

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

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Study objective: We investigate the effect of ondansetron on the incidence of vomiting in children who receive intravenous (IV) ketamine for procedural sedation and analgesia in the emergency department (ED).

Methods: In this double-blind, randomized, placebo-controlled trial in a children's hospital ED, patients receiving IV ketamine (1 mg/kg) for ED procedures were randomized to receive either IV ondansetron (0.15 mg/kg; maximum 4 mg) or identical placebo. We recorded whether vomiting occurred in the ED postsedation or up to 12 hours after discharge with telephone follow-up and compared ED length of stay and parental satisfaction.

Results: One hundred twenty-seven children were randomized to placebo and 128 to ondansetron. The groups were similar in age, sex, and fasting duration. ED vomiting was less common with ondansetron: 6 of 128 (4.7%) versus 16 of 127 (12.6%), $P=.02$, difference 7.9% (95% confidence interval 1.1% to 14.7%), number needed to treat 13. Follow-up was successful in 82.7%, with vomiting in the ED or after discharge less frequent with ondansetron: 10 of 128 (7.8%) versus 24 of 127 (18.9%), $P=.01$, difference 11.1% (95% confidence interval 2.7% to 19.5%), number needed to treat 9. ED length of stay and parental satisfaction were similar between groups.

Conclusion: IV ondansetron significantly reduces the incidence of vomiting associated with IV ketamine procedural sedation in children. [Ann Emerg Med. 2008;52:30-34.]

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INTRODUCTION

Background

Ketamine is widely used for emergency department (ED) procedural sedation and analgesia in children.^{1,2} Important adverse events associated with ketamine include hypoxia, laryngospasm, apnea, vomiting, and emergency reactions.²⁻⁴ The reported frequency of vomiting ranges from 3.8% to 18.7%.^{1,2,5-11} Ondansetron has been widely used in a variety of settings to reduce vomiting associated with viral illnesses, chemotherapy, and anesthesia.¹²⁻¹⁶ This antiemetic is increasingly used in the ED, including for the treatment of ketamine-associated vomiting.

Importance

Although ondansetron is often used to treat ketamine-associated vomiting, its efficacy for prophylaxis is unknown.

Vomiting may increase ED length of stay and decrease patient satisfaction. Although clinically apparent pulmonary aspiration has never been reported during ED procedural sedation and analgesia in children, vomiting during such sedation could increase its risk.^{17,18}

Goals of This Investigation

We wished to determine whether vomiting associated with intravenous (IV) ketamine may be reduced or eliminated by the addition of prophylactic ondansetron.

MATERIALS AND METHODS

Study Design

A convenience sample of children was enrolled in a randomized, double-blind, placebo-controlled trial of ondansetron with ED ketamine sedation. Written, informed

Editor's Capsule Summary

What is already known on this topic

Vomiting is a common adverse effect after ketamine sedation in children.

What question this study addressed

Does intravenous ondansetron reduce the frequency of emesis with ketamine?

What this study adds to our knowledge

In this randomized, double-blind, placebo-controlled trial with 268 children, ondansetron significantly reduced the frequency of vomiting (12.6% to 4.7%). The number needed to treat was 13.

How this might change clinical practice

This study provides compelling evidence that ondansetron can reduce emesis after ketamine sedation; however, the effect is modest because 13 children must be treated to eliminate a single occurrence.

consent was obtained from all parents or guardians, as well as assent from all children 7 years of age or older, before enrollment into the study. The study was approved by the Colorado Multiple Institutional Review Board.

Setting

This study was conducted at a university-affiliated, urban children's hospital ED, which is a regional pediatric referral center and Level I trauma center. The annual census is 47,000 ED visits.

Selection of Participants

Inclusion criteria were patients between 1 year and 18 years of age who were American Society of Anesthesiologists I or II (either a normally healthy patient or a patient with a mild systemic disease)¹⁹ who received IV ketamine for an ED procedure. Exclusion criteria included patients with a concurrent vomiting illness; those with a previous adverse reaction to ketamine or ondansetron; those with a parent, guardian, or patient unwilling to provide informed consent; and those with contraindications for ketamine, such as hypertension, glaucoma or acute globe injury, increased intracranial pressure or central nervous system mass lesion, major psychiatric disorder, or porphyria.

Interventions

After giving informed consent, patients were randomized with a computer-generated random-number table, supplied by a statistician, within blocks of 8 and within strata determined by fasting status (less than or equal to 6 hours versus greater than 6 hours). This blocked-stratified randomization ensured that the arms of the study were balanced within each non per os stratum.

Patients received either ketamine 1 mg/kg IV (maximum single dose 100 mg) + ondansetron (0.15 mg/kg/dose; maximum dose 4 mg) or ketamine 1 mg/kg IV (maximum single dose 100 mg) + 2 ml normal saline solution IV (placebo). The ketamine and the study drug (either ondansetron or placebo) were administered at the same time but in separate syringes. The study drug order was sent to the pharmacy, where the randomization schedule was located. The pharmacist then prepared the study drug syringe, which contained either the ondansetron or the placebo of equivalent volume in a nondescript syringe that was then sent back to the ED labeled as "sedation study drug." The medical staff, parents, and patients were blinded to the contents of the "sedation study drug" syringe.

In addition, all patients received the antisialagogue glycopyrrolate 5 µg/kg (maximum dose 250 µg) administered simultaneously IV. Additional doses of ketamine alone were given at the discretion of the ED attending physician.

All patients were monitored after published sedation guidelines.²⁰⁻²³ Monitoring data were recorded at baseline, during the procedure (every 5 minutes), and postprocedure.

Methods of Measurement and Data Collection and Processing

Vomiting, time of medication administration, and time ready for discharge were observed and recorded by bedside nurses on a standard data collection sheet.

Parents or guardians were queried on completion of sedation about their level of satisfaction with sedation, from 1 (least satisfied) to 7 (most satisfied), using a Likert scale. Patients' parents or guardians were also contacted by telephone within 48 hours after discharge from the ED to determine whether vomiting occurred within 12 hours after discharge.

Outcome Measures

The primary outcomes in this study were vomiting in the ED and after discharge, as determined by telephone follow-up. Secondary outcome measures were length of ED stay and patient or parent satisfaction with their sedation. Length of ED stay was defined as the time the initial dose of ketamine was given until time ready for discharge. Discharge criteria were as follows: (1) airway patent with adequate oxygenation; (2) awake or easily aroused; minimal tactile or vocal stimulation may be necessary; (3) swallowing reflex present, demonstrating ability to swallow clear liquids while protecting the airway; (4) pre-sedation level of responsiveness achieved. Readiness for discharge was documented by the bedside nurse with the Vancouver Sedation Recovery Scale.²⁴ Patients achieving a score of 18 or higher were determined to be ready for discharge.

Primary Data Analysis

Differences between groups for categorical variables were analyzed with χ^2 testing. Differences between the treatment groups for continuous variables were analyzed with Mann-

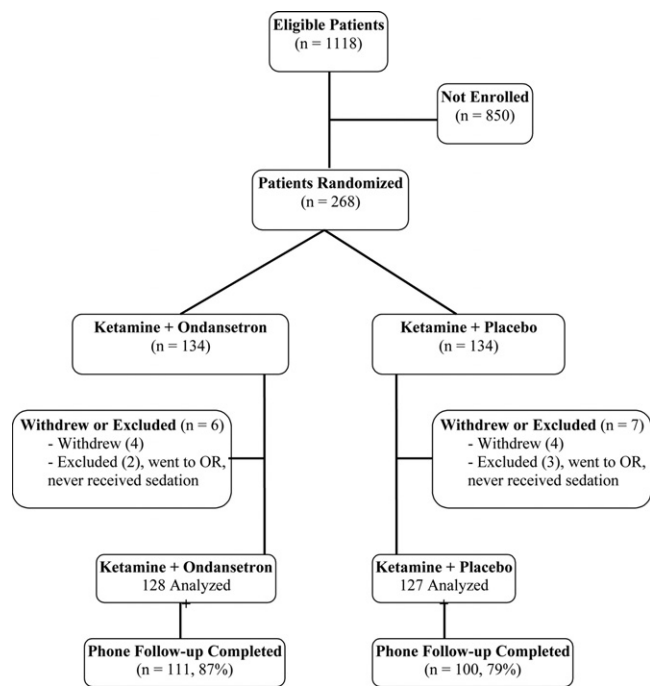


Figure. Patient flow diagram.

Whitney *U* testing. The number needed to treat, along with corresponding 95% confidence intervals (CIs), was calculated. Statistical analysis was performed with SPSS (version 14; SPSS, Inc., Chicago, IL).

A sample size calculation (assuming an $\alpha=0.05$, and a $\beta=0.20$) showed that 125 children in each group would permit detection of a decrease in vomiting from 17% to 5%.

RESULTS

This study was conducted from January 2003 to August 2005. Eligible and enrolled patients during the study period are shown on the patient flow diagram (Figure). Two hundred sixty-eight patients were randomized; 850 patients met criteria but were not enrolled because of parent or patient refusal or, more commonly, nonavailability of a research assistant to enroll patients during busy ED patient volume times. Characteristics of the enrolled patients are listed (Table 1).

Patients who received ondansetron were less likely to vomit than those who received placebo (Table 2). No patients experienced clinically apparent pulmonary aspiration.

Telephone follow-up was obtained for 211 of 255 (82.7%) patients. Some patients in both arms of the study vomited after discharge even if they did not vomit in the ED. Vomiting either in the ED or after discharge was less common with ondansetron (Table 2).

Given that vomiting seems more common in children aged 5 years or older,²⁵ a subgroup analysis of these older children was also performed and showed significant improvement with ondansetron (Table 3).

Length of ED stay was similar between groups: 90.6 minutes (range 29 to 321 minutes) in the ondansetron group versus 97.3

Table 1. Patient characteristics.

Characteristics	Ondansetron (n=128)	Placebo (n=127)
Age, y		
Mean	7.9	7.6
Range	1–17.4	1–17.9
Males: No. (%)	81 (63)	67 (53)
Fasting <6 h: No. (%)	70 (55)	71 (56)
Fracture reduction: No. (%)	98 (77)	89 (70)
Premedication narcotics: No. (%)	57 (45)	51 (40)
Total ketamine, mg/kg		
Mean	1.5	1.6
Range	0.5–5.2	0.66–5.0

minutes (range 25 to 325 minutes) in the placebo group, mean difference –6.7 minutes (95% CI –18.5 to 5.1 minutes).

Parental or guardian satisfaction of sedation was documented in 105 of 128 (82%) patients in the ondansetron arm and 106 of 127 (83%) in the placebo arm, and the results were similar between groups: median satisfaction score was 7 (range 3 to 7) in the ondansetron group versus 7 (range 1 to 7) in the placebo group, Mann-Whitney $P=.49$.

LIMITATIONS

This study has several important limitations. Because of our inability to enroll consecutive patients in a busy ED, this work represents a convenience sample of patients. Failure to enroll all eligible patients makes this study susceptible to selection bias. As a result of our sample size, the 95% CI for the number needed to treat is relatively wide, suggesting the true effect may be larger or smaller. In addition, although telephone follow-up was obtained for almost 83% of patients, those not contacted could have experienced vomiting after discharge, which is not reflected in our results. If all of the patients not contacted in the ondansetron group ($n=17$) had vomited and none of the patients in the placebo group ($n=27$) had vomited, then the difference between the groups would have been much closer ($23/128=18\%$ ondansetron versus $16/127=13\%$ placebo). Also, ketamine was administered by the IV route only in this study. Previous studies have shown higher rates of vomiting in children who received higher doses of ketamine intramuscularly.^{2,11} Differences detected in the ability of ondansetron to prevent vomiting in this study may have been different had patients who received ketamine intramuscularly been included.

Most important, the external validity of this study may be limited as a result of the wide range of vomiting rates reported in previous studies (3.8% to 18.7%).^{1,2,5-11} Physicians at institutions with low rates of vomiting associated with ketamine may be less inclined to pretreat patients with ondansetron. Institutional variations in vomiting rates limit the generalizability of these results.

DISCUSSION

Previous studies of IV ketamine in the ED have reported a wide range of vomiting (3.8% to 18.7%), with research from

Table 2. Vomiting in the ED and after discharge.

Vomiting in the ED	Ondansetron (n=128)	Placebo (n=127)	Difference, % (95% CI)	NNT (95% CI)
Number of patients (%)	6 (4.7)	16 (12.6)	7.9 (1.1–14.7)	13 (7–91)
Vomiting either in the ED or after discharge	(n=111)	(n=100)		
Number of patients (%)	10 (7.8)	24 (18.9)	11.1 (2.7–19.5)	9 (5–36)

NNT, Number needed to treat.

Table 3. Vomiting in the ED and after discharge: aged 5 years or older.

Vomiting in the ED	Ondansetron (n=95)	Placebo (n=85)	Difference, % (95% CI)	NNT (95% CI)
Number of patients (%)	6 (6.3)	16 (18.8)	12.5 (2.8–22.7)	8 (5–34)
Vomiting either in the ED or after discharge	(n=85)	(n=68)		
Number of patients (%)	9 (9.5)	20 (23.5)	14.0 (3.2–25)	7 (4–30)

our institution reporting 9.3% to 18.7%.^{2,11,26} In addition, some children (3.6% to 9.1%) who do not vomit in the ED do vomit after discharge.^{2,11} Because of these relatively high rates of vomiting, we sought to determine whether the addition of the antiemetic drug ondansetron could decrease or prevent vomiting associated with ketamine.

Several factors may influence vomiting rates at our institution. Although 2 previous studies found no association between preprocedural fasting times and the incidence of adverse events such as vomiting,^{27,28} we sought to eliminate the effects of this potential confounder by block randomization of patients by length of fasting. Other studies have found increased vomiting associated with increasing patient age²⁵ and less vomiting in patients who also received atropine for hypersalivation.¹⁰ Regardless of the cause of differing vomiting rates, others have found rates similar to ours.^{9,10} Our results suggest that for children who receive IV ketamine, the addition of ondansetron decreases vomiting in the ED and after discharge. The clinical significance of this finding remains to be determined. Our patients who received placebo did not experience an increased length of ED stay, nor was there a significant difference in parental satisfaction between the 2 groups. These findings do not support aggressive measures to prevent vomiting associated with ketamine. However, in the subset of children aged 5 years and older, the addition of ondansetron was associated with an even greater reduction in vomiting, and these higher-risk patients appear more likely to benefit from this intervention.

Orally administered ondansetron was not available during this study. However, with its known effectiveness in the ED¹² and its increased availability and use, oral ondansetron administration may also be considered as a prophylactic medication with ketamine, particularly when given intramuscularly. Considering that oral ondansetron was not studied, final recommendations on its use cannot be made.

In summary, we found that children administered IV ondansetron before IV ketamine experienced a significantly reduced incidence of vomiting. Because the administration of ondansetron did not significantly affect length of ED stay or parental satisfaction with sedation and the number of patients

needed to treat to prevent a single episode of vomiting was relatively high, the clinical applicability of this practice remains in question. Patients aged 5 years and older may benefit the most from the intervention. As the cost of ondansetron decreases, those sites that experience higher rates of vomiting may consider pretreatment with ondansetron with ketamine, especially for children aged 5 years and older.

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Author contributions: WTL, JEW, and MGR conceived of the study and designed the trial. WTL and JEW supervised data collection. LB provided statistical analyses of the data. MR drafted the article, and all authors contributed to its revision. JEW takes responsibility for the paper as a whole.

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CORRECTION NOTICE

In the April 2008 issue, in abstract 22 by O'Connor, Sabbaj, and Fu ("Changes in Oxygen Saturation and Optic Nerve Sheath Diameter Help Predict Acute Mountain Sickness in Individuals at High Altitude"; pages 477-478), on page 478, under "Results," "For every 2mm increase in ONSD. . ." should have said, "For every 0.2mm increase in ONSD. . ." and ". . .and for every 5mm increase in ONSD" should have said, ". . .for every 0.5mm increase in ONSD."