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Original Article (Pages: 7511-7518)

Effect of Ondansetron on the Incidence of Ketamine Associated Vomiting in Procedural Sedation and Analgesia in Children: A Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Background
Vomiting is a common side effect of ketamine in children's sedation and there is still controversy about the use of an anti-emetic drug along with ketamine to reduce this complication. The aim of this study was to evaluate the effectiveness of ondansetron in controlling vomiting induced by intramuscular (IM), and intravenous (IV) ketamine for procedural sedation and analgesia in children in the emergency department (ED).

Materials and Methods
In a double-blind, randomized, placebo-controlled clinical trial, children aged 1 to 10 years who received ketamine for ED procedures were randomized into four groups receive IV ketamine (1.5 mg/kg), and placebo, IM ketamine (5mg/kg) and placebo, IV ketamine and IV ondansetron (0.15 mg/kg), and IM ketamine and oral ondansetron. The incidence of nausea and vomiting and ED length of stay were compared as the outcome of the study.

Results
One hundred eighty children were enrolled and randomized to four groups; 29 patients (15.0%) had nausea and vomiting. The incidence of vomiting was 26.7% in the IV ketamine-placebo group and 8.9% in the IV ketamine/ IV ondansetron group (P = 0.02). The incidence of vomiting was 17.8% in the IM ketamine-placebo group and 11.1% in the IM ketamine/oral ondansetron group (P = 0.17). ED length of stay was similar between groups.

Conclusion
According to current results, children administered IV ondansetron before IV ketamine experienced a significantly reduced incidence of vomiting but did not significantly affect length of ED stay and the addition of oral ondansetron to IM ketamine dose not reduce vomiting.

Key Words: Children, Conscious sedation, Ondansetron, Ketamine.

*Please cite this article as: Majidi Nejad S, Goudarzi L, Heydari F. Effect of Ondansetron on the Incidence of Ketamine Associated Vomiting in Procedural Sedation and Analgesia in Children: A Double-Blind, Randomized, Placebo-Controlled Trial. Int J Pediatr 2018; 6(4): 7511-18. DOI: **10.22038/ijp.2018.29446.2577**

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Received date: Jan.23, 2018; Accepted date: Feb.22, 2018

1- INTRODUCTION

Procedural sedation and analgesia are performed to reduce the level of consciousness of patients without affecting cardio-respiratory function during painful diagnosis and treatment (1-3). Many of the medical interventions in the emergency department (ED) of children, such as reduction of fractures, casting, imaging and suturing, require sedation (4). Meanwhile, the number of non-invasive and minimally invasive procedures required sedation in the ED is increasing (5-7). So far, various drugs have been proposed for this purpose, but ketamine, an N-methyl-D-Aspartate (NMDA) receptor antagonist, has been widely used in this field. The characteristics of this drug include the onset of fast effects, no effect on blood pressure and airway reflexes and cardiovascular function. This drug is soluble in fat and water, and therefore the intramuscular (IM) and Intravenous (IV) form are available (2, 8). However, the use of ketamine will be associated with complications. Important adverse events associated with ketamine include hypoxia, laryngospasm, apnea, vomiting, and emergency reactions. This complication sometimes causes aspiration, prolonging the patient's hospitalization and even death. The reported frequency of vomiting ranges from 3.8% to 18.7% (5, 7, 8). But some studies show the incidence of 28.9% of nausea and vomiting following ketamine administration (9). Accordingly, some studies suggest that it be used as an adjunct to an anti-emetic drug along with ketamine (10). Ondansetron is a serotonin receptor antagonist introduced to the market in the mid-1980s. It has no effect on dopaminergic and muscarinic receptors, along with anti-emetic effects (11). Ondansetron has been widely used in a variety of settings to reduce vomiting associated with viral illnesses, chemotherapy, and anesthesia. Studies show that the incidence of nausea and vomiting in those receiving ketamine and ondansetron is almost half that seen in ketamine alone (12). However, there are some studies suggesting that administration of ondansetron with ketamine does not affect the incidence of nausea and vomiting in children (9). Therefore, there is still controversy regarding the use of ondansetron as an anti-emetic drug along with ketamine in sedation of children. The aim of this study was to evaluate the effectiveness of ondansetron with IV and IM ketamine in reducing vomiting in children during sedation for emergency procedures.

2- MATERIALS AND METHODS

2-1. Study Design

The present study is a randomized, double-blind, placebo-controlled trial that was performed in children with ED ketamine sedation referred to the ED. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.mui.REC.1394.3.187) and was registered at the Iranian Center for Clinical Trials (IRCT20180129038549N1). Before the study, written informed consent was obtained from all parents, before enrollment into the study. Throughout the length of the study, the researchers adhered to the principles of the Helsinki Treaty. A sample size calculation (assuming α=0.05, and β=0.20) showed that 45 children in each group would permit detection of a decrease in vomiting from 29% to 10%.

2-2. Method

This study was conducted at Alzahra Hospital in Isfahan, Iran, a university-affiliated hospital ED, which is a regional referral center and Level I trauma center. The annual census is 74,000 ED visits. Inclusion criteria were children aged 1-10 years who received IV or IM ketamine for laceration repair in ED. Exclusion criteria

included patients with history of psychosis, hypertension, intracranial hemorrhage, concurrent vomiting illness; those with a previous adverse reaction to ketamine or ondansetron; use of anti-emetic drugs before treatment, the presence of vomiting before prescribing the drug, need an additional dose of ketamine and parents unwilling to provide informed consent. Nothing-by-mouth (NPO) time was defined as at least 3 hours of fasting.

2-3. Interventions

A random allocation sequence was determined from a computer-generated random number table. The parents provided written informed consent to attending or resident physicians of the research team. After informed consent was given, an emergency medical resident involved in the research opened one of the sequentially numbered envelopes, thus randomly assigning the patient to the IV ketamine-placebo group, the IV ketamine/IV ondansetron group, IM ketamine-placebo group or the IM ketamine/oral ondansetron group. Since the administration of ketamine (IV or IM) was different in the groups, it was not possible to blinding the researcher but we divided the patients into IM and IV groups and in each group received double-blind placebo or ondansetron.

In the IV ketamine-placebo group, patients received ketamine 1.5 mg/kg IV (maximum single dose 100 mg) plus 2 ml distilled water IV (placebo). In the IV ketamine/IV ondansetron group, patients received ketamine 1.5 mg/kg IV (maximum single dose 100 mg) plus ondansetron 0.15 mg/kg/dose IV (maximum dose 4 mg).

In the IM ketamine-placebo group, patients received ketamine 5 mg/kg IM (maximum single dose 100 mg) plus 2 ml oral distilled water (placebo). In the IM ketamine/oral ondansetron group, patients received ketamine 5 mg/kg IM (maximum single dose 100 mg) plus oral ondansetron 0.15 mg/kg/dose (maximum dose 4 mg). The drugs used in this study were prepared by an emergency medicine specialist, which did not relate to data collection that was then sent to the ED labeled as "study drug". The medications were given to the ED nurses who had already been identified and did not know the contents of the medications, and did not relate to data collection. These nurses were administered the ketamine and the study drug (contained either the ondansetron or the placebo of equivalent volume) at the same time, but in separate syringes.

The medical staff, parents, and patients were blinded to the contents of the "study drug" syringe. The first dose of ketamine and additional doses of ketamine were given at the discretion of the ED attending physician. Patients in need of ketamine sedation were selected according to the physician's opinion and standard guidelines. Used ondansetron (Demetron) was made by Tehranchemie Company (Iran), Ketamine was also made by Rotex Medica (Germany) and distilled water was made by Osve Company (Iran).

Before administering the "study drug", patients or their parents were questioned. Age, gender, site of trauma and history of drug allergy were recorded. All patients were monitored after published sedation guidelines and were eventually discharged from the department by order of the physician. When discharged, parents were given discharge information. Parents were contacted by telephone within 24 hours after discharge from the ED to determine whether vomiting occurred within 12 hours after discharge. Data was collected by Resident of Emergency Medicine.

2-4. Outcome Measures

The primary outcome in this study was the incidence of nausea and vomiting in the ED and after discharge, as determined by telephone follow-up. Secondary outcome

measures were other complications of Ketamine and Ondansetron and length of ED stay. Length of ED stay was defined as the time from when an initial dose of ketamine was given until the time of discharge.

2-4. Data Analysis

Statistical analysis was performed with STATA version 11.0. The difference between the four groups for categorical variables, were analyzed with Chi-square and Fisher's exact test. Findings were reported as frequencies and percentages. For all analyses, $p \leq 0.05$ were statistically significant.

3-RESULTS

This study was conducted from December 2015 to January 2016. During the study period, one hundred eighty children aged 1 to 10 years received ketamine sedation for the repair of various lacerations. Patients were randomized into four equal groups treated with IV ketamine + placebo, IM ketamine + placebo, IV ketamine + ondansetron and IM ketamine + ondansetron (**Figure.1**).

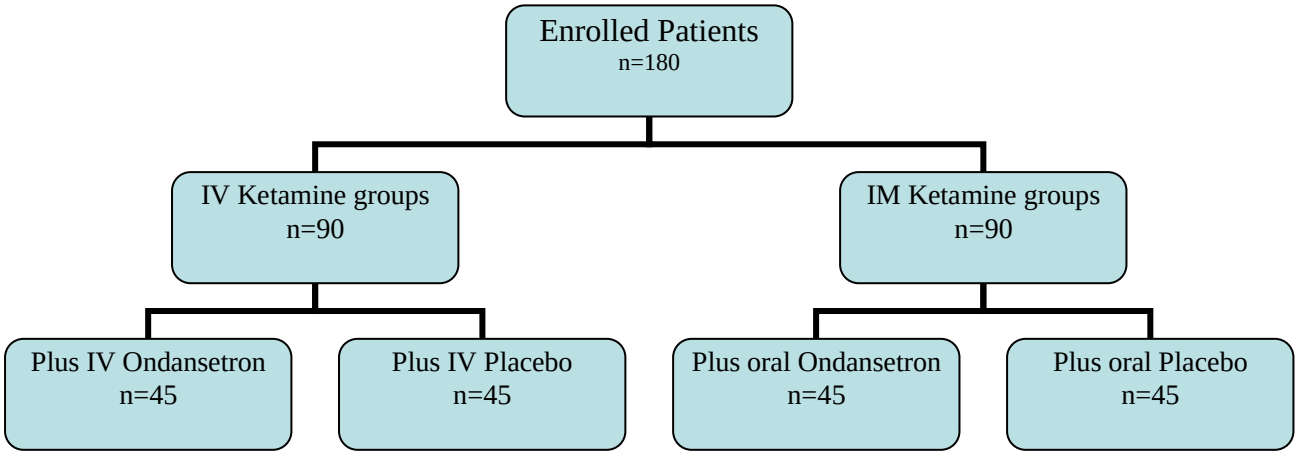

Fig.1: Study Flow Diagram.

Most of the children were in the age group of 2-7 years old (66.7%), and 79 patients (65.8%) were boys. The most common laceration site was facial (37.5%), oral cavity (35.8%), and upper limb (15.0%), respectively. Characteristics of the enrolled patients are listed (**Table.1**).

Table-1: Patient characteristics in studied groups

Variables	IV Ketamine+ placebo	IM Ketamine+ placebo	IV Ketamine+ Ondansetron	IM Ketamine+ Ondansetron	P- value
Age, year (%)					
< 2	12(26.7)	10(22.2)	13(28.9)	9(20)	
2 - 6	27(60)	30(66.7)	29(64.4)	32(71.1)	0.52
6 - 10	6(13.3)	5(11.1)	3(6.7)	4(8.9)	
Gender (%)					
Boy	33(73.3)	27(60.0)	29(64.4)	30(66.7)	0.45
Girl	12(26.7)	18(40.0)	16(35.6)	15(33.3)	
Laceration Site					
Face	22(48.9)	20(44.4)	16(35.6)	13(28.9)	
Oral cavity	12(26.7)	15(33.3)	16(35.6)	24(53.2)	0.12
Upper limb	6(13.3)	4(8.9)	9(20.0)	9(20.0)	
Others	6(13.3)	7(15.6)	6(13.4)	1(2.2)	

IM: intramuscular; IV: intravenous.

Twenty-seven patients (15%) had nausea and vomiting. The incidence of vomiting in the IV ketamine + placebo group, IM ketamine + placebo group, IV ketamine + ondansetron group, and IM ketamine + ondansetron group were 26.7%, 17.8%, 8.9% and 11.1%, respectively. The comparison of vomiting in the four study groups are shown in **Figure.2**. No children experienced pulmonary aspiration or laryngospasm. Patients who received ondansetron were less likely to vomit than those who received placebo. There was no significant difference in the control of vomiting among the two groups that were received IM ketamine (p = 0.17), but in two groups that received IV ketamine showed significant improvement with ondansetron (p=0.02) (**Table.2**).

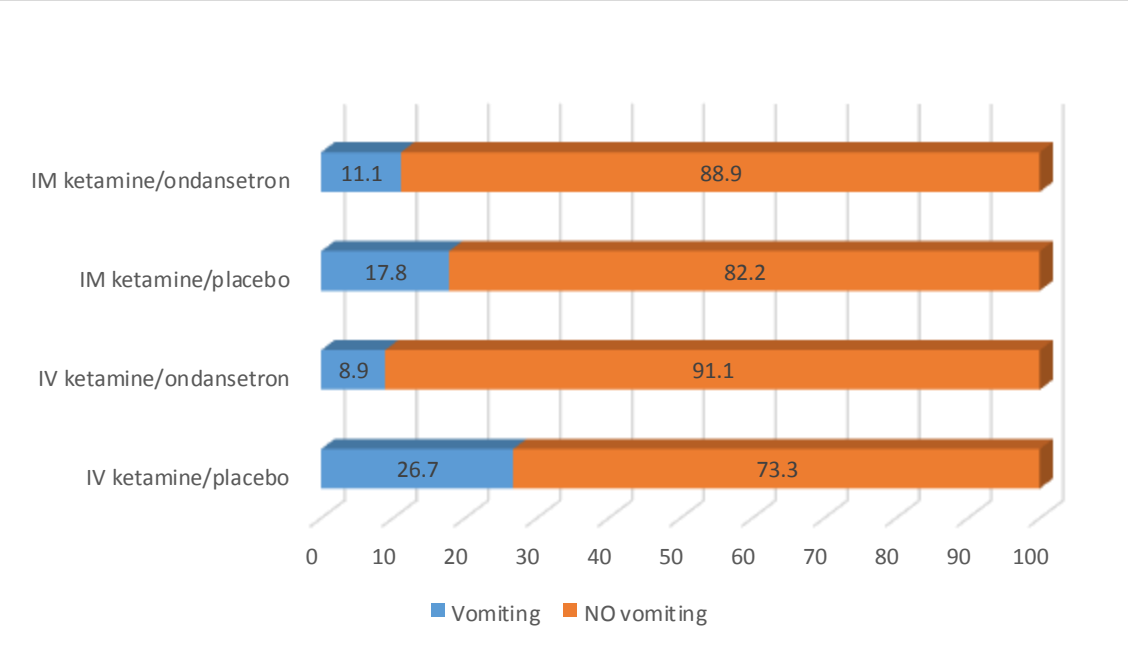

Fig.2: Incidence of vomiting (%) in studied groups**.**

Table-2: Incidence of Vomiting in studied Patients

Variables	Incidence of Vomiting (%)		P- value
	Placebo groups	Ondansetron groups	
IM Ketamine	17.8	11.1	0.17
IV Ketamine	26.7	8.9	0.02

Length of ED stay was similar between IV groups: 88 minutes (range 29 to 214 minutes) in the ketamine and ondansetron group versus 93 minutes (range 25 to 235 minutes) in the ketamine and placebo group. Also length of ED stay was similar between IM groups: 119 minutes (range 56 to 264 minutes) in the ketamine and ondansetron group versus 112 minutes (range 61 to 255 minutes) in the ketamine and placebo group (**Table.3**).

Table-3: Length of Emergency Department Stay in studied groups

Variables	Length of ED stay (minute)		P- value
	Placebo groups	Ondansetron groups	
IM Ketamine	112(61-255)	119(56-264)	0.84
IV ketamine	93(25-235)	88(29-214)	0.78
P- value	<0.01	<0.01	

IM: intramuscular; IV: intravenous.

4- DISCUSSION

Based on the results of this study, it seems that the use of ondansetron in IM ketamine administration has no effect on reducing the complications of nausea and vomiting, but in patients receiving IV ketamine administration of ondansetron reduces nausea and vomiting. Nausea and vomiting is one of the most common side effects of ketamine in children sedation. The incidence of nausea and vomiting in this study was 15%. Previous studies show that the incidence of nausea in children receiving ketamine is very wide. The range of vomiting in studies with a high sample size was reported to be between 3.5 and 11.4 percent (10, 14-17), while in studies with a lower sample size, was estimated to be up to 29.7 percent (9, 18-20). Since the sample size in the present study is relatively low, the incidence of vomiting is similar to studies with the same limitation. Because of these relatively high rates of vomiting, according to studies, the use of an anti-emetic drug may reduce the incidence of this complication (13).

According to Roback et al. (17) rates of vomiting were higher using IM ketamine versus IV (26.3% vs. 11.9%), as in the present study (26.7% vs. 17.8%). The findings of this study were in line with Lee et al., Which showed that the use of oral ondonestrone with a dose of 2 to 8 mg had no effect on IM ketamine induced vomiting in children (9) as in the present study (16% vs. 10%). But Lanston et al. reported contradictory findings. The researchers stated that IV administration of 0.1mg / kg of ondonestrone effectively reduces vomiting following IV ketamine administration (13). Our results suggest that for children who receive IV ketamine, the addition of ondansetron decreases vomiting in the ED (26% vs. 7%). The patients who received placebo did not experience an increased length of ED stay. This finding is consistent with previous studies (9, 13). Several series and a systematic review revealed no apparent association between a fasting state and emesis. (15, 16, 19); therefore, fasting time was not investigated in this study. In summary, we found that children administered IV ondansetron before IV ketamine experienced a significantly reduced incidence of vomiting but did not significantly affect length of ED stay. Due to the low cost of ondansetron and a relatively high incidence of vomiting, it is recommended that children who receive IV ketamine have an administration of ondansetron before it.

4-1. Limitations of the study

This study has several important limitations. There is a possibility of selection bias in this study. On the other hand, the incidence of ketamine-induced vomiting in older children is much higher than younger (14, 21). Therefore, if the sampling was limited to children over 7 years of age, the findings might change. Finally, it should be said that because of the low sample size in the present study,

the generalizability of the findings is in doubt.

5- CONCLUSION

Based on the results of this study, it seems that the addition of IV ondansetron to IV ketamine lead to reduce of vomiting in children. Also the addition of IV ondansetron to IM ketamine dose not reduces vomiting. However, due to the limitations of the present study, further studies will be needed. Due to the low cost of ondansetron and a relatively high incidence of vomiting, it is recommended that children who receive IV ketamine have an administration of ondansetron before it.

6- AUTHORS' CONTRIBUTION

All authors had four proposed criteria for the International Committee of Medical Journal Publishers to obtain a writer's condition.

7- CONFLICT OF INTEREST: None.

8- ACKNOWLEDGMENT

This study was supported by the Isfahan University of Medical Sciences, Iran (ID number: NO: 394187). The authors appreciate the insightful cooperation of Medical Sciences and the staffs of the emergency department of Al-Zahra Hospital, Isfahan, Iran.

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