



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

Hassan Motamed<sup>1</sup>, \*Mohammadreza Maleki Verki<sup>1</sup>, Javad Mozafari<sup>1</sup>, Arash Forouzan<sup>1</sup>

<sup>1</sup>Department of Emergency Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

### 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.

\*Please cite this article as: Motamed H, Maleki Verki M, Mozafari J, Forouzan A. Ketamine Associated Vomiting in Children Requiring Sedation: A Prospective Randomized Open Trial Study. *Int J Pediatr* 2018; 6(12): 8611-18. DOI: **10.22038/ijp.2018.33524.2960**

#### \*Corresponding Author:

Mohammadreza Maleki Verki (M.D), Department of Emergency Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Tel/Fax: +986133921637

Email: drmalaki676@yahoo.com

Received date: Apr.26, 2018; Accepted date: Jul.12, 2018

## 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 ( $\chi^2$ ) 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  $1.98 \pm 1.03$

years (from 3 months to 6 years) and  $2.34 \pm 1.85$  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 $\pm$ SD, year	$1.73 \pm 1.26$ (3 Mo-6)	$2.25 \pm 1.3$ (1-6)	$2.22 \pm 2.02$ (3 Mo-12)	$2.47 \pm 1.64$ (9 Mo-8)	$2.13 \pm 1.57$ (3 Mo-12)
Gender, Boy, Number (%)	37 (67.27 %)	33 (63.46 %)	26 (59.09 %)	24 (61.53 %)	120 (63.2 %)
Weight, mean $\pm$ SD, kg	$11.84 \pm 4.55$	$12.54 \pm 4.01$	$12.11 \pm 6.00$	$12.82 \pm 3.51$	$12.30 \pm 4.59$
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.

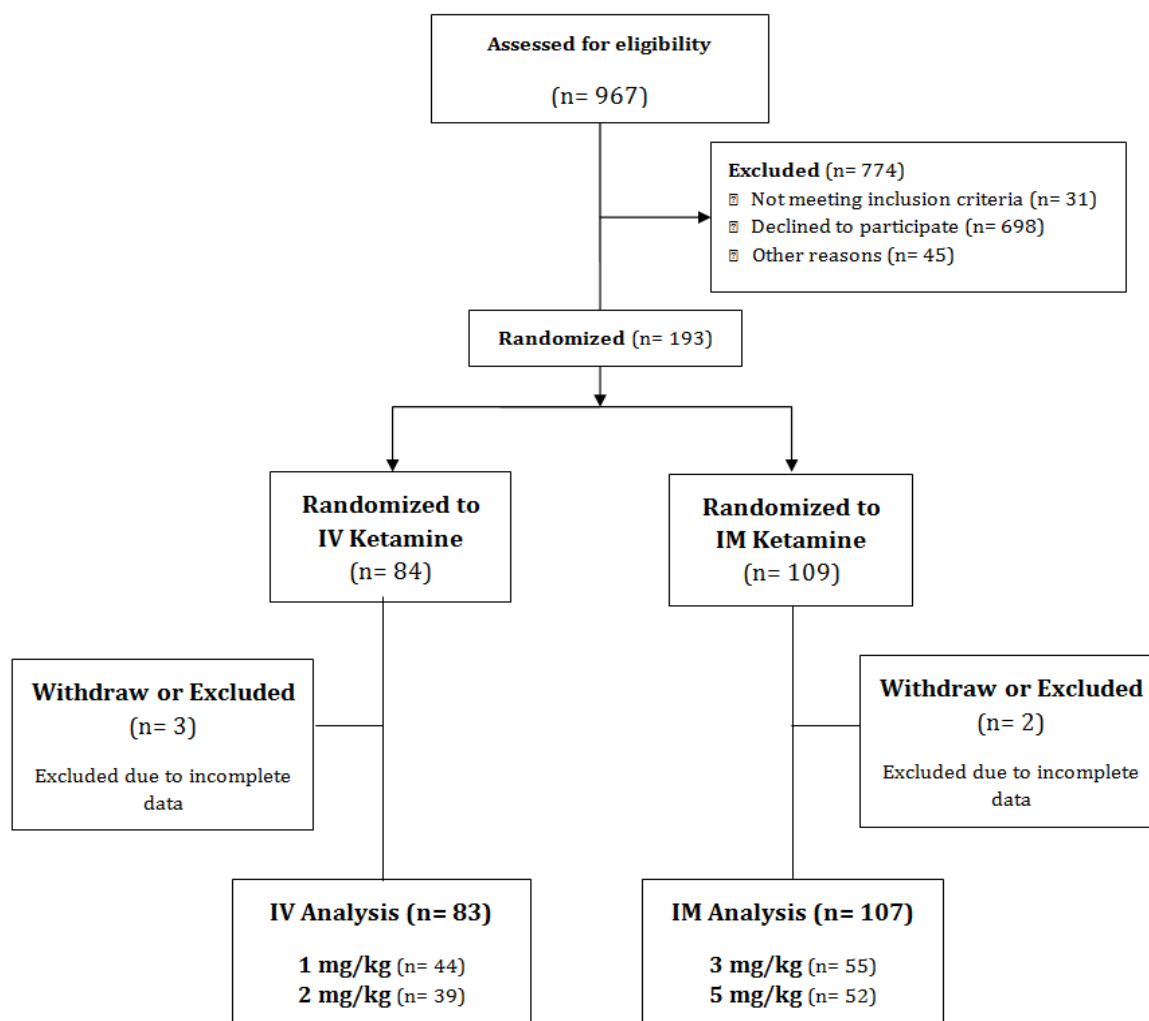


Fig.1: Study flowchart.

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

This research was the result of a project affiliated by Deputy of Research Affairs, Ahvaz Jundishapur University of Medical Sciences.

## 9- REFERENCES

1. Johnston CC, Stevens BJ, Boyer K, Porter FL. Development of Psychologic Responses to Pain. *Pain in infants, children, and adolescents. Pediatric Clinics of North America.* 1989; 36(4): 823-36.
2. Alimohammadi H, Shojaee M, Samiei M, Abyari S, Vafae A, Mirkheshti A. Nerve Stimulator Guided Axillary Block in Painless Reduction of Distal Radius Fractures; a Randomized Clinical Trial. *Emerg (Tehran).* 2013;1(1):11-4.
3. Lee JS, Jeon WC, Park EJ, Min YG, Jung YS, Kim GW, et al. Adjunctive Atropine Versus Metoclopramide: Can We Reduce Ketamine-associated Vomiting in Young Children? A Prospective, Randomized, Open, Controlled Study. *Academic Emergency Medicine.* 2012;19(10):1128-33.
4. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Annals of emergency medicine.* 2009;54(2):158-68 e1-4.
5. Mace SE, Barata IA, Cravero JP, Dalsey WC, Godwin SA, Kennedy RM, et al. Clinical policy: evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department. *Annals of emergency medicine.* 2004;44(4):342-77.
6. Abbasivash R, Aghdashi MM, Sinaei B, Kheradmand F. The effects of propofol-midazolam-ketamine co-induction on hemodynamic changes and catecholamine response. *Journal of clinical anesthesia.* 2014;26(8):628-33.
7. Dachs RJ, Innes GM. Intravenous ketamine sedation of pediatric patients in the emergency department. *Annals of emergency medicine.* 1997;29(1):146-50.
8. Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. *Annals of emergency medicine.* 1998;31(6):688-97.
9. Qureshi FA, Mellis PT, McFadden MA. Efficacy of oral ketamine for providing sedation and analgesia to children requiring laceration repair. *Pediatric emergency care.* 1995;11(2):93-7.
10. Maurice S, O'donnell J, Beattie T. Emergency analgesia in the paediatric population. Part II Pharmacological methods of pain relief. *Emergency medicine journal.* 2002;19(2):101-5.
11. Marx J, Walls R, Hockberger R. *Rosen's Emergency Medicine-Concepts and Clinical Practice E-Book: Elsevier Health Sciences;* 2013.
12. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine.* 2005;12(6):508-13.
13. Pitetti RD, Singh S, Pierce MC. Safe and efficacious use of procedural sedation and

analgesia by nonanesthesiologists in a pediatric emergency department. *Archives of pediatrics & adolescent medicine*. 2003;157(11):1090-6.

14. Peña BM, Krauss B. Adverse events of procedural sedation and analgesia in a pediatric emergency department. *Annals of emergency medicine*. 1999;34(4):483-91.

15. Doyle E. Emergency analgesia in the paediatric population. Part IV Paediatric sedation in the accident and emergency department: pros and cons. *Emergency medicine journal : EMJ*. 2002;19(4):284-7.

16. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC medicine*. 2010;8(1):18.

17. Hinkelbein J, Lamperti M, Akeson J, Santos J, Costa J, De Robertis E, et al. European Society of Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults. *Eur J Anaesthesiol*. 2018;35(1):6-24

18. American Academy of P, American Academy of Pediatric D, Cote CJ, Wilson S, Work Group on S. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update. *Pediatrics*. 2006;118(6):2587-602.

19. Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesthesia progress*. 1999;46(1):10.

20. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesthesia and analgesia*. 2003;97(6):1730-9.

21. Green SM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation in children. *Annals of emergency medicine*. 2004;44(5):460-71.

22. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Annals of emergency medicine*. 2011;57(5):449-61.

23. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, et al. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. *Annals of emergency medicine*. 2009;54(2):171-80 e1-4.

24. Tong Y, Ding XB, Wang X, Ren H, Chen ZX, Li Q. Ketamine peritonsillar infiltration during tonsillectomy in pediatric patients: An updated meta-analysis. *International journal of pediatric otorhinolaryngology*. 2014;78(10):1735-41.

25. Lee JS, Jeon WC, Park EJ, Min YG, Kim GW, Jung YS, et al. Does ondansetron have an effect on intramuscular ketamine-associated vomiting in children? A prospective, randomised, open, controlled study. *Journal of paediatrics and child health*. 2014;50(7):557-61.

26. Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Annals of emergency medicine*. 2000;36(6):579-88.

27. Almenrader N, Passariello M, D'Amico G, Haiberger R, Pietropaoli P. Caudal additives for postoperative pain management in children: S(+)-ketamine and neostigmine. *Paediatric anaesthesia*. 2005;15(2):143-7.

28. Yenigun A, Yilmaz S, Dogan R, Goktas SS, Calim M, Ozturan O. Demonstration of analgesic effect of intranasal ketamine and intranasal fentanyl for postoperative pain after pediatric tonsillectomy. *International journal of pediatric otorhinolaryngology*. 2018;104:182-5.

29. Hadi BA, Sbeitan SM. Clinical pharmacy intervention post tonsillectomy: a randomized control trial. *Int J Clin Pharm*. 2015;37(1):133-8.

30. Thorp AW, Brown L, Green SM. Ketamine-associated vomiting: is it dose-related? *Pediatric emergency care*. 2009;25(1):15-8.

31. Roback MG, Wathen JE, MacKenzie T, Bajaj L. A randomized, controlled trial of iv versus im ketamine for sedation of pediatric patients receiving emergency department orthopedic procedures. *Annals of emergency medicine*. 2006;48(5):605-12.
32. Lepouse C, Lautner CA, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. *British journal of anaesthesia*. 2006;96(6):747-53.
33. Roback MG, Bajaj L, Wathen JE, Bothner J. Preprocedural fasting and adverse events in procedural sedation and analgesia in a pediatric emergency department: are they related? *Annals of emergency medicine*. 2004;44(5):454-9.
34. Green SM, Kuppermann N, Rothrock SG, Hummel CB, Ho M. Predictors of adverse events with intramuscular ketamine sedation in children. *Annals of emergency medicine*. 2000;35(1):35-42.
35. Green SM, Denmark TK, Cline J, Roghair C, Abd Allah S, Rothrock SG. Ketamine sedation for pediatric critical care procedures. *Pediatric emergency care*. 2001;17(4):244-8.
36. Kinder KL, Lehman-Huskamp KL, Gerard JM. Do children with high body mass indices have a higher incidence of emesis when undergoing ketamine sedation? *Pediatric emergency care*. 2012;28(11):1203-5.