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Ketamine Associated Vomiting in Children Requiring Sedation: A Prospective Randomized Open Trial Study

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Abstract

Background

In recent years, ketamine has been the most used sedative in Emergency Department (ED) procedures for pain management. Therefore, this study evaluated ketamine associated vomiting (KAV) in children requiring sedation.

Materials and Methods

This is a prospective, randomized, and open trial study carried out on children of ages 3 months to 13 years requiring sedation for medical diagnostic or treatment procedures. The patients were randomized into 1 mg/kg IV, 2 mg/kg IV, 3 mg/kg IM and 5 mg/kg IM groups.

Results

A total of 190 patients were enrolled for this study. In total, 17.37% of the children were reported to have vomited after ketamine administration. In the IV group, 21.69% of the children vomited, while in the IM group, 14.02% vomited (p= 0.18). In the 1 mg/kg IV group, 22.72% of the children vomited compared to 20.51% (p= 0.51) in the 2 mg/kg IV group. In the 3 mg/kg IM group, 14.54% of the children vomited as against 13.46% in the 5 mg/kg IM group (p= 0.54). There were no significant differences between sex and dose group on the incidence of vomiting (p= 0.40).

Conclusion

This study showed that the administration of ketamine via IV and IM in a standard dose is a safe method for sedating children. However, there is need to study the combination of ketamine with anti-vomiting agents in different injection routes, as well as to review the combination with tranquilizer to minimize the rate of vomiting in children requiring sedation in the ED.

Key Words: Emergency Department**,** Ketamine, Sedation, Vomiting.

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1- INTRODUCTION

Children may suffer pain during the lowest interventions, especially without an existing tissue injury or any medical procedures (1). Sedation and analgesia are used to reduce the level of consciousness in patients without affecting cardiorespiratory function during painful medical procedures (2). In recent years, ketamine has been the most used sedative in emergency departments (ED) procedures for pain management (3, 4). Compared to other drugs used for sedation, it has several advantages of which respiratory depression is the most important with no analgesic effect (5). Furthermore, it prevents the re-uptake of catecholamine and generally supports blood pressure. It also relaxes the smooth muscles of the bronchial tubes and is well-tolerated in patients with infectious airborne diseases (6).

Ketamine is administered intravenously (IV) or intramuscularly (IM) (7, 8). After the injection, the drug is quickly distributed in the brain tissue. The effects are preserved until the drug is transmitted to the peripheral tissues and metabolized by the liver. The duration of sedative effects is 10 min in the intravenous method and 40 min in the intramuscular route while complete recovery generally requires 1 to 2 hours (9-11). Previous studies have reported important side effects associated with ketamine such as hypoxia, laryngospasm, apnea, vomiting, and emergency reactions (12-14). These side effects are a challenge for physicians in ED, when faced with children whose needed treatment or diagnosis involves sedation (15). Accordingly, there is the need for drugs with less complications and effective sedation. Therefore, this prospective randomized open trial study evaluated doses of ketamine-associated vomiting (KAV) in children requiring sedation, who were referred for diagnostic or treatment services.

2- MATERIALS AND METHODS

2-1. Methods

This study was conducted according to the Consolidated Standards of Reporting Trials (CONSORT)(16).

2-2. Study design

This is a prospective, randomized, open trial study registered in the Iranian registry of clinical trials (IRCT20151114025027N6, http://www.irct.ir). Ketamine was administered via IV or IM in children that required sedation in medical procedures**.** The study was approved by the Ethics Committee from Ahvaz Jundishapur University (ID-code: ajums.REC.1392.346).

2-3. Selection of Participants

After obtaining informed consent from parents, patients aged 3 months to 13 years requiring sedation for medical diagnosis or treatment procedures were enrolled for the study in 2018. Children with psychiatric disorder, asthma or previous adverse reactions to ketamine, porphyria, cardiovascular diseases or hypertension, thyroid disease, taking anti-nausea medicines and sleepy before the visit, airway tract infections, increased intracranial pressure and patients with open globe injuries (17, 18) were excluded.

2-4. Interventions

Random allocation software was used to generate a random number list to assign patients into two groups: IV and IM ketamine administration (Rotexmedica, Trittau, Germany). Accordingly, patients were randomized to receive a minimum dose of ketamine (1 mg/kg IV or 3 mg/kg IM) and maximum dose of ketamine (2 mg/kg IV or 5 mg/kg IM).

2-5. Discharge criteria

The length of ED stay after ketamine administration was 2 h after the procedure. The children were monitored by two researchers for airway patency, ability to talk (if of appropriate age), and ability to sit, stand or walk unaided (if of appropriate age), management of any nausea and vomiting.

2-6. Statistical Methods

All recorded data were statistically analyzed using SPSS software version 22.0. Data were presented as frequencies and percentages. The level of significance was set at 5% for all analyses. The incidence of vomiting and other demographic characteristics were reported using descriptive statistics. The similarity of the test groups was reviewed in terms of age and sex. Comparisons with continuous data were done using t-test while categorical data were analyzed using Chi-square (χ^2) test.

3- RESULTS

Eligible patients enrolled in the study are shown in **Figure.1**. Among the 967 eligible patients, 190 were enrolled and allocated into the two study groups. 120 (63.2%) patients were male and 70 (36.8%) were female. The mean ages of the IM and IV groups were 1.98±1.03 years (from 3 months to 6 years) and 2.34±1.85 years (from 3 months to 12 years), respectively. CT-scan examination, inserting chest tube, suture and fracture were the procedures that required sedation in children. The characteristics of enrolled patients are listed in **Table.1**. In total, 17.37% of children vomited after ketamine administration (**Table. 2**). In the IV and IM groups, 21.69 and 14.02% of the children vomited (p= 0.18), respectively. In the 1 mg/kg IV group, 22.72% of the children vomited, and in the 2 mg/kg IV group, it was 20.51% (p= 0.51).

In the 3 mg/kg IM group, 14.54% of the children vomited, and in the 5 mg/kg IM group, it was 13.46% (p= 0.54). After comparing, it was found that there were no significant differences at p= 0.29 and 0.37 between vomiting at minimum doses (1 mg/kg IV or 3 mg/kg IM) and maximum doses (2 mg/kg IV or 5 mg/kg IM), respectively. There were no significant differences between sex and doses group in the incidence of vomiting (p= 0.40), and there was also no significant differences between age and vomiting (p= 0.56). Agitation was reported as a side effect in the 1 mg/kg IV group. After discharge, no side effects were reported or observed.

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

Variables	IM (n= 107)		IV (n= 83)		Total (n= 190)
	3 mg/kg, (n= 55)	5 mg/kg (n= 52)	1 mg/kg (n= 44)	2 mg/kg (n= 39)	
Age, mean ± SD, year	1.73±1.26 (3 Mo-6)	2.25±1.3 (1-6)	2.22±2.02 (3 Mo-12)	2.47±1.64 (9 Mo-8)	2.13±1.57 (3 Mo-12)
Gender, Boy, Number (%)	37 (67.27 %)	33 (63.46 %)	26 (59.09 %)	24 (61.53 %)	120 (63.2 %)
Weight, mean ± SD, kg	11.84±4.55	12.54±4.01	12.11±6.00	12.82±3.51	12.30±4.59
Medical Procedure	Number (%)	Number (%)	Number (%)	Number (%)	Number
CT-Scan	54 (29.34)	52 (28.26)	42 (22.82)	36 (19.56)	184
Chest tube	---	---	1 (100)	---	1
Suture	1 (50)	---	---	1 (50)	2
Fracture	---	---	1 (33.33)	2 (66.67)	3

SD: Standard deviation; IM: Intramuscular; IV: Intravenous.

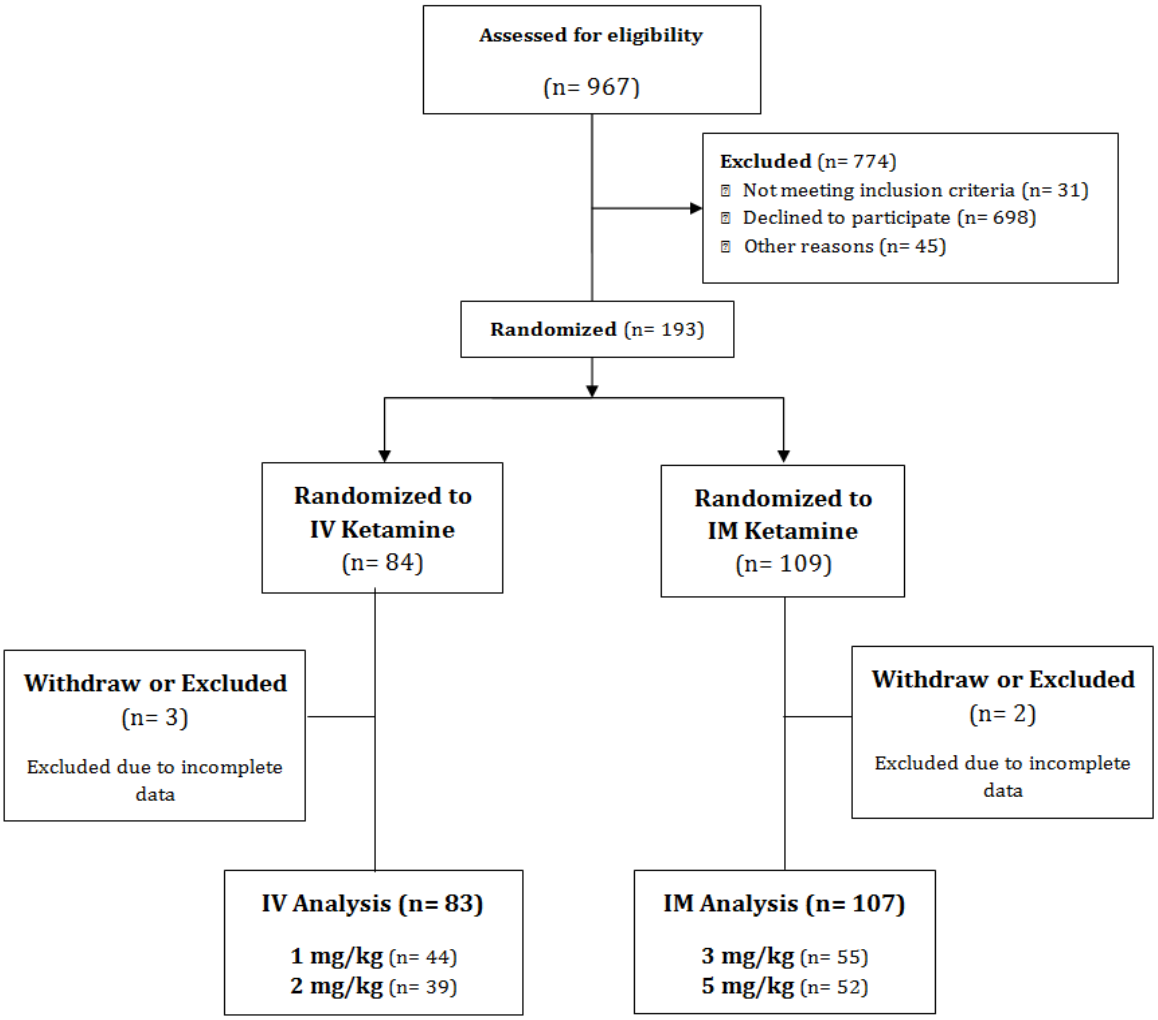

Fig.1: Study flowchart.

Table-2: Vomiting in the emergency department and after discharge

Vomiting	IM, (n= 107)		IV, (n= 83)		Total (n= 190)
	3 mg/kg (n= 55)	5 mg/kg (n= 52)	1 mg/kg (n= 44)	2 mg/kg (n= 39)	
Yes, Number (%)	8 (14.54)	7 (13.46)	10 (22.72)	8 (20.51)	33 (17.37)
No, Number (%)	47 (85.45)	45 (86.54)	34 (77.28)	31 (79.49)	157 (82.63)

IM: Intramuscular; IV: Intravenous.

4- DISCUSSION

This study evaluated ketamine associated vomiting (KAV) in children requiring sedation. Ketamine is an ion channel antagonist, N-methyl-D-aspartic acid (NMDA) (19); was approved by the US Food and Drug Administration (FDA) in 1970. It acts as a blockage to glutamate receptors in the thalamus of the brain and prevents the transmission of pain messages to the limbic area (20). Clinical practice guideline states the administered dose of

ketamine is typically 4 to 5 mg/kg intramuscularly, and 1.5 to 2 mg/kg intravenously for sedation in children (21, 22). Previous meta-analytical studies found no dose related side effect across the standard dosing range, with only unusually high IV doses increasing the risk of vomiting (4, 23). Another study reported that the ketamine group had significantly fewer incidences of vomiting than the placebo (normal saline) group (24). This study is the first prospective trial to investigate the effect of IV and IM ketamine administration at four different doses (1 and 2 mg/kg IV or 3 and 5 mg/kg IM) on ketamine-associated vomiting. Previous studies on ketamine have reported a wide range of vomiting of 0 to 27.1% (12, 25-29).

A prospective observational study with total IV ketamine doses ranging from 1 to >7 mg/kg, and incidence of vomiting of 7 to 16.63%, indicated a direct relationship between vomiting and ketamine dosage (30). The IM route is associated with a higher incidence of vomiting (4, 31). However, in this study, there were no significant differences between both groups. Agitation, also known as restlessness, disorientation, excitation, and inconsolable crying, was also reported as a common phenomenon (32). It was found that less than 1 to 2% of patients have agitation. Agitation was more common in adolescent and adult females, and in people with psychiatric disorders; it was a rare occurrence in children (11).

In this study, agitation was reported in only a boy in the 1 mg/kg IV group, who was not vomiting. This study shows that vomiting did not occur in patients after discharge, however, several studies have reported a wide range of vomiting incidence ranging from 3.5 to 10 % (3, 8, 33, 34). The prevalence of ketamine induced vomiting in older children is higher than in younger children (4, 22) as indicated guidelines showed that KAV occurs more frequently especially in children older than 5 years (22, 34). However, there were no significant differences between ketamine induced vomiting in older and younger children. The challenges faced by physicians in ED include dose application and the use of an appropriate type of injection for sedation in children. The IM route has a longer recovery and late sedation effect compared to the IV route (35). However, evidence from our study strongly emphasizes the same safety level between the IV and IM routes (4, 8, 23, 31).

4-1. Limitations of the study

The present study has several limitations. First, as a result of the routes of ketamine administration (intravenous and intramuscular), blinding was not possible. The second limitation is the failure to perform a long-term follow-up of all patients, after the medical procedure. Third, the number of patients studied was not large enough to make a definitive statement about the safety of one route over the other. Fourth, Body mass index (BMI) is a factor that can contribute to the increased vomiting in children undergoing ketamine sedation (36); however, it was not possible to measure BMI in the ED. Fifth, if the number of children above and below the five-year old groups was equal, the results of age and vomiting might have been different.

5- CONCLUSION

The results of this study showed that administering a standard dose of ketamine intramuscularly or intravenously is a safe method of sedation in children. However, it is necessary to evaluate the combination of ketamine with anti-vomiting agents in different injection routes, as well as review the combination of tranquilizers to minimize the rate of vomiting in children requiring sedation in the ED.

6- CONTRIBUTORS' STATEMENT

Mohammadreza Maleki Verki: implemented the study, drafted and revised the paper, designed data collection tools, cleaned and analyzed the data; *Hassan Motamed*: monitored data collection, wrote the statistical analysis plan, drafted and revised the paper, analyzed the data; *Javad Mozafari*: monitored data collection, analyzed the data and *Arash Forouzan*: monitored data collection, drafted and revised the paper.

7- CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

8- ACKNOWLEDGMENT

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