

Placebo-controlled Randomized Trial Evaluating Efficacy of Ondansetron in Children with Diarrhea and Vomiting: Critical Appraisal and Updated Meta-analysis

SOURCE CITATION: Danewa AS, Shah D, Batra P, Bhattacharya SK, Gupta P. Oral ondansetron in management of dehydrating diarrhea with vomiting in children aged 3 months to 5 years: A randomized controlled trial. *J Pediatr.* 2016; 169:105-9.

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SUMMARY

In this double blind randomized placebo-controlled trial from New Delhi, India, 170 children (age 3 mo to 5 y) with acute diarrhea with vomiting and some dehydration were randomized equally to receive either single dose of oral ondansetron or placebo 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. Failure of ORT was significantly less in children receiving ondansetron compared with those receiving placebo (31% vs 62%; $P < 0.001$; RR 0.50, 95% CI 0.35, 0.72). 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. The authors concluded that a single oral dose of ondansetron, given before starting ORT to children <5 years of age having acute diarrhea and vomiting, results in better oral rehydration.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Clinical experience suggests that vomiting is often a significant barrier to successful oral rehydration therapy (ORT) in children with acute gastroenteritis. Vomiting can result in reluctance among family members/caregivers to administer adequate quantity of oral fluid; it sometimes impels physicians to prescribe intravenous fluids to avoid the delays associated with oral rehydration; and it also creates difficulties for individual children to accept oral rehydration salt (ORS) solution in appropriate amounts. Available systematic reviews suggest that anti-

emetic therapy administered in conjunction with ORS solution (ORS) may enhance the efficacy of ORT [1-4]. Against this background, the recent trial by Danewa, *et al.* [5] comparing oral ondansetron *versus* placebo for management of dehydration among children with diarrhea having associated vomiting, is a significant value addition to existing literature. The authors identified some of the lacunae in existing knowledge [1] and addressed these. **Table I** summarizes the main features of the trial.

Critical appraisal: Critical appraisal of the trial [5] adapting various standard tools [6,7] is summarized in **Table II**. The trial fulfilled all criteria for low risk of bias. It is interesting to note that children in the ondansetron group could take 75 mL/kg fluid over 4 hours. Incidentally this is the exact target volume for children with 'some dehydration'. In contrast, those in the placebo group could take an average of 63.7 mL/kg in the same duration. This means that in real world situations, children having vomiting are unable to accept the required volume of ORS solution. While this readily explains why nearly two-thirds of children in the placebo group required another round of ORT or intravenous fluids, it also suggests that current protocols recommending 75 mL/kg ORS solution may be chasing a futile goal in such children. The issue is somewhat complicated by the fact that majority of participants in this trial were infants receiving breast milk. Since the number of breastfeeding infants in each group and estimation of number/volume of feeds was not measured, its implications are unclear.

On the other hand, if children were able to take 75 mL/kg ORS solution within 4 hours, why did some require intravenous fluids? This issue gains even more importance considering that all the previous trials and systematic reviews on this subject reported statistically significant reduction in the need for intravenous rehydration. The absence of this finding here [5] necessitates updating

TABLE I SUMMARY OF THE TRIAL

Objective	To compare the efficacy and safety of orally administered ondansetron <i>versus</i> placebo, for the management of dehydration in children prescribed oral rehydration therapy for diarrhea and vomiting.
Study design and setting	Single center, placebo controlled double-blinded, randomized controlled trial in a tertiary care, teaching hospital in Delhi, India.
Population (P)	<i>Inclusion criteria:</i> Children (3mo-5y) with diarrhea (<14 d duration) with WHO-defined 'some dehydration' and >2 episodes vomiting in the preceding 6 h prior to presentation. <i>Exclusion criteria:</i> Children with severe acute malnutrition, altered sensorium, seizures, peripheral edema, paralytic ileus, previous receipt of any anti-emetic medication and/or prior intravenous fluids.
Intervention (I)	Ondansetron (oral) (0.2 mg/kg) just before starting ORT. Unlike previous trial, the investigators used precise rather than empiric dosage.
Comparison (C)	Placebo (oral) administered in a similar dose.
Outcomes (O)	<i>Efficacy:</i> Failure of ORT (defined as persistence or worsening of dehydration after 4 h of therapy); Need for intravenous fluids (with clear criteria for the same); Total volume of ORS accepted within 4 hours of treatment; Vomiting episodes; Duration of dehydration; Parent/caregiver satisfaction with treatment. <i>Safety:</i> Adverse events (diarrhea, headache, rash) recorded by investigators during therapy.
Time-frame (T)	All outcomes were assessed within a short time-frame of 8 hours.
Sample size	Sample size was calculated <i>a priori</i> for each of the three primary outcomes, and the total number randomized was adequate to cover for any drop outs following randomization.
Similarity of groups at baseline	Children in the intervention and comparison groups had similar characteristics at baseline in terms of age distribution, gender, duration of diarrhea, dehydration status, nutritional status, and vomiting frequency.

current systematic reviews.

Literature search was conducted through PubMed and the Cochrane Library (search terms: *ondansetron diarrhea*) on 14th January 2016, to identify randomized controlled trials (RCTs) comparing ondansetron (oral) *versus* placebo in children with diarrhea and vomiting, for clinically meaningful outcomes. Trials reporting studies in children with specific causes of diarrhea (such as irritable bowel syndrome) were excluded. A total of 141 and 104 citations, respectively were found. Screening by title, abstract and full text resulted in identifying 5 eligible RCTs, including the current trial [5,8-11]. One trial [12] was excluded as it used intravenous ondansetron. **Web Table I** summarizes the key features of the additional trials. **Fig. 1** presents the updated meta-analysis incorporating data from the present trial for the pertinent outcome. The updated relative risk is 0.44 [95% CI 0.32, 0.60; 5 trials, 741 participants; $I^2=0$), confirming that ondansetron reduces need for intravenous fluids by about 55%.

Although ondansetron is perceived as a relatively safe medication, it has the potential to create unpleasant [8,9,13] and even dangerous side effects [14-16]; although the dose, route, and participant characteristics may have a bearing. Rarer side effects may not be observed in a trial with limited participants; this point has been emphasized by the investigators also [5]. In the absence of a surveillance system to identify adverse events, physicians themselves should carefully monitor and report adverse

effects. Since orally administered ondansetron has a short half-life of 3-4 hours [17], it may be prudent to monitor recipients for at least 24 hours. It is pertinent that two professional European societies have recommended caution before ondansetron is routinely used [18].

Extendibility: This well-designed and well-executed RCT was conducted in a setting familiar to most healthcare facilities in India and much of the developing world. Participant selection, intervention administration, healthcare setting, and outcome monitoring were similar to the real-world scenarios in centers equipped to handle acute diarrhea and dehydration. Therefore, the results are readily extendible to similar settings across the world. It may be possible to cautiously extend the results to field/community settings where a combination of ondansetron and ORT administration may begin at home/primary centres before/while the dehydrated child is transferred to a facility with resources/personnel to administer intravenous fluids if required. The enthusiasm for using ondansetron should be tempered with caution concerning its potential adverse effects.

Conclusion: Ondansetron administered before ORT in children with diarrhea having additional vomiting results in better rehydration. However, physicians should be careful to monitor and *report* (note emphasis) any side effects of ondansetron occurring in the first 24 hours. These results are not extendible to children presenting with severe dehydration.

TABLE II: CRITICAL APPRAISAL OF THE TRIAL

<i>Trial Parameter</i>	<i>How it was Done</i>	<i>Interpretation</i>
Randomization	The allocation sequence was generated by a computer program. Varying block sizes were used to allocate participants.	Adequate
Allocation concealment	The allocation sequence was not revealed to anyone involved in the study. Intervention and placebo were made available in identical bottles labelled with a code representing the allocation.	Adequate
Blinding	Participants, their parents, and professionals who delivered the intervention, managed the children, and assessed the outcomes, were all blinded. The intervention and placebo were prepared to have similar concentration, taste, colour, and odour. They were packaged in identical bottles with no distinguishing features. The same volume (mL/kg) was administered to both groups.	Adequate
Selective outcome reporting	All relevant short-term outcomes were included in this trial.	Adequate
Incomplete outcome reporting	Of the 170 participants randomized, only 3 (1.8%) did not complete the study per protocol. This low attrition is probably owing to the short term outcomes in the trial.	Adequate
Statistical methods	Appropriate statistical tests were used for most outcomes. Per protocol analysis was chosen, rather than intention-to-treat analysis. However, as the attrition rate was very low, it may not compromise the validity.	Adequate
Main results (Ondansetron vs placebo)	Failure of ORT: RR 0.50 [95% CI 0.35, 0.72], NNT rounded to 4 Need for intravenous fluids: RR 0.56 [95% CI 0.30, 1.07], NNT 9 Volume of ORS accepted: Mean difference 91 mL [95% CI 35 mL, 147 mL] Vomiting episodes: Mean difference -1.80 [-2.5, -1.1] Duration of dehydration: These are presented as survival curves and demonstrate superiority of ondansetron starting from 3 hours after administration. Parent/care-giver satisfaction: Statistically significant superiority with ondansetron for each component. However, overall score not presented; hence need not be synonymous with clinical significance. Adverse events: No events in either group, hence differences (if any) cannot be determined.	Ondansetron superior for all outcomes except need for intravenous fluids.
Overall impression	<i>Validity:</i> RCT with a low risk of bias. <i>Results:</i> Clinically meaningful results for almost all outcomes. <i>Applicability:</i> Applicable in most health-care settings.	

ORT: Oral rehydration therapy; NNT: Number needed to treat; RCT: Randomized controlled trial.

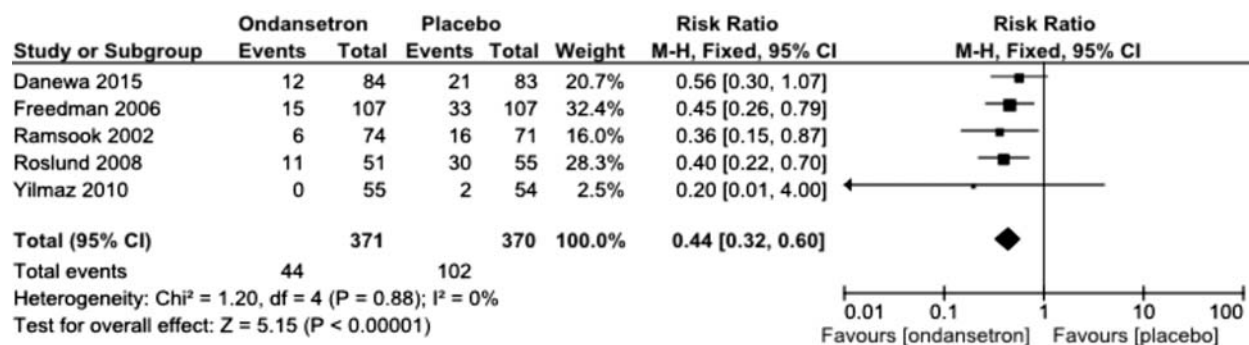


FIG. 1 Updated meta-analysis of ondansetron versus placebo for need of intravenous fluids.

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Pediatric Gastroenterologist's Viewpoint

Vomiting associated with acute gastroenteritis is a distressing symptom for children and their parents. Persistent vomiting is also one of the main causes of failure of oral rehydration therapy and need for intravenous rehydration. Decision of using antiemetic drugs should be guided by their efficacy, side effects and cost. A cochrane review published in 2011 and a systemic review published in 2012 concluded that use of ondansetron when compared to placebo increased the proportion of patients with cessation of vomiting (RR 1.44, 95% CI 1.29, 1.61), reduced the need of immediate hospitalization (RR 0.40, 95% CI 0.19, 0.83) and need for intravenous rehydration (RR 0.41, 95% CI 0.29, 0.59) [1,2]. All studies done so far were done in emergency department, in children with persistent vomiting and mild to moderate dehydration. There is lack of evidence from ambulatory settings, in children with vomiting and no dehydration, and in children with moderate to severe acute malnutrition. Most of studies have used a single dose. Studies have also reported prolongation of diarrhea in children who received ondansetron [1]. There is also some concern regarding prolongation of QT interval in patients with potential electrolyte abnormalities who receive intravenous ondansetron [3].

In the present study, authors evaluated the role of a single dose of oral ondansetron in facilitating successful rehydration of under-five children. This study also reported similar efficacy by demonstrating lesser failure

of ORT (31% vs 62%) and lesser need of intravenous fluids. This study is most probably the first double-blind randomized placebo controlled trial on this topic from a developing country. Present study confirms efficacy of single oral dose of ondansetron on cessation of vomiting, resulting in better oral rehydration and parents' satisfaction. At present there is lack of evidence for repeated doses, use in ambulatory settings, and in children with malnutrition.

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Pediatrician's Viewpoint

Oral rehydration therapy (ORT) has been the cornerstone of all the diarrhea treatment protocols since 1970s. However, in this era of indiscriminate use of antibiotics

and other drugs, ORT is being grossly underused. One of the major barriers to ORT is vomiting which makes pediatricians prefer intravenous fluids many a times only for parental reassurance. Literature suggests that wealthier family children are 1.5 times less likely to receive oral rehydration salt (ORS) solution. Till ORS is made more palatable, we have to rely on other cost-effective strategies to promote its use.

In this study, the authors have carried out a systematic randomized controlled trial (RCT), and supported the use of single dose of ondansetron in acute diarrhea with vomiting for successful delivery of ORT. However, lack of follow-up to see readmission rates or assessment for worsening of diarrhea, as reported in previous studies, has not been done.

In the Indian context, it could be an excellent step to scale up ORS use as motivating parents and even healthcare providers to give ORT despite vomiting is not easy, and traditional antiemetics have been marred with side effects. However, we should resist from a tendency to jump to this drug as it was originally intended for severe vomiting in chemotherapy and post-operative patients. More robust studies are needed to address the concerns of safety and benefit in ambulatory settings, and in select group of children such as those with severe malnutrition and other co-morbidities.

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