Oral Ondansetron in Management of Dehydrating Diarrhea with Vomiting in Children Aged 3 Months to 5 Years: A Randomized Controlled Trial

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Objectives To evaluate the role of oral ondansetron in facilitating successful rehydration of under-5-year-old children suffering from acute diarrhea with vomiting and some dehydration.

Study design Children (n = 170) aged 3 months to 5 years with acute diarrhea with vomiting and some dehydration were enrolled in this double blind, randomized, placebo-controlled trial. The participants were randomized to receive either single dose of oral ondansetron (n = 85) or placebo (n = 85) in addition to standard management of dehydration according to World Health Organization guidelines. Failure of oral rehydration therapy (ORT), administration of unscheduled intravenous fluids, and amount of oral rehydration solution intake in 4 hours were the primary outcomes. Secondary outcome measures included duration of dehydration correction, number of vomiting episodes, adverse effects, and caregiver satisfaction.

Results Failure of ORT was significantly less in children receiving ondansetron compared with those receiving placebo (31% vs 62%; $P < .001$; relative risk 0.50, 95% CI 0.35-0.72). Almost one-half of the children in the ondansetron group received intravenous fluids compared with those in the placebo group, but it was not statistically significant ($P = .074$; relative risk 0.56, 95% CI 0.30-1.07). The oral rehydration solution consumption was significantly more in the ondansetron group (645 mL vs 554 mL; mean difference 91 mL; 95% CI: 35-148 mL). Patients in the ondansetron group also showed faster rehydration, lesser number of vomiting episodes, and better caregiver satisfaction.

Conclusion A single oral dose of ondansetron, given before starting ORT to children <5 years of age with acute diarrhea and vomiting results in better oral rehydration. *(J Pediatr 2015;■:■-■).*

Trial registration Clinical Trial Registry of India: CTRI-2011/07/001916.

Diarrheal illnesses are the leading cause of death beyond infancy in developing countries.[1] Oral rehydration therapy (ORT) with oral rehydration solution (ORS) remains the cornerstone of appropriate case management of diarrheal dehydration but, unfortunately, is grossly underused.[2-4] Data from periodic National Surveys from India report that less than one-half of children use ORS during an episode of diarrhea.[2-4] Many health care providers perceive vomiting a barrier to success of ORT.[3,5] Vomiting in children suffering from acute gastroenteritis may interfere with oral rehydration process, and frustrates parents and health care providers.[6] This prompts health care providers to use intravenous fluids even when these may not be indicated. Trials in developed countries have suggested benefit of anti-emetics like domperidone, metoclopramide, promethazine, and ondansetron in acute gastroenteritis, when vomiting is a major symptom.[5-7] However, there is a paucity of literature addressing functional outcomes such as failure of ORT and use of unscheduled intravenous fluids related to anti-emetic use in these studies. As the etiological and clinical profile of diarrhea, caregivers' expectations, and the management practices differ significantly in developing countries, we planned this study to evaluate the role of oral ondansetron in successful rehydration of under-5-year-old children suffering from acute dehydrating diarrhea in the setting of a hospital catering mainly to urban poor population in Northern India.

Methods

This double-blind randomized placebo-controlled trial was carried out in the emergency pediatric unit of a tertiary care hospital over a period of 1 year. Approval was provided by the institutional ethical committee.

Study participants included children aged between 3 months and 5 years with a clinical diagnosis of acute diarrhea (duration <14 days) with some dehydration as per World Health Organization (WHO) criteria,[8] and at least 2 reported

ORS	Oral rehydration solution
ORT	Oral rehydration therapy
WHO	World Health Organization

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The drug (ondansetron) was supplied by Mankind Pharma Ltd, and the placebo was prepared in the Department of Pharmacology at University College of Medical Sciences. Mankind Pharma Ltd had no role in (1) study design; (2) the collection, analysis, and interpretation of data; (3) the writing of the report; or (4) the decision to submit the paper for publication. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.10.006

episodes of non-bilious, non-bloody vomiting within the last 6 hours. Children having severe malnutrition (weight for length/height <−3 SD of WHO standards), edema, unconsciousness, convulsions, or paralytic ileus were excluded. Paralytic ileus was defined as presence of abdominal distension, not passing stools, and diminished or absent bowel sounds. Children who had received any anti-emetic within 24 hour prior to enrollment, and those who received intravenous fluids before enrollment, were also excluded.

Computer-generated block randomization with variable block sizes was used to assign patients to the ondansetron or the placebo group. Bottles were coded with this randomization scheme by a person not directly involved with the study. Drug was supplied by a pharmaceutical company, and placebo (similar composition, except for the active ingredient) was prepared in the pharmacy of our hospital. Drug and placebo were identical in appearance, taste, and odor. Ten mL bottles were procured from the market, and drug and placebo were repackaged and labeled for the purpose of the study by the pharmacy of the hospital. Bottles were given a unique identification number according to the randomization scheme. Study subjects, their caregivers, person assigning intervention, doctors managing the patient, and outcome assessors were blinded to the content of formulation given. The codes were broken only at the end of the study after complete data entry and data cleaning.

Detailed clinical history, physical examination, and anthropometry were recorded in all patients. The child was assessed every 30 minutes for intake of amount of ORS, frequency of vomiting, frequency of loose stools, and hydration status; findings were recorded in a predesigned case record form. Hydration was assessed using WHO criteria and also by dehydration score devised by Freedman et al.[9]

Syrup ondansetron (2 mg/5 mL) or placebo was given orally in a dose of 0.5 mL/kg (providing 0.2 mg/kg of ondansetron in drug group) single dose at enrollment before start of ORS therapy. Exact doses of drug/placebo were measured with a syringe and administered to the patient with a spoon by one of the investigators. Same dose of drug/placebo was repeated once if the patients vomited within 30 minutes of receiving first dose. After receiving drug or placebo, children were given WHO ORS at the rate of 75 mL/kg in first 4 hours. ORS was given with a spoon or small sips frequently. A repeat course of 75 mL/kg of ORS over 4 hours was given to children who continued to have features of some dehydration after initial 4 hours of therapy. Children who had features of severe dehydration or shock any time during assessment, persistence of signs of some dehydration even after 8 hours of ORS therapy, or appearance of convulsions, altered sensorium, or paralytic ileus during ORS therapy were shifted to intravenous fluid therapy. Breastfed infants continued to breastfeed during oral rehydration. Other fluids were avoided during treatment. The study participants were admitted for at least 2 hours after dehydration correction. After dehydration correction, children were advised to take oral zinc (zinc acetate) in the dose of 10 mg/d for 3 months to 6 months age group and 20 mg/d in 2 divided doses for the 6 months to 5 years age group. Oral zinc was advised to be continued for a total duration of 14 days.

The primary outcome measures were failure of ORT (features of some dehydration persisting after 4 hours of ORT or severe dehydration at any time during assessment), administration of unscheduled intravenous fluids and amount of ORS intake in 4 hours. Secondary outcomes were duration of dehydration correction, number of vomiting episodes in 4 hours, adverse effects (eg, rash, headache, diarrhea), and caregiver satisfaction as assessed on a 5-point Likert scale[10] on the basis of mood, activity, alertness, comfort, number of vomiting, and fluid intake. Single caregiver, which was either mother or the one who was present with the child at that time, was assessed for caregiver satisfaction.

Sample size was calculated on the basis of study by Freedman et al[9] who documented 31% unscheduled intravenous fluid use in placebo group and a better ORS intake in ondansetron groups. Also, our hospital data suggested that almost 50% of under-5-year-old children with some dehydration require a second course of ORT (defined as failure of ORT for this study). Assuming a 50% reduction in failure of ORT in ondansetron group with 90% power and α of 0.05, sample size calculated was 77 children in each group. A sample size of 82 in each group was calculated to be sufficient to reduce the intravenous fluid use from an estimated 30%[9] to 10%, with 90% power and α of 0.05. For ORS intake, a sample size of 72 in each group was required to demonstrate 50 mL difference in ORS intake between the two groups with group SD of 92 mL[9] with 90% power and α of 0.05. We decided to enroll a total of 170 children (85 in each group) so as to be sufficient for these 3 primary outcomes.

SPSS version 17.0 (IBM, Armonk, New York) was used for data analysis. Frequencies of children who failed ORT, those requiring intravenous fluids, and those having at least 1 point to 2 points improvement in caregiver satisfaction scores were compared by χ^2 test. Mean (SD) amount of ORS intake and change in caregiver satisfaction scores after 4 hours were compared in two groups by Student t test. The duration of dehydration correction in each group was compared by Kaplan-Meier survival analysis censoring the cases at 8 hours if they fail to correct dehydration by that time. For children who needed intravenous fluids earlier than 8 hours or for subjects who withdrew from the study earlier, censoring was done at the last observation period.

Results

A total of 204 eligible children were screened during the study period (April 2011 to July 2011 was the initial period of procurement and repackaging of the drug, development of placebo, testing for similarity in color, taste, and smell, and designing randomization; patient enrollment occurred August 2011 to March 2012), out of which 34 were excluded. **Figure 1** (available at www.jpeds.com) shows the flow diagram of study and reasons for exclusion from study.

Table I. Comparison of baseline and anthropometric variables in ondansetron and placebo group

	Total (N = 170)	Ondansetron (N = 85)	Placebo (N = 85)
Age (mo), mean (SD)	15.3 (10.1)	15.5 (10.7)	15.0 (9.5)
Sex, N (%)			
Female	71 (41.8)	31 (36.5)	40 (47.1)
Male	99 (58.2)	54 (63.5)	45 (52.9)
Fever, N (%)	61 (35.9)	25 (29.4)	36 (42.4)
Duration of diarrhea before enrollment (d), Mean (SD)	2.2 (1.7)	2.0 (1.6)	2.3 (1.7)
Number of vomiting in last 6 h, mean (SD)	6 (2.6)	6 (2.6)	6 (2.6)
Dehydration score at admission (0 h)	12.8 (1.8)	12.5 (1.8)	13.1 (1.7)
Weight (kg), mean (SD)	8.6 (2.0)	8.7 (2.0)	8.6 (2.1)
Weight for age Z score, mean (SD)	−1.30 (1.05)	−1.29 (1.10)	−1.30 (1.01)
Height/length (cm), mean (SD)	74.3 (8.4)	74.5 (8.4)	74.2 (8.5)
Height for age Z score, mean (SD)	−1.23 (1.21)	−1.23 (1.25)	−1.24 (1.19)
Weight for height Z score, mean (SD)	−0.88 (1.34)	−0.95 (1.36)	−0.81 (1.34)
Mid-arm circumference (cm), mean (SD)	13.06 (1.20)	13.03 (1.45)	13.08 (1.05)

Most of the study participants were infants (60%) and a majority (93%) of them had watery diarrhea. The children in both groups were comparable for baseline variables such as anthropometry, duration of diarrhea, duration of vomiting, and dehydration score (Table I).

Table II shows the comparison of outcome variables among the drug and placebo group. Failure of ORT was almost one-half (30% absolute reduction) in children receiving ondansetron in comparison with those receiving placebo ($P < .001$, relative risk 0.50, 95% CI 0.35-0.72). Around 20% of study subjects needed intravenous fluids; the fluid requirement was seen in twice the number of children in the placebo group in comparison with the drug group. However, this did not reach statistical significance. The amount of ORS consumed in 4 hours was significantly more in children receiving ondansetron than those in the placebo group. Figure 2 (available at www.jpeds.com) depicts the survival function for the outcome of duration of dehydration correction. Median duration of dehydration correction was significantly less in children receiving ondansetron than placebo (4 h vs 6 h, $P < .001$). The mean number of vomiting episodes during 4 hours of observed ORT was also significantly less in children receiving ondansetron. Caregiver satisfaction in all fields (mood, activity, alertness, comfort, number of vomiting episodes, fluid intake) was better in the drug group compared with the placebo group (Table III; available at www.jpeds.com). Improvement by at least 2 points in score was seen in almost twice the number of parents in the drug group compared with the placebo group in all fields. The study participants were observed for adverse effects like headache, rash, or any other reported event, and no such adverse effect was seen. No increase in diarrheal episodes was seen with the use of anti-emetics.

Discussion

Diarrhea is one of the major causes of morbidity and mortality in children from the developing countries.[1] Many healthcare providers perceive vomiting as a barrier to successful execution of ORT. In our study, we found that a single oral dose of ondansetron resulted in significantly fewer children failing ORT, faster correction of dehydration, reduction of vomiting episodes, and better caregiver satisfaction, without any significant adverse event. The proportion of children receiving intravenous fluids was, however, not statistically different between the drug group and the placebo group.

The strength of the present study was the randomized, double blind, placebo controlled design, and evaluation of functional outcomes such as failure of ORT, receipt of intravenous fluids, duration of dehydration correction, and caregiver satisfaction. We did not limit ourselves to evaluation of cessation of vomiting as was done in some previous studies. The bias because of seasonal variation was minimized by continuous enrollment throughout the year, and by block randomization. We defined failure of ORT as "persistence of features of some dehydration after 4 hours of ORT." Varied definitions for failure of ORT have been used by different researchers in different studies[11,12]; persistence of some level of dehydration after completion of rehydration period is an acceptable definition.[11] As we used WHO guidelines for rehydration, which recommend a duration of 4 hours for

Table II. Comparison of outcome variables in ondansetron and placebo group

Outcome variable	Ondansetron (N = 84)	Placebo (N = 83)	*P* value	Relative risk (95% CI)
Failure of ORT, N (%)	26 (31.0)	51 (61.5)	<.001	0.50 (0.35, 0.72)
Intravenous fluid use, N (%)	12 (14.3)	21 (25.3)	.074	0.56 (0.30, 1.07)
ORS intake in 4 h (mL), mean (SD)	645 (193)	554 (175)	.002	91.3* (35.0, 147.6)
Number of vomiting in 4 h	1.8 (2.3)	3.6 (2.6)	<.001	−1.8* (−2.6, −1.1)

*Mean difference and 95% CI for outcome of ORS intake and number of vomiting in 4 h.

rehydration, we defined treatment failure as "some dehydration persisting after 4 hours of ORT." Receipt of intravenous fluids was a composite definition that depended on the clinical indications of intravenous fluids. Although these 2 outcomes are inter-related, we believed that though persistence of intravenous fluids after 1 full course (4 hours) of ORT may not be an indication for using intravenous fluids, it is an important functional outcome to be evaluated separately.

The main limitation of our study was the short duration of monitoring and lack of follow-up to know the revisit rate. We also did not investigate the etiology of diarrhea in our study. Use of WHO definition for dehydration might have induced some subjectivity; we utilized it for assessing the outcomes as it is the most widely used definition for management of diarrhea in our and similar settings. We could document an increase in ORS intake, but the results related to intravenous fluid use were not statistically significant. This could be because of less proportion (than estimated) of children requiring intravenous fluids, because of strict criteria used for administration of intravenous fluids. Moreover, we were looking at a larger difference in reduction of intravenous fluids use (30% to 10%), and our study may not be powered enough to detect smaller (may still be clinically meaningful) difference. The sample size was too small to evaluate rare adverse effects due to drug.

The direction of the results of our study was comparable with that reported in the Cochrane review[13] on the role of anti-emetics for reducing vomiting related to acute gastroenteritis in children and adolescents, where 60% reduction in the use of intravenous therapy was shown in the ondansetron group compared with controls. The drug was found to be effective in reducing the number of vomiting episodes. Yilmaz et al[14] found a higher proportion of subjects in the ondansetron group who were able to tolerate ORT compared with the placebo group (relative risk 1.17; 95% CI: 0.99 to 1.38, $P = .06$). Higher ORS intake in initial 4 hours of ORT in ondansetron group in our study was similar to results by Freedman et al[9] (239 mL vs 196 mL, $P < .001$). A study by Mullarkey et al[15] documented 19% reduction in intravenous fluid administration on adding oral ondansetron to ORT regimen. A systematic evaluation of all Cochrane reviews evaluating commonly used interventions in developed countries by Freedman et al showed significant reduction in the hospital admission and intravenous rehydration rates with oral ondansetron.[16] We documented faster correction of dehydration after single dose of oral ondansetron and better caregiver satisfaction. These outcomes, though important, have not been evaluated in earlier studies.

In the present study, we did not find any adverse effect during the initial 4 hours of observation. A systematic review and meta-analysis by Decamp et al[17] on use of antiemetic agents in acute gastroenteritis reported that diarrheal episodes increased in ondansetron group. We did not observe any increase in diarrhea with ondansetron use.

The Canadian Pediatric Society recommended considering the use of a single dose of oral ondansetron in children aged 6 months to 12 years presenting with acute gastroenteritis and vomiting as a prominent symptom, mild to moderate dehydration, or have failed ORT.[18] Current WHO diarrhea management guidelines and American Academy of Pediatrics guidelines[19] do not recommend the use of anti-emetics in management of diarrheal dehydration. There are no definite guidelines from other parts of the world, but the hospital-level analysis from the US has documented a marked increase in the use of ondansetron between 2002 and 2011.[20] This, however, did not result in reduction of intravenous fluid use, probably because of improper use (not given timely, not waiting for its effect before intravenous fluid administration) in real settings.[21,22] Our results favored the use of ondansetron to overcome the barrier of vomiting in successful implication of ORT therapy by reducing the proportion of children who failed ORT. However, one needs to study the metrics around failure of ORT other than vomiting and decision to administer ondansetron. ■

Submitted for publication Jun 8, 2015; last revision received Aug 25, 2015; accepted Oct 2, 2015.

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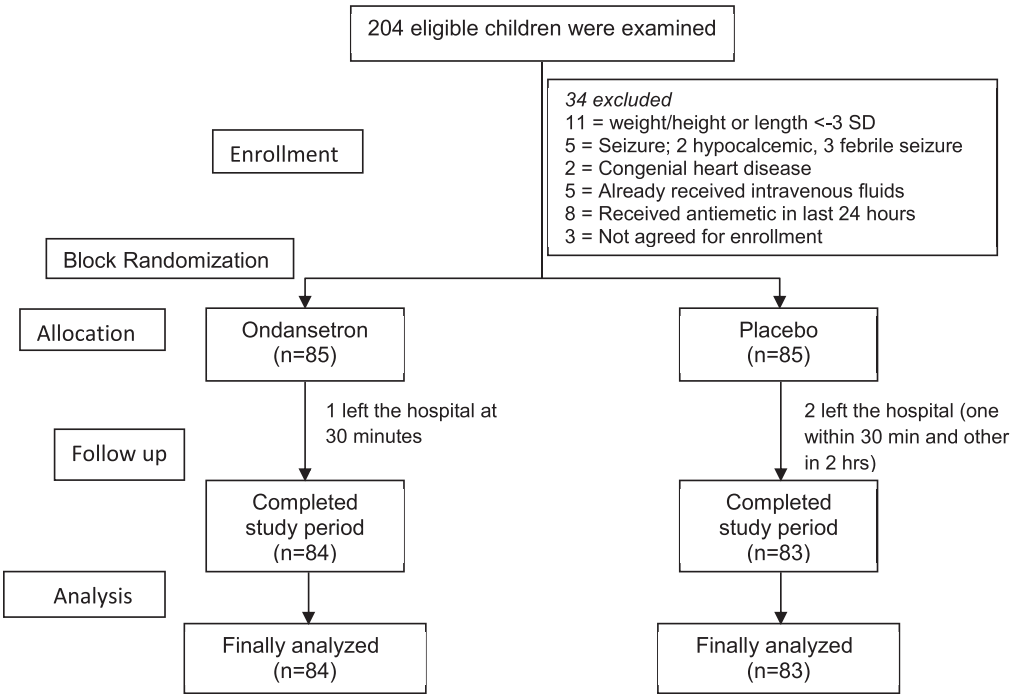

Figure 1. Flow of participants in the study.

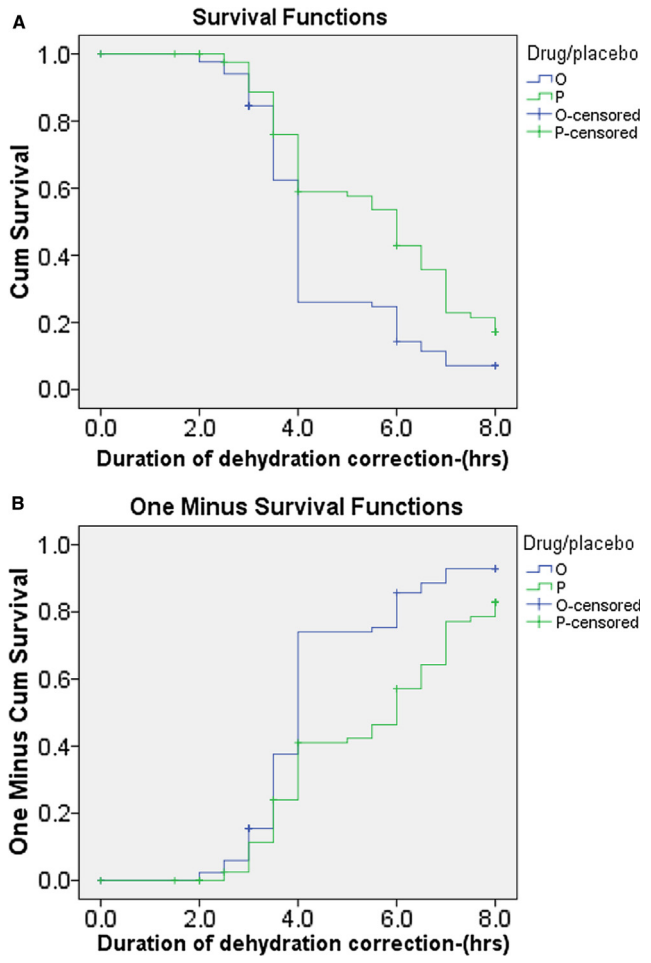

Figure 2. **A,** Kaplan-Meier survival and **B,** one minus survival curves for duration of dehydration correction.

Table III. Comparison of caregiver satisfaction after 4 hours of ORT in ondansetron and placebo groups

	Ondansetron (N = 84)	Placebo (N = 83)	*P* value*
Mood			
Change in score from baseline, mean (SD)	1.2 (0.99)	0.6 (1.12)	.01
Improvement by at least 1 score, N (%)	68 (81.0)	51 (61.5)	.005
Improvement by at least 2 scores, N (%)	42 (50)	20 (24.1)	<.001
Activity			
Change in score from baseline, mean (SD)	1.1 (0.98)	0.6 (1.00)	.004
Improvement by at least 1 score, N (%)	69 (82.1)	51 (61.5)	.003
Improvement by at least 2 scores, N (%)	32 (38.1)	13 (15.7)	.001
Alertness			
Change in score from baseline, mean (SD)	1.1 (0.94)	0.6 (1.06)	.001
Improvement by at least 1 score, N (%)	70 (83.3)	50 (60.2)	<.001
Improvement by at least 2 scores, N (%)	33 (39.3)	14 (16.9)	.001
Comfort			
Change in score from baseline, mean (SD)	1.1 (0.98)	0.4 (1.11)	<.001
Improvement by at least 1 score, N (%)	66 (78.6)	46 (55.4)	.001
Improvement by at least 2 scores, N (%)	32 (38.1)	15 (18.1)	.004
Vomiting			
Change in score from baseline, mean (SD)	1.4 (1.18)	0.5 (1.15)	<.001
Improvement by at least 1 score, N (%)	66 (78.6)	40 (48.2)	<.001
Improvement by at least 2 scores, N (%)	46 (54.8)	20 (24.1)	<.001
Fluid intake			
Change in score from baseline, mean (SD)	1.2 (0.91)	0.5 (1.12)	<.001
Improvement by at least 1 score, N (%)	70 (83.3)	46 (55.4)	<.001
Improvement by at least 2 scores, N (%)	33 (39.3)	17 (20.5)	.008

*By Student *t* test for comparing mean (SD) score and χ^2 test for comparing proportion.