Original Article

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Effect of Oral Ondansetron on Decreasing the Vomiting Associated with Acute Gastroenteritis in Iranian Children

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Abstract

Objective: The aim of this study was to determine the effect of oral ondansetron in decreasing the vomiting due to acute gastroenteritis in children.

Methods: In a single center, randomized, double blind, controlled trial, the effect of oral ondansetron was compared with placebo on 176 patients between 1 and 10 years old with acute gastroenteritis. 30 minutes after drug administration, oral rehydration therapy (ORT) was initiated. Severity of vomiting was evaluated during emergency department (ED) stay and 48 hours follow up. Data were collected and analyzed by SPSS16.

Findings: Fifty two of children (58.5%) were males with the mean age of 3.12 (±2.30) years. Ten patients in ondansetron and 14 in placebo group had persistent vomiting during ED stay. After analyzing, there was no significant relation between vomiting in 4 and 48 hours and need for intra venous fluid therapy between the two groups although ondansetron generally decreased ORT failure (P=0.03).

Conclusion: Although administrayion of oral ondansetron in gastroenteritis could decrease failure of ORT, it seems that further well-conducted clinical studies are needed to determine effects of oral ondansetron precisely.

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Key Words: Ondansetron; Acute Gastroenteritis; Vomiting; Oral Rehydration Therapy

Introduction

Acute gastroenteritis (AGE) is one of the most common diseases in children, and the second leading cause of morbidity and mortality worldwide[1]. In the United States, gastroenteritis accounts for more than 1.5 million pediatric outpatient visits and 200,000 hospitalizations annually[2]. Current recommendations for the treatment of acute gastroenteritis focus primarily on the correction of dehydration and electrolyte abnormalities. Oral rehydration is safe and effective and is the preferred therapy in mild to moderate dehydration, whereas intravenous fluids are recommended in more severe cases[3].

Vomiting is a common symptom in children with gastroenteritis, but its treatment remains controversial[4]. In the clinical practice antiemetic drugs are frequently used in children with gastroenteritis. A recent retrospective survey retrieved data from 4 national and international databases showed that prescription of antiemetic medication varied considerably[5].

It is also a controversial topic in treatment of pediatric gastroenteritis. Antiemetics are commonly prescribed by physicians[6], in

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particular, between 2% and 23% of children with gastroenteritis received prescriptions for antiemetic medications[7] and many physicians believe that vomiting is a contraindication to oral rehydration therapy (ORT)[8].

Multiple medications have been used in an attempt to limit vomiting and facilitate oral rehydration but have not gained acceptance, because of their limited success and high rates of complicating adverse effects[9]. According to previous studies administering promethazine, prochlorperazine, and metoclopramide can cause extrapyramidal reactions, lethargy, respiratory depression, and cardiac dysrhythmias[2,10,11]. Ondansetron is a 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonist which has been documented to be an effective anti-emetic in preventing and treating Postoperative nausea and vomiting (PNOV) with few side effects[12].

Orally disintegrating ondansetron has been shown to be effective in preventing chemotherapy induced nausea and vomiting[13,14]. It has an excellent safety profile and is well tolerated by patients[15]. Recently ondansetron has been studied for a possible use in acute gastroenteritis in children. Although it has shown great effectiveness in reducing vomiting when compared with other antiemetic drugs or placebo, it causes an increased incidence of diarrhea. Literature documenting ondansetron usage in gastroenteritis is limited and most studies focus on its application as an intravenous medication.

The aim of this study was to determine the effect of oral ondansetron in decreasing the vomiting due to acute gastroenteritis in children.

Subjects and Methods

Our study was double-blind, randomized, placebo-controlled clinical trial to compare the effect of a single dose oral ondansetron and placebo in decreasing vomiting due to acute gastroenteritis in children. We attempted to determine whether the use of oral ondansetron would facilitate ORT tolerance in dehydrated vomiting children with gastroenteritis and decrease the need for intravenous rehydration therapy. This investigation was conducted in the emergency department of Children's Hospital in Rasht, Iran between September 1, 2010 and March 1, 2011. The Ethics Committee of Guilan University of Medical Sciences approved the study.

We hypothesized that patients receiving ondansetron would tolerate ORT by oral rehydration solution (ORS) better than patients receiving placebo and lower proportion of them would require intravenous hydration therapy.

We enrolled a sample of patients with the clinical diagnosis of acute gastroenteritis and dehydration. All children with symptoms of gastroenteritis were screened for eligibility by the supervising physician. Specific inclusion criteria were: age between 1 and 10 years, clinical presentation of simple acute gastroenteritis, dehydration, onset of disease in preceding 24 hours prior to the study, at least one episode of vomiting in previous 6 hours, no fever or low grade fever (less than 38.2 °C). Exclusion criteria included: any antiemetic drug usage in last 24 hours, any chronic disease, and alarming signs such as headache, abdominal distention, severe dehydration or shock, severe diarrhea more than one episode in one hour, any previous unfavorable response to $5HT_3$ receptor inhibitor drugs and any other situation in which ORT is not recommended.

After enrollment demographic features and clinical data like patient's name, age, sex, weight, height and telephone number were recorded. We used the World Health Organization protocol (The Treatment of Diarrhea, A manual for physicians and other senior health workers) to classify severity of dehydration and treat patients with ORS which was one of the main differences in our study because of extent of application in many developing and developed countries, our local policy and its feasibility for outpatient setup (Table 1).

The patients were randomized in two groups by computer randomization using a block of two, to receive ondansetron or placebo. Also investigators were blinded to group assignment until after complete statistical analysis (Fig. 1). The oral ondansetron and the placebo tablets were 4 mg tablets provided by Tehran Chemie Pharmaceutical Company and dissolved in 2 cc water. Drug dosing was weight based in which children less than 15 kg received 2 mg (½ tablets), children between 15 to 30 kg received 4 mg (1 tablet) and more than 30 kg received 6 mg (1.5 tablets).

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Table 1: Approximate amount of oral rehydration therapy to give in the first 4 hours[16]

Age	Less than 4 months	4– 11 months	12– 23 months	2 – 4 years	5 – 14 years	15 years or older
Weight	Less than 5 kg	5-7.9 kg	8-10.9 kg	11-15.9 kg	16-29.9 kg	30 kg or more
In ml	200-400	400-600	600-800	800-1200	1200-2200	2200-4000

Thirty minutes after the medication was given, ORT was initiated and continued based on the WHO recommendations on ORT. If they tolerated the ORS and vomiting did not occur during oral rehydration therapy, treatment was considered successful, but if vomiting occurred and continued, treatment was considered unsuccessful and patient was hospitalized and underwent treatment with intravenous fluids based on hospital protocol.

Again After 4 hours, the physician evaluated those who tolerated oral rehydration therapy and discharged them based on WHO guidelines.

After 48 hours, investigator called the child`s family and asked whether the child had any vomiting episode, was brought to an emergency department, had received intravenous fluid treatment or had any additional symptoms.

Our primary outcome was the proportion of subjects receiving ondansetron versus placebo who had vomiting episodes during 4 hours of ORT initiation and also 48 hours after discharge. We hypothesized that because of stopped vomiting, subjects receiving ondansetron would tolerate ORT better than subjects receiving placebo and then lower proportion of them would require intravenous rehydration therapy in 4 and 48 hours. Secondary outcome included those subjects who were hospitalized.

Comparative analysis entailed calculating the relative risk plus 95% confidence interval for dichotomous outcomes, the mean difference (plus 95% confidence interval) for normally distributed continuous outcomes, and the median difference plus 95% confidence interval) for skewed continuous variables. To account the number of comparisons 99% confidence intervals were used for subgroup analyses. *P* value less than 0.05 was considered to indicate statistical significance.

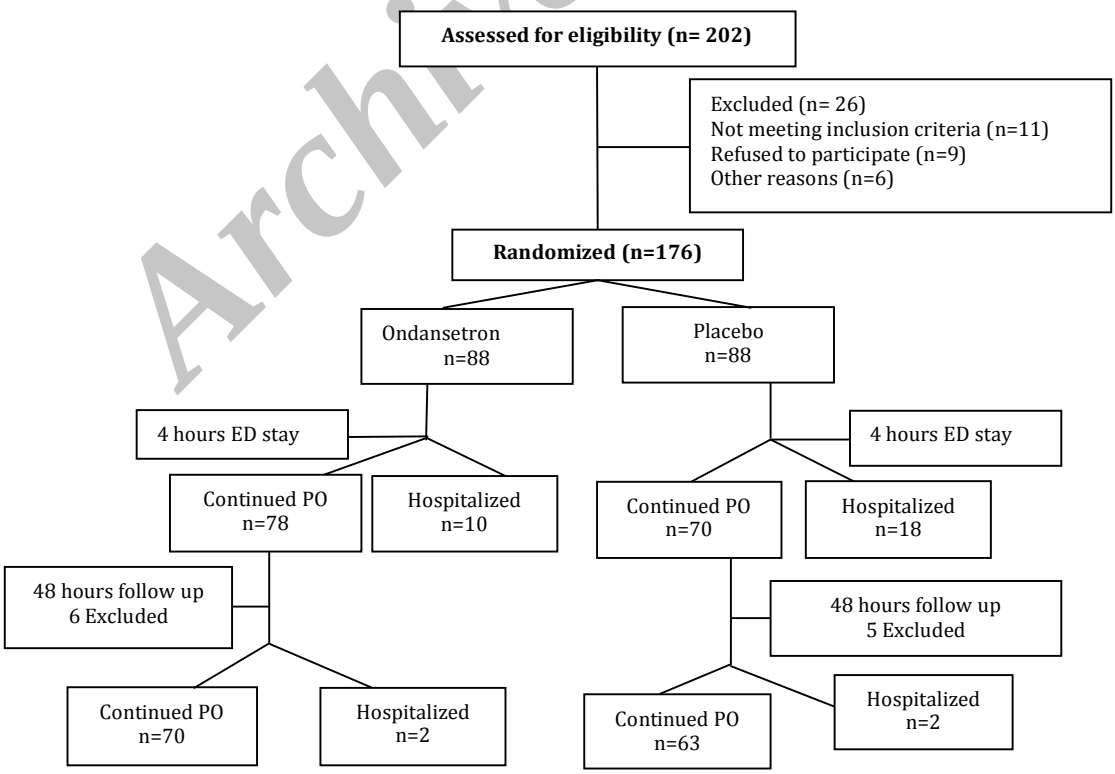

Fig. 1: Enrollment and outcomes

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Findings

During the study period, 202 patients aged 1 to 10 years were approached for study enrollment and 176 eligible patients were randomly assigned to two treatment groups. 88 patients were randomized in ondansetron and 88 in placebo group (Fig. 1).

Eleven cases of 176 patients did not contribute to 48-hour follow up. Therefore, 165 patients were included in data analysis as an intention-to-treat analysis. Of the 176 patients, 58.5% were males and 11 cases of 176 patients who did not contribute 41.5% were females with a mean age of 3.12 years (±2.30) (Table 2).

Table 3 shows primary outcome of the participants in this study in ondansetron and placebo. According to primary outcome, 10 patients in ondansetron and 14 in placebo group had persistent vomiting during ED stay. Twenty two and 31 patients in ondansetron and placebo groups experienced persistent vomiting during 48 hours follow up respectively. Failure of ORT in ondansetron and placebo groups was respectively 13.6% and 28.9%, which showed significant relation in both groups (*P*=0.04). Furthermore, results showed significant relation between failure of re-hydration therapy during 6 hours after diarrhea and vomiting initiation in both groups (*P*=0.03) and secondary outcomes in both groups showed no significant difference (Table 4).

According to Binary Logistic Regression test, sex, age, weight, first vomiting and diarrhea had no effect on failure of ORT (Table 5). More ever in ondansetron and placebo group, no evidence of complications such as headache, vertigo, dermal rash were reported and there were no significant differences with regard to diarrhea and constipation between the two groups.

Discussion

Ondansetron is a 5-HT3 receptor antagonist which has been documented to be an effective anti-emetic in preventing and treating PNOV with few side effects[12]. Orally disintegrating ondansetron has been shown to be effective in preventing chemotherapy induced nausea and vomiting[13,14]. In 1997, Cubeddu was the first to demonstrate the antiemetic effect of ondansetron in AGE[17].

Although In developed communities children with severe dehydration are routinely admitted for intravenous therapy[18] and ondansetron's

Table 2: Demographic variables of participants in ondansetron and placebo groups

Parameter			Ondansetrone (n=88)	Placebo (n=88)	*P.* value
Sex		Male female	52 36	51 37	>0.05
Age	**groups (years)**	≤2 2-3 3-4 4-5 5-10	49 14 7 7 11	39 19 12 7 11	>0.05
	mean (±SD)	2.30 (3.12)			
Weight (kg)	**groups**	≤10 10-20 ≥20	12 60 16	8 65 15	>0.05
	mean (± SD)	5.10 (16.13)			
Beginning of diarrhea and vomiting	**groups**	≤6 6-12 12-18 18-24	9 51 21 7	9 53 18 8	>0.05
	mean (± SD)	4.08 (11.49)			
No. of vomiting episodes in preceding 6 h	**group**	1-4 5-8 ≥9	36 46 6	34 50 4	>0.05
	mean (± SD)	2.11 (5.42)			

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Table 3: Primary outcomes of the study of the study in the ondansetron and placebo groups

Outcome			Ondansetron	Placebo	*P.* value
No of vomiting episodes during ED stay (4 hours)		Persistent vomiting	10	14	>0.05
		Vomiting cessation	78	74	
No of vomiting episodes during 48 hours follow-up		Persistent vomiting	22	31	>0.05
		Vomiting cessation	60	52	
Failure in oral re-hydration therapy		Fail	12	24	0.04
		Success	70	59	
Failure in oral re-hydration therapy according to sex	Male	Fail	7	18	0.01
		Success	44	31	
	Female	Fail	5	6	>0.05
		Success	26	28	
Failure in oral re-hydration therapy according to age range	≤2 yr	Fail	7	9	>0.05
		Success	37	28	
	2-3 yr	Fail	2	9	0.047
		Success	11	9	
	3-4 yr	Fail	1	4	>0.05
		Success	6	8	
	4-5 yr	Fail	1	1	>0.05
		Success	6	6	
	5-10 yr	Fail	1	1	>0.05
		Success	10	8	
Failure in oral re-hydration therapy according to weight	≤10 kg	Fail	3	1	>0.05
		Success	8	7	
	10-20 kg	Fail	6	21	0.004
		Success	49	40	
	≥20 kg	Fail	3	2	>0.05
		Success	13	12	
Beginning of diarrhea and vomiting	≤6	Fail	0	4	0.03
		Success	9	4	
	6-12	Fail	6	14	0.08
		Success	40	36	
	12-18	Fail	4	4	>0.05
		Success	17	14	
	18-24	Fail	2	2	>0.05
		Success	4	5	
No. of vomiting episodes in preceding 24 h	1-4	Fail	1	5	>0.05
		Success	32	28	
	5-8	Fail	8	15	>0.05
		Success	35	31	
	≥9	Fail	3	4	>0.05
		Success	3	0	

efficacy as an intravenous antiemetic is well documented, its effect as an oral antiemetic drug is controversial yet.

In our study results showed that ondansetron decreases failure in ORT that was similar to Freedman et al results which showed that a single dose of ondansetron improves the success of oral rehydration in dehydrated children with gastroenteritis. The oral dose was well tolerated and resulted in a reduction of more than 50 percent in both the proportion of children who vomited during oral rehydration and the proportion treated with intravenous fluids[19]. In addition, Roslund demonstrated an improved

Table 4: Secondary outcomes of the study in the ondansetron and placebo groups

Outcome		Ondansetron	Placebo	*P.* value
Hospitalization during ED stay (4 hours)	Hospitalized	10	18	>0.05
	Out-patient	78	70	
Hospitalization during 48 hours follow up	Hospitalized	2	2	>0.05
	Out-patient	70	63	

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Table 5: Effect of confounding factors on failure of oral rehydration therapy by regression logistic

Parameter	Exp (β)	S.E	*P*. value	EXP (B)	CI 95%
Age range	0.17	0.25	0.498	1.18	0.72-1.93
Sex	0.092	0.49	0.851	1.09	0.41-2.86
Weight range	0.027	0.53	0.96	1.02	0.29-3.54
Beginning of vomiting and diarrhea	0.62	0.38	0.103	1.87	0.88-3.99

CI: confidence interval; SE: Standard error

success rate of ORT and a decreased need for intra venous fluid in patients with AGE treated with a single dose of oral ondansetron[20].

Furthermore, in this survey results showed no difference of vomiting episodes during ED stay and 48-hour follow up in the two groups and no significant reduction in hospital admissions in ondansetron group. However, Roslund et al and Freedman et al demonstrated fewer vomiting episodes in the ondansetron group and both demonstrated a slightly lower admission rate in the ondansetron group[19]. Also, Ramoosk found that patients receiving ondansetron had significantly fewer emetic episodes (*P*=.001) and most of them did not vomit at all during the initial observation period in the emergency department (87% versus 65%, *P*=.004); on the other hand, a statistically significant difference was not found during a 48-hour follow-up period. In the ondansetron group, there were fewer admissions and shorter length of stay in hospital[21].

According to previous studies traditional antiemetics such as promethazine, prochlorperazine, and metoclopramide reveal limited success and high rates of complicating adverse effects such as extra pyramidal reactions, lethargy, respiratory depression, and cardiac dysrhythmias[2,10,11].

Ondansetron was well tolerated in our study sample, and as mentioned, no evidence of complications was reported in ondansetron group. Only diarrhea and constipation was reported in both groups which showed no significant difference between groups during the ED stay and in the 48 hours after ED discharge. Freedman et al reported a statistically significant increase in diarrhea during the ED stay in patients treated with ondansetron but did not evaluate the incidence of diarrhea during follow-up[19]. Furthermore, Ramsook et al did not detect a difference in diarrheal episodes during the ED stay but reported a statistically significant increase in diarrheal episodes in the 48 hours after ED discharge[21]. More diarrheal episodes were also reported in the 24 hours after drug administration in the ondansetron group by Cubeddu et al[17]. Neither Roslund et al nor Reeves et al detected a difference in diarrheal episodes among study groups during five to seven days after ED discharge[20,3].

Conclusion

According to results mentioned which revealed decreased failure of ORT by administering oral ondansetron in gastroenteritis and no significant difference between groups regarding complications, and while ondansetron tablet is easy to administer, has few side effects, and is safe and effective, it can be a useful therapy in the emergency department for children with vomiting and mild-to-moderate dehydration as a result of gastroenteritis.

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Conflict of Interest: None

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