight there was no statistical significance ( $p = 0.21$ ). Nausea and vomiting were observed in 40 (33.3%) patients of the IV group and 18 (15.0%) patients of the IM ones ( $p = 0.21$ ). Hallucinations were detected in 16 (13.1%) and 12 (10.0%) of the IV and IM groups, respectively ( $p = 0.30$ ). IV and IM injections of ketamine resulted in agitation in 24 (20.0%) and 12 (10.0%) patients, respectively ( $p = 0.88$ ). The frequency of respiratory depression was eight (6.8%) and 18 (15.0%) in the IV and IM groups, respectively ( $p = 0.29$ ). Need to rescue dose was significantly higher in IV group (26.7% vs. 10.0%;  $p < 0.001$ ) (Table 2). Finally, the recovery was tranquil and comfortable in 88 patients (73.3%) of the IV group and 108 patients (90.0%) of the IM group ( $p = 0.06$ ).

### Discussion:

The results of the present study showed that although the sedative and analgesic effects of IM and IV ketamine were not significantly different, duration of effect and onset of action were more desirable in the IV group for suturing, fracture reduction, and foreign body removal. Meanwhile, the IM method led to fewer need to rescue doses. In general, because of no difference in side effects and recovery time between IV and IM methods, it was suggested that IV infusion of ketamine might be safer and more effective than IM injection for PSA.

In 2006, Roback et al. compared the side effects, efficacy, and duration of sedation induced by IV and IM injection of ketamine in patients required orthopedic procedures. While respiratory complications in the two groups were similar (8.3% in the IV group vs. 4.0% in the IM group), the frequency of vomiting was higher in the IM group (26.3% vs. 11.9%). Moreover, the IM administration of ketamine was associated with significantly lower levels of pain and higher duration of sedation compared to the IV route. The researchers concluded that although IM injection of ketamine had better sedative properties compared to IV application, it was clearly accompanied by longer recovery and more vomiting (11). In spite of similar methodology, the findings of Roback et al. were in contrast with ours. The mean onset of action was 1.67 minutes in the IV group and 8.65 minutes in the IM group. In addition, mean time until emergency department discharge was 65.33 and 72.25 minutes in the above-mentioned groups, respectively. Consequently, the IV method was more favorable based on both speed of onset of action and time spent in the emergency department. Since the efficacy difference between the two





**Figure 1:** Comparing intravenous (IV) and intramuscular (IM) ketamine injections based on onset of action, duration of effect, and efficacy in children presenting in the emergency department. \*, significant difference based on generalized linear model adjusted for age, gender, and weight of patients.

groups was not significant, no route of administration was favorable in terms of effectiveness (i.e. those causing optimal sedation and analgesia). In evaluation of the side effects, we did not detect any significant difference between groups. Unlike our findings, Roback et al. suggested this side effect to be more frequent following IM injections (11). In addition, in Ramaswamy et al. study side effects were seen in 35% of the IM group and 20% of the IV group. Moreover, time until discharge after the injection was 21 minutes shorter in the IV group. However, time from the beginning of triage until discharging was similar in two groups. The time required for catheterization in the IV method was suggested to be responsible for such findings (13). Nevertheless, as we did not consider the time required for venipuncture, similar results were obtained regarding time until discharge. In a review study in 2010, Deasy et al. reported that IV ketamine injections were generally associated with fewer side effects and shorter duration of action compared to IM administration of the medicine. They concluded that when it is performed by a skilled person, the IV method could induce sedation more effectively than the IM method (16). Another review study by Green et al. in 2006 indicated shorter time until discharge and less efficacy following the IV injections of ketamine. However, the researchers state that selecting the best route of administration depends on the physician's decision based on the conditions and facilities of the hospital, particularly the emergency department and skillfulness of the staff (12). As the two groups in the current study had no significant difference in terms of efficacy, we recommend the same criteria for selecting the appropriate method. On the other hand, racial and environmental factors might have influenced on the effectiveness and side effects of the medicine, too.

The present study contained some limitations. Because of difference in the method of administration, there was

no possibility to blind the patient to the intervention, so the study was done as single-blind fashion. Furthermore, although the person who gathered the data was not informed about the injection method, he might be aware of the group that underwent therapy during clinical assessments. Thus, it could be possible to influence the blindness of the observer in some cases. To avoid such a problem, the observer was trained not to ask anything from the patient regarding therapeutic interventions.

#### Conclusion:

It was found that although the sedative and analgesic effects of IM and IV ketamine were not significantly different, duration of effect and onset of action were more desirable in the IV group for suturing, fracture reduction, and foreign body removal. Meanwhile, using the IM method can lead to lesser need for rescue doses.

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