Efficacy of a New Hypotonic Oral Rehydration Solution Containing Zinc and Prebiotics in the Treatment of Childhood Acute Diarrhea: A Randomized Controlled Trial

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Objective To evaluate the efficacy of a hypotonic oral rehydration solution (ORS) containing zinc and prebiotics for treatment of acute diarrhea in children.

Study design We conducted a single-blind, prospective, controlled trial including children (age range, 3-36 months) with acute diarrhea randomly assigned to standard hypotonic ORS (group 1) or to new hypotonic ORS containing zinc and prebiotics (group 2). The main outcome was the rate of resolution of diarrhea at 72 hours.

Results A total of 60 children in group 1 (34 male; mean age, 18.58 months; 95% CI, 15.5-21.6) and 59 in group 2 (36 male; mean age, 19.26 months; 95% CI, 15.9-22.6) completed the study protocol. The rate of diarrhea resolution at 72 hours was higher in group 2 (50% versus 72.9%, $P = .010$). Total ORS intake in the first 24 hours was higher in group 2 (50 mL/kg; 95% CI, 41-59 versus 22 mL/kg; 95% CI, 17-29; $P < .001$). The mean number of missed working days by the parents of children in group 2 was lower (0.39; 95% CI, 0.08-0.70 versus 1.45; 95% CI 1.02-1.88; $P < .001$). Fewer patients in group 2 needed adjunctive drugs for the treatment of diarrhea 6/59 versus 19/60, $P = .004$. No adverse events were observed in either of the two groups.

Conclusion The addition of zinc and prebiotics to ORS limits diarrhea duration in children. *(J Pediatr 2011;158:288-92)*.

Acute diarrhea, a major cause of childhood morbidity, is also a source of anxiety to families of affected children, representing a heavy economic burden for families and for society as a whole. Oral rehydration solution (ORS) is the first-line therapy for the treatment of children with acute diarrhea worldwide.[1-4] Currently available ORSs efficiently cure and prevent dehydration, but are unable to reduce the duration and the severity of diarrhea. Several substrates and substances that affect transepithelial fluid transport have been added to ORS to limit diarrhea duration and severity, and the costs deriving from this condition, but conclusive clinical data about their effect are scanty[1,5,6] Studies and meta-analyses indicate that zinc-fortified ORS reduces diarrhea duration and severity in children with acute diarrhea.[7-13] Despite the evidence of benefit, there has been little progress on widespread introduction of low osmolarity ORS and zinc for treatment of acute diarrhea. In addition, most data came from studies of malnourished children living in developing countries.[8-13] Thus, at present there is not sufficient evidence to recommend either in favor or against the addition of zinc to ORS in children living in developed countries. Despite this, there is a large use of several formulations of ORS containing such substances as zinc, prebiotics, probiotics, and glutamine on the market without clear evidence of their efficacy in children living in developed countries.[1] The aim of this study was to investigate the efficacy of a new hypotonic ORS containing zinc plus fructooligosaccharides (FOS) and xilooligosaccharides in the treatment of children observed in the pediatric office for acute diarrhea.

Methods

We performed a prospective, randomized, single-blind controlled trial in collaboration with family pediatricians, who care for children up to 14 years of age in the Italian Public Health System. The study protocol was illustrated and discussed during 3 meetings. The study protocol was reviewed and approved by the ethics committee of the University Federico II of Naples.

From November 2007 to March 2008, all children aged 3 to 36 months consecutively observed in pediatrician offices with diarrhea lasting <24 hours with mild-moderate dehydration were considered eligible for the study. Diarrhea was defined as ≥3 outputs of loose or liquid stools per day.[15] At the enrollment,

FOS	Fructooligosaccharides
ORS	Oral rehydration solution

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dehydration was assessed in each patient by using standardized criteria, as previously described.[16] Exclusion criteria were: diarrhea lasting >24 hours; malnutrition as judged by a body weight/height ratio <5th percentile; clinical signs of severe dehydration; clinical signs of a coexisting severe acute systemic illness (meningitis, sepsis, pneumonia); immunodeficiency; underlying severe chronic disease; malnutrition; cystic fibrosis; food allergy or other chronic gastrointestinal diseases; endocrinopathy; use of prebiotics/probiotics in the previous 3 weeks; and use of antibiotics or any antidiarrheal medication in the previous 3 weeks. Informed consent was obtained from the parents of all enrolled children. Microbiologic and other laboratory investigations were performed only when required for specific clinical reasons.

Enrolled patients were randomly allocated to standard hypotonic ORS (group 1) or super-hypotonic ORS containing zinc and prebiotics (group 2). We used two commercial ORS preparations available on the market as sachets, with similar cost and packaging. The composition of the two ORSs is reported in Table I. The parents were instructed to rehydrate their children orally with ORS in 3 to 4 hours and then to administer ORS for dehydration prevention until cessation of symptoms, and re-feed their child with a normal appropriate-for-age diet including full strength lactose-containing formula or cow's milk (per guidelines[1]).

To circumvent the problems in performing a blind study on commercially available products in a large population, we used the third-part blind observer method to assess the efficacy of the ORS preparations. Patients were allocated to each group according to a computer-generated randomization list. The researchers responsible for enrolling patients allocated the next available number on entry in the trial. To maintain the concealed randomization procedure, each number of the randomization list corresponded to the number of a closed envelope containing a written prescription of the name of the ORS product and instructions about how it should be administered. The parents of enrolled children were instructed to record daily on a specific form: (1) time and the number of fecal outputs; (2) amount of daily ORS consumed by the child; (3) occurrence of adverse events; and (4) missed days work, hospital admission, and use of other medications. To ensure unbiased efficacy assessment, the investigators collecting the reporting forms completed by the parents were blind to the patients' treatment assignments, whereas the family pediatricians in charge of treatment allocation were excluded from efficacy assessment. We previously used this procedure in a study in children affected by acute diarrhea.[15]

Table I. Composition of the two oral rehydration solutions compared in the study

	Standard ORS	Super ORS
Commercial brand name	**Reidrax**	**Prereid**
Assigned group	**Group 1**	**Group 2**
Osmolarity (mOsm/L)	225	200
Na^+ (mmol/L)	60	50
K^+ (mmol/L)	20	20
Cl^- (mmol/L)	60	40
Glucose (mmol/L)	75	77
Citrate (mmol/L)	10	10
Zn^{2+} (mmol/L)	0	1
FOS (g/L)	0	0.35
Xilooligosaccharides (g/L)	0	0.35

Reidrax is a brand name of the EG SpA, Milan, Italy. Prereid is a brand name of the Milte Italia SpA, Milan, Italy

The principal outcome measure of the study was the rate of resolution of diarrhea 72 hours after starting oral rehydration therapy. We selected this time point according to an earlier study that demonstrated an increased risk of dehydration during this period and an effective use of zinc in reducing diarrhea after the first 72 hours of treatment.[17] The latter finding was recently confirmed in a Cochrane meta-analysis.[7] Diarrhea was considered to have stopped after a patient had passed the last abnormal (loose or liquid) stool preceding a normal stool output, as applied in an earlier study.[15]

To obtain a power of the study of 80% (type 1 error = 0.05; 2-tailed test), considering a difference of 25% (75% versus 50%) in the rate of resolution of diarrhea at 72 hours between the study groups, 57 patients in each group were required. This estimation was based on our preliminary data and on earlier results obtained in children with acute diarrhea treated with zinc.[17] We decided to enroll 65 patients per group, considering a possible drop out rate as high as 15%.

Statistical Analysis

A statistician blind to individual ORS preparations received performed statistical analysis by children in the two groups. Continuous variables were expressed as means plus or minus standard deviation. For categorical variables, the Pearson χ^2 test or Fisher exact test were performed as appropriated. The two groups were compared for continuous variables with the *t* test for equality of means. The Kaplan-Meier method was used to estimate the probability of diarrhea at 72 hours in each study group, and the resulting functions were compared with the log-rank test. Analyses were conducted on an intention-to-treat and per-protocol basis. All tests of significance were two-sided. A *P* value <.05 was considered to be significant. The statistical analysis was performed by using the SPSS software package for Windows (release 16.0.0; SPSS Inc, Chicago, Illinois) and Stats Direct (release 2.6.6, Altrincham, United Kingdom).

Results

Figure 1 (available at www.jpeds.com) shows the flow of children through the study; 65 children in each group were allocated to intervention. The baseline, demographic, and clinical characteristics were similar in the 2 groups (Table II). Resolution of diarrhea at 72 hours was observed in 30 of 60 children in group 1 (50.0%) and in 43 of 59 children in group 2 (72.9%, *P* = .010; Figure 2). The number of daily outputs was significantly reduced in group 2 compared with group 1 at 24 hours (4.5; 95% confidence interval [CI], 3.89-5.11 versus 5.9; 95% CI, 5.28-6.63; *P* = .002), 48 hours

Table II. Baseline main demographic and clinical characteristics of the study population

	Group 1	Group 2	*P*
n	60	59	
Age, months*	18.58 (15.5-21.6)	19.26 (15.9-22.6)	.765
Body weight, kg*	10.68 (9.79-11.58)	11.25 (9.79-12.72)	.474
Male, n (%)	34 (56.7)	36 (61.0)	.630
Duration of symptoms before treatment, hours*	9.0 (8.3-9.9)	10.0 (9.3-10.8)	.083
Presence of vomiting, n (%)	14 (23.3)	22 (37.3)	.098

*Mean (95% CI) when not specified.

(4.06; 95% CI, 3.46-4.66 versus 5.11; 95% CI, 4.29-5.94; P = .037), and 72 hours (2.88; 95% CI, 2.44-3.32 versus 3.89; 95% CI, 3.13-4.65; P = .020). The total ORS intake in the first 24 hours of rehydration therapy was significantly lower in group 1 (22 mL/kg; 95% CI, 17-29) than in group 2 (50 mL/Kg; 95% CI, 41-59; P < .001). The number of missed working days was significantly higher for parents of children enrolled in group 1 (1.45; 95% CI, 1.02-1.88 versus 0.39; 95% CI, 0.08-0.70; P < .001). The rate of parents who missed at least one working day was significantly higher in group 1 (51.7% versus 15.3%, P < .001). The rate of patients requiring hospitalization because of worsening of symptoms was similar in the 2 groups (5.0% versus 1.7%). Adjunctive medications within the first 72 hours were not used by any patients in the two groups, whereas after the first 72 hours additional treatments were used by 19 of 60 patients of group 1 and by 6 of 59 patients of group 2 (P = .004). In particular, the medications used were probiotics (n = 12), diosmectite (n = 4), racecadotril (n = 2), in group 1, and probiotics (n = 4), and domperidone ((n = 2) in group 2.). No adverse events related to the use of the ORS were observed in the study groups.

Discussion

In this trial, we investigated the therapeutic efficacy of a new commercially available hypotonic ORS containing zinc and prebiotics in the treatment of acute diarrhea in children. The positive clinical effect exerted by this new ORS on diarrhea could be related to a synergistic effect between prebiotics and zinc. Prebiotics have been proposed for the prevention and treatment of acute diarrhea, but efficacy data of FOS and xilooligosaccharides in the treatment of acute diarrhea are still scant and conflicting.[1,18-26] Many of the effects attributed to prebiotics are related to the consequences of their use on gut microbiota composition. The ability to target specific groups of organisms (ie, bifidobacteria) in the large intestine by prebiotics is increasingly seen as being of significant health value. Many studies have established that prebiotics increase bifidobacterial numbers in infant stool to levels comparable with breast-fed infants.[19-25] Several investigations have demonstrated an increased sIgA response resulting from the use of prebiotics.[21,22] However, trials on diarrhea have been essentially limited to FOS, and all except one have been carried out in animals. The exception is a promising study involving 244 people at increased risk of acquiring traveler's diarrhea. This investigation showed that travelers who received FOS had a reduced incidence of diarrheal events compared with the placebo group, although the reduction was not significant.[24]

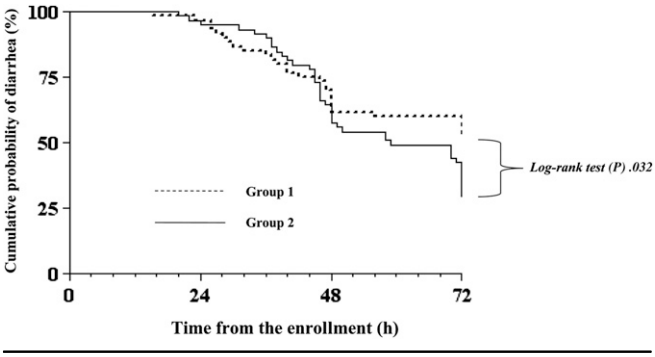

Figure 2. Kaplan-Meyer analysis showing a significant difference (P = .032) of unresolved diarrhea at 72 hours after starting treatment with standard hypotonic ORS (group 1) or with new hypotonic super ORS containing zinc and prebiotics (group 2).

A large body of evidence supports the use of zinc in the treatment of acute diarrhea, and the mechanisms of action of zinc are becoming clearer.[7-13,27-29] Zinc is now included in the World Health Organization essential medicine list for diarrhea treatment, and in the 2008 Copenhagen Consensus, a group of leading global economists ranked zinc supplementation as the most effective intervention for advancing human development.[6,30] Clinical trials, reviews, and meta-analyses have demonstrated that zinc reduces diarrhea duration, stool output, and stool frequency. In particular, a Cochrane meta-analysis demonstrated that zinc is effective in reducing the duration of diarrhea at 72 hours.[7] This coincides with our finding that significantly fewer children who were treated with zinc-containing ORS had diarrhea 72 hours after symptom onset versus the group treated with standard hypotonic ORS. Although most studies reported positive effects elicited by zinc in the treatment of childhood acute diarrhea, some negative results have recently been published.[31] This discrepancy could be caused by such factors as nutritional status, zinc status, or both,[7-13] age, race, sex,[7-14,32,33] and the causative pathogen.[13,27,28,34,35] Notwithstanding the discrepancy, zinc is widely used in the treatment of acute diarrhea in developing countries, where it is responsible for saving >400 000 lives a year.[32] Moreover, a universal zinc-containing super-ORS has been proposed by various authors.[5,6,36] These results will hopefully stimulate further investigation.

Zinc supplementation induces a therapeutic effect by stimulating water and electrolyte absorption across the intestinal mucosa, thereby preventing villous atrophy and improving overall immunity.[27,28,37-39] We previously demonstrated that zinc induces a pro-absorptive effect on ion transport in basal condition and inhibits the main intracellular pathways of intestinal ion secretion that are involved in

acute diarrhea by directly interacting with enterocytes.[27,28] We have demonstrated that zinc affects ion transport when used at concentrations (10-22 μmol/L) that are within normal plasmatic ranges and very similar to the plasma concentrations reported in clinical studies in patients with diarrhea treated with zinc.[8,9] The "super-ORS" used in this study contains a zinc concentration of 3.75 mg/100 mL. This concentration compares well with the United Nations Childrens Fund and World Health Organization recommendations for the use of zinc as a universal treatment of children with acute diarrhea, namely 10 to 20 mg zinc daily.[6] The mean intake of 49.7 mL/kg corresponds to an average daily intake between 10 and 20 mg.

The positive therapeutic effects of this new "super-ORS" containing zinc and prebiotics are probably responsible for the reduction of drug use and parental work days missed. The Italian Society of Pediatric Gastroenterology Hepatology and Nutrition estimated an average cost of approximately 137.00 € per episode of acute diarrhea in ambulatory children aged <3 years, mostly related to drugs and to loss of work days of parents.[40] In this light, the use of this new "super-ORS" could be responsible for a substantial reduction of the cost related to acute diarrhea.

The results of our trial suggest that a new hypotonic ORS containing zinc and prebiotics is useful in the treatment of ambulatory children with acute diarrhea living in a developed country. ■

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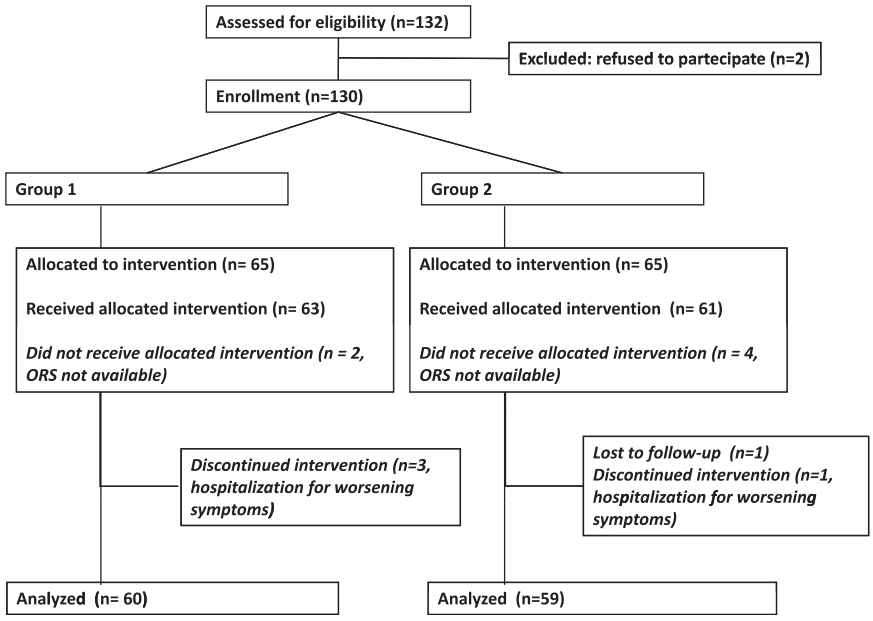

Figure 1. Flow of children through the study. A total of 130 patients were enrolled and allocated to intervention. A total of 119 patients completed the study protocol.