RESEARCH PAPER

Single-dose Intravenous Ondansetron in Children with Gastroenteritis: A Randomized Controlled Trial

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Objective: To evaluate the efficacy of ondansetron for the treatment of vomiting and thus reducing the need for intravenous (IV) rehydration in children with gastroenteritis.

Design: Double-blind, placebo-controlled, randomized trial.

Setting: Pediatric ward of An Giang General Hospital, South Vietnam, between December 2013 and June 2014.

Participants: 61 inpatient children (age 11-60 mo) suffering from gastroenteritis with vomiting. Exclusion criteria were: underlying chronic conditions, immunodeficiency, malnutrition or history of allergy to ondansetron.

Intervention: Single bolus of IV ondansetron at a dose of 0.2 mg/kg or placebo.

Outcome measures: Proportion of patients who needed IV rehydration, proportion of patients with cessation of vomiting, amount of oral rehydration solution intake, duration of diarrhea and the length of hospital stay.

Results: After drug administration, 22 (73%) of the 30 patients in the ondansetron group had complete cessation of vomiting compared with 7 (23%) of the 31 patients in the placebo group (RR 0.32; 95% CI 0.16 to 0.63, *P*<0.001). 3 (10%) patients in the ondansetron group required IV rehydration as compared with 12 (39%) in the placebo group (RR 0.51; 95% CI 0.33 to 0.79, *P*=0.009). The median amount of oral rehydration solution intake in 24 hours was significantly greater in the ondansetron group (450 mL *vs* 350 mL, *P*=0.019).The duration of diarrhea and the length of hospital stay were not different between the two groups.

Conclusion: In hospitalized children having gastro-enteritis associated with emesis, ondansetron is effective in the cessation of episodes of vomiting and in lowering the rates of IV rehydration, without reducing the duration of diarrhea and hospital stay.

Keywords: *Acute diarrhea, Antiemetics, Therapy, Vomiting*.

Treatment of childhood diarrhea is by correction of fluid and electrolyte using oral rehydration therapy (ORT) or using intravenous (IV) fluids for severe cases [1]. Vomiting associated with gastroenteritis limits the success of ORT in children and increases the incidence of IV rehydration [2,3]. Augmentation of IV fluid therapy in the hospital increases the burden on staff and the cost of treatment [4].

Ondansetron is a safe and effective antiemetic in preventing vomiting induced by chemotherapy or radiation therapy in oncologic patients, as well as vomiting in postoperative patients [5-7]. When used orally in infants and children, few studies demonstrate improved success rate of ORT, a decreased need for IV rehydration, and decreased hospitalization rate [8,9]. In addition, ondansetron is generally well tolerated and appears to have minimal side effects [2,10].

We hypothesized that subjects receiving intravenous ondansetron would have further reduction in emesis, will tolerate ORT better, and would have a lower chance of requiring IV rehydration. The objective of this study was to evaluate the efficacy of IV ondansetron for the treatment of vomiting and thus reducing the need for IV rehydration in children with gastroenteritis.

METHODS

This double-blind, randomized, placebo-controlled clinical trial was performed between December 2013 and June 2014 in the Pediatric Ward of An Giang General Hospital, South Vietnam which serves as a catchment area of approximately 2.3 million people with approximately 10,000 pediatric patients annually. Consent forms were signed by the parents of guardians of all the children enrolled in the study. This study was approved by the Science and Technology Board of An Giang General Hospital.

The criteria for enrollment were: patients aged 11-60 months, admitted to the Pediatric ward with acute

diarrhea (>3 stools in 24 hours), no blood in feces, mild to moderate dehydration, three or more episodes of vomiting in the previous 4 hours, and not having received any antiemetics. Patients were excluded if they had underlying chronic conditions (*e.g.*, malignancy, gastroesophageal reflux, congenital heart diseases), immunodeficiency, malnutrition, history of allergy to ondansetron or severe gastroenteritis requiring immediate IV rehydration.

The sample size was calculated on the basis of study by Roslund, *et al.* [11] who documented a 34% reduction in IV fluids in ondansetron group. For 80% power and α error of 5%, sample size of 31 subjects in each group was required.

The random number sequence was generated in Excel. The treatment assignments were concealed in opaque, sealed envelopes. After all inclusion and exclusion criteria were checked, and informed consent obtained, the study physician opened the envelope to determine which treatment the subject would receive.

The intervention group was given Ondansetron (Prezinton, Ferron Par Pharmaceuticals, Indonesia) calculated to provide a dose of 0.2 mg/kg (maximum of 8 mg) or an equal volume of 0.9% saline solution. The appearance of ondansetron was indistinguishable from that of 0.9% saline. After allocation, the contents of the syringe were administered intravenously over 2 minutes before start of oral rehydration salt (ORS) therapy. In order for study to comply with double-blinding, both drug and placebo were provided in the same volume (10 mL) in syringes, with code numbers, by a clinical pharmacist.

After drug administration, children were given (ORS) as prescribed by WHO (Oresol solution; sodium citrate 2.9 g, potassium chloride 1.5 g: sodium chloride 2.6 g and glucose 13.5 g). ORS was given 0.5 mL/kg every 2 minutes with a spoon, glass or cup. After every 4 hours, a treating physician re-evaluated the level of dehydration and the amount of ORS consumed. Rehydration was considered adequate when the child consumed ≥40 mL/kg of ORS solution.

Children with features of severe dehydration or shock any time during assessment, appearance of convulsion or altered sensorium during ORT were shifted to IV fluid therapy. Children with signs of persistent vomiting and dehydration after 4 hours of ORS therapy received IV rehydration at the discretion of the treating physician.

During hospital stay, nurses and physicians closely monitored the symptoms of vomiting, diarrhea, fever, ORS intake, signs of dehydration and adverse effects of drug. Patients were discharged after the cessation of emesis and diarrhea (<2 times/day).

The primary outcome was the frequency of patients who needed IV rehydration. The secondary outcomes were the frequency of patients with cessation of vomiting after 4 hours, the number of vomiting episodes at 4, 8 and 24 hours after drug/placebo administration, the amount of oral rehydration solution intake in 4 and 24 hours, number of diarrhea episodes, duration of diarrhea, length of hospital stay, and adverse effects of ondansetron. Episodes of vomiting separated by no more than two minutes were counted as a single episode. Non-productive retching, spilling of oral contents, and drooling were not considered vomiting. All patients were monitored for the adverse reactions of ondansetron such as headache, dizziness, extrapyramidal symptoms, skin allergies, cardiovascular symptoms and others. Cardiac monitoring was not used in detecting the cardiac rhythm abnormalities.

Statistical analysis: For categorical variables, the Chi-square test was used or Fisher's exact when the expected values in any of the cells of a contingency table are below 5. For continuous variables, Student's *t* test or the Mann-Whitney U test was used depending on the validity of the normality assumption. Analyses were performed with SPSS software (version 22.0). *P* value of less than 0.05 was considered to indicate statistical significance.

RESULTS

During the study period, 62 patients diagnosed as acute gastroenteritis (AGE) by the treating physicians in the pediatric ward were recruited. One child left the hospital after allocation to the ondansetron group. Out of the remaining 61 patients (35 males), 30 patients in ondansetron and 31 patients in the placebo group, were included in the per protocol analysis.

The median age of patients was 16 (range 11-54) months. The baseline characteristics of the patients in the two groups are presented in ***Table* I**. Overall, there were no differences in gender, age, body weight, proportion of fever, grade of dehydration between the two groups. Before patient enrolment, the median number of episodes of vomiting in the previous 4 hours and episodes of diarrhea in the previous 24 hours were also not different between the two groups (***Table* I**).

After drug administration, 22 (73%) of the patients in the ondansetron group had complete cessation of vomiting, compared with 7 (23%) in the placebo group. For patients who continued to have vomiting, the median number of episodes of vomiting was significantly lower among children who received ondansetron than among those who received placebo at 4 h (0 *vs*. 1, $P<0.001$), 8 h

TABLE I BASELINE CHARACTERISTICS OF THE PATIENTS ENROLLED IN TRIAL

Characteristic	*Ondansetron group (N=30)*	*Placebo group (N=31)*	*P value*
Male sex	20 (67%)	14 (45%)	0.091
Age (mo)**	14 (11-53)	17 (12-54)	0.128
Body weight (kg)*	10.8 (2,8)	10.7 ± 1,7	0.836
Fever ≥38^{0}C	19 (63%)	19 (61%)	0.869
Vomiting episodes in preceding 4 h**	4 (3-8)	4 (3-11)	0.582
Diarrhea episodes in preceding 24 h**	6 (4-20)	8 (3-15)	0.544
Dehydration grade			
Mild	26 (87%)	27 (87%)	
Moderate	4 (13%)	4 (13%)	0.960

*Values in n(%), *mean (SD) or **median (range).*

(0 *vs*. 1, *P*<0.001) and 24 h (1 *vs*. 3, *P*<0.001) after drug administration (***Table* II**).

The median amount of ORS consumption was significantly greater in the ondansetron group in 4 h (250 mL *vs*. 190 mL, *P*<0.001) and in 24 h (450 mL *vs*. 350 mL, *P*=0.019) (***Table* II**). Three children in the ondansetron group (10 percent) and 12 in the placebo group (39 percent) received IV rehydration (RR was 0.51; 95% CI 0.33 to 0.79; *P*=0.003).

The number of diarrhea episodes, duration of diarrhea and the length of hospital stay were not statistically different between the ondansetron and the placebo group (***Table* II**). There were no cardiovascular, respiratory and dermatological side effects. One patient in the ondansetron group had perspiration 30 minutes after administration of ondansetron; blood glucose test was in normal range.

DISCUSSION

In this study, we found that children receiving a single dose (0.2 mg/kg) of IV ondansetron had fewer episodes of vomiting up to 24 hours post-administration. Our findings are consistent with an earlier study [12], which reported that a single IV dose of ondansetron (0.3 mg/kg) reduced number of vomiting episodes and maintained its antiemetic effect during 24-hour period. A recent meta-analysis [9] of 10 RCTs involving 1215 participants found that patients treated with oral ondansetron had higher frequency of vomiting-cessation up to 1 h after drug administration compared to placebo (RR, 1.49; 95% CI 1.17-1.89), but there was no difference between drug and placebo groups at 4, 24 and 48 hours.

TABLE II OUTCOMES IN TWO GROUPS ENROLLED IN THE TRIAL

Outcome	*Ondansetron (N=30)*	*Placebo (N=31)*	*P value**
Vomiting episodes at 4 h	0 (0-3)	1 (0 - 8)	<0.001
Vomiting episodes at 8 h	0 (0-10)	1 (0 - 10)	<0.001
Vomiting episodes at 24 h	1 (0 - 20)	3 (0-11)	<0.001
ORS intake in 4 h (mL)	250 (100-500)	190 (90-400)	<0.001
ORS intake in 24 h (mL)	450 (150-800)	350 (150-800)	0.019
Diarrhea episodes at 24 h	5 (2 - 18)	6 (1-18)	0.913
Duration of diarrheal symptoms (h)	66 (24-144)	72 (24-130)	0.632
Hospital stay (d)	4 (2-8)	4 (2-8)	0.828

Data are presented as median and range; Mann-Whitney U test.

Ondansetron treatment in previous studies has also showed that children vomited less often and tolerated ORT well. Freedman, *et al.* [13] showed that children who received ondansetron had greater oral intake (239 mL *vs*. 196 mL, *P*=0.001). Similarly, in a study of Indian children, Danewa, *et al.* [14] found that oral rehydration solution consumption was significantly more in the ondansetron group (645 mL *vs* 554 mL, *P*= 0.002). Lower rate of IV rehydration has also been reported in the pooled results from three previous RCTs [9], where 55% reduction in the use of IV therapy was shown in the ondansetron group compared with controls. However, all three previous studies used oral rather than IV ondansetron.

There were several limitations to this study. First, using a shorter time period, such as the presence of vomiting within the past 4 hours rather than during the prior 24 hours, may have identified children most likely to benefit from an antiemetic. Second, Use of WHO definition for dehydration might have induced some subjectivity. In our pediatric ward, when patients could not drink, the treating physician had a tendency to prescribe IV fluid sooner instead of using nasogastric rehydration. Third, the stool volume was not measured. Fourth, the treating physicians prescribed anti-diarrheal medications such as smectite or racecadotril for some patients, which could have affected the duration of emesis and diarrhea. Lastly, the sample size may have been inadequate to detect small differences in some outcomes, especially adverse effects.

In summary, single dose of intravenous ondansetron seems to be effective for the cessation of episodes of emesis and in lowering the rates of IV rehydration, without affecting the duration of diarrhea and hospital stay, in hospitalized patients with gastroenteritis associated with emesis.

WHAT IS ALREADY KNOWN?

- Oral ondansetron lowers the rates of intravenous rehydration in patients with vomiting due to acute gastroenteritis.in Emergency Department

WHAT THIS STUDY ADDS?

- Single dose of intravenous ondansetron increases and prolongs the efficacy for the treatment of emesis and reduces the frequency of intravenous rehydration in hospitalized patients with gastroenteritis.

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