ORS Containing Zinc Does Not Reduce Duration or Stool Volume of Acute Diarrhea in Hospitalized Children

*Nitya Wadhwa, †Uma Chandra Mouli Natchu, ‡Halvor Sommerfelt, ‡Tor A. Strand, *Vishal Kapoor, *Savita Saini, §Udaypal S. Kainth, and *Shinjini Bhatnagar

ABSTRACT

Background and Aim: The World Health Organization recommends oral zinc (tablets or syrups) as adjunct therapy with oral rehydration solution (ORS) for acute childhood diarrhea. Mixing zinc with ORS can be an attractive approach for simultaneous provision of these 2 effective interventions. This double-masked randomized controlled trial evaluated the efficacy of ORS containing 40 mg/L elemental zinc per liter (zinc-ORS) in reducing stool weight and duration of diarrhea.

Patients and Methods: Five hundred northern Indian children ages 1 to 35 months with diarrhea <7 days' duration were randomized to zinc-ORS or ORS. The primary outcomes were total stool output and time to recovery.

Results: The median total stool output was $2.12\,g \cdot kg^{-1} \cdot h^{-1}$ (interquartile range [IQR] 0.9–3.76) in the zinc-ORS group compared with $1.78\,g \cdot kg^{-1} \cdot h^{-1}$ (IQR 0.83–3.45) in the ORS group. The time to recovery was also similar in the 2 groups (hazard ratio 1.06 [95% confidence interval 0.88–1.27]). In subjects who received zinc-ORS, the median (IQR) zinc intakes were 27 (16–46) mg on day 1, 15 (6–27) mg on day 2, and negligible thereafter.

Conclusions: The World Health Organization–recommended daily dose of zinc for diarrhea was not achieved in most children beyond the first day of treatment. This is the likely explanation for the lack of improvement in outcomes from zinc-ORS when compared with ORS alone. Our findings do not support a change from using zinc syrup or dispersible tablets for treatment of acute diarrhea in children.

Key Words: acute diarrhea, dehydration, oral rehydration solution, zinc

(*JPGN* 2011;53: 161–167)

Despite the success of oral rehydration solution (ORS), diarrheal diseases still contribute substantially to the overall burden of childhood mortality accounting for ~2 million deaths every year (1,2). Oral zinc is effective in reducing the severity of the diarrheal episode and the World Health Organization (WHO) now recommends oral zinc (tablets or syrups) for 10 to 14 days for acute childhood diarrhea (3–8).

Mixing zinc with ORS seems an attractive approach for public health programs for simultaneous provision of these 2 effective interventions, particularly in remote areas. A study in Italy of 120 children enrolled on the first day of diarrhea compared locally available hypotonic ORS (225 mOsm/L) to a ''superhypotonic'' ORS (200 mOsm/L) containing zinc (37.5 mg/L), fructo-oligosaccharides, and xylooligosaccharides. The superhypotonic ORS was associated with a 25% higher rate of resolution of diarrhea at 72 hours in the group receiving ORS containing zinc and the additional saccharides (9). In contrast, in an earlier community-based randomized controlled trial of northern Indian children 6 to 35 months old with acute diarrhea, addition of 40 mg elemental zinc per liter of ORS reduced the mean number of stools during the episode only marginally and less than when zinc was given separately in syrup. Moreover, the intake of zinc from zinc-ORS varied substantially, and, contrary to zinc syrup, zinc-ORS did not reduce the duration of diarrhea (10).

Children brought to the hospital with diarrhea are likely to experience more severe disease when compared with children visiting a community health center or being treated at home. This hospital-based study was intended to measure the efficacy of adding zinc to ORS in more severe diarrhea requiring visits to the hospital, with or without dehydration. In a double-masked, randomized controlled clinical trial, we evaluated the efficacy of adding 40 mg of elemental zinc per liter of reduced-osmolarity WHO ORS (zinc-ORS) on total stool output and time to recovery from diarrhea in hospitalized children (1–35 months old) with acute diarrhea.

PATIENTS AND METHODS

Study Setting and Recruitment of Participants

We enrolled 1- to 35-month-old children who attended the diarrhea treatment units of the All India Institute of Medical Sciences and Deen Dayal Upadhyay Hospital in New Delhi between December 2003 and March 2007, if they had passed ≥3 loose stools per day, and at least 1 in the last 12 hours, for fewer than 7 days. We

Received September 14, 2010; accepted February 2, 2011.

From the *Centre for Diarrheal Diseases and Nutrition Research, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, the †Department of Nutrition, Harvard School of Public Health, Boston, MA, the ‡Centre for International Health, University of Bergen, Bergen, Norway, and the §Deen Dayal Upadhyay Hospital, New Delhi, India.

Address correspondence and reprint requests to Dr Shinjini Bhatnagar, Pediatric Biology Centre, Translational Health Science and Technology Institute, Udyog Vihar Phase III, Gurgaon, Haryana-122016, India (e-mail: shinjini.bhatnagar@thsti.res.in).

The study was funded by the Norwegian Agency for Development Cooperation as part of the Indo-Norwegian Programme of Institutional Cooperation between All India Institute of Medical Sciences, New Delhi in India and the Centre for International Health at the University of Bergen in Norway. T.A.S. was funded through a grant from the Research Council of Norway (grant no. 172226).

ClinicalTrials.gov number: NCT00370968.

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0b013e318213ca55

enrolled boys to ensure stool collection without urine. The exclusion criteria were severe malnutrition (as defined by WHO), visible blood in stool, intake of zinc supplements in the previous 4 weeks, severe systemic illness such as tuberculosis, nephrotic syndrome, malignancy, and any surgical disorder.

Sample Size

The sample size was calculated for 80% power and 95% confidence to detect a reduction of ≥30% in total stool weights and a hazard ratio of 0.77 for time to recovery from diarrhea in the zinc-ORS group compared with the ORS group. The expected values in the control group were based on previously reported mean stool weights of 291 g/kg (standard deviation [SD] 291) from 1 of our hospital trials. A sample size of 176 per group was estimated to be sufficient for total stool output and 230 per group for time to recovery. We therefore decided to enroll 250 children per group to account for at least 5% attrition.

Stratification and Randomization

After baseline assessment, eligible participants were stratified according to age (1–5 months, 6–35 months) and presence of some dehydration at admission. Using STATA software (version 9.0, StataCorp, College Station, TX), staff otherwise not involved in the study generated randomization lists using permuted blocks of 6 for each stratum and each hospital. The randomization codes were kept with the randomization team until completion of the trial.

Allocation Concealment, Masking, and Intervention

A team of research physicians at the study hospitals screened and enrolled eligible subjects at all times of the day while providing clinical care. Children with some or no dehydration were randomized immediately and managed as per WHO guidelines (8).

ORS and zinc-ORS were similar in color, taste, and appearance, and were packed in identical sealed sachets. The contents of each packet were to be dissolved in 1 L of clean water. Ten such sachets were packed for each subject in a larger transparent sealed polyethylene bag. Each such bag, including the 10 smaller sachets, was labeled with a unique serial number that corresponded to the randomization list before they were arranged sequentially and sent to the investigators. The packages were purchased from Wallace Pharmaceuticals Ltd (Mumbai, India) and stored in a cool, dry place. Each group was identified only by a letter during data analysis.

The children in the intervention group received reduced-osmolarity ORS (245 mOsm/L) containing 40 mg/L elemental zinc as zinc gluconate, which was mixed with the salts before packaging. The children in the control group received reduced-osmolarity ORS. The 2 ORS preparations differed only with respect to zinc gluconate (Table 1).

TABLE 1. Composition of the 2 ORS used as interventions

	Zinc-ORS	ORS
Osmolarity, mOsm/L	245	245
Glucose, mmol/L	75	75
Na^+, mmol/L	75	75
K^+, mmol/L	20	20
Chloride, mmol/L	65	65
Citrate, mmol/L	10	10
*Zinc (elemental), mg/L	0	40

ORS = oral rehydration solution.
* Does not contribute significantly to osmolarity of the ORS.

Outcome Measures

All of the enrolled participants were monitored intensively by research physicians around the clock. The primary outcomes were total stool output defined as weight of stools passed from the time of randomization to recovery and time to recovery. We defined recovery as the time of the last abnormal stool before a 12-hour period when no stool had been passed or before the passage of 2 consecutive formed stools. An abnormal stool was a watery stool with no fecal matter or a loose stool with a rim of more than 1 cm of fluid around it visualized on the diaper. Each stool was measured in preweighed disposable diapers using a triple beam scale (Ohaus Corporation, Pine Brook, NJ) that measured to the nearest 1 g; consistency was noted and recorded immediately by the research physician on duty. Urine was separated from stools in a urine collection bag connected to a condom.

Secondary outcomes were proportion of episodes lasting longer than 72 hours after randomization, need for unscheduled intravenous fluids for management of severe dehydration at any point after randomization, incidence of vomiting, and daily ORS intake. Vomitus was weighed on preweighed disposable gauze pads. Nude body weights were taken at enrollment, after rehydration at 6 hours, and every 24 hours subsequently on an electronic scale (SECA, Hamburg, Germany) measuring to the nearest 5 g until the patient's participation in the study ended.

Quality Assurance

Quality assurance was performed by conducting regular standardization exercises at both sites with research staff on collection of stools, vomitus, and measurements of weights and lengths to minimize inter- and intraobserver variability.

Standard Case Management

Rehydration therapy was as per WHO guidelines (8). Water (measured to contain 0.06 mg/L elemental zinc) and breast-feeding were allowed ad libitum. Feeding of children who had started receiving complementary food was resumed immediately after completion of rehydration, with a traditional milk-cereal diet (calorie density 92.4 cal/100 g; zinc 0.27 mg/100 g, 0.32 mg/110 kcal) that was offered at 110 $kcal \cdot kg^{-1} \cdot day^{-1}$ in participants older than 6 months. Mothers of infants <6 months old were encouraged to breast-feed exclusively. Intakes were compiled every 24 hours. Participants requiring treatment for severe systemic infection or dysentery detected after randomization continued in the study if they could take oral liquids but were given additional standard treatment by hospital physicians.

Monitoring and Follow-up

Monitoring continued for at least 48 hours after enrollment or until recovery from diarrhea, whichever was later, and for a maximum period of 168 hours, that is, 7 full days. Recovery could not be documented in participants who withdrew their consent and were considered as lost to follow-up and excluded. Participants who did not recover by 168 hours or in whom intervention was stopped

for worsening of an associated clinical condition were excluded from that point in time.

Laboratory Parameters

Venous blood specimens were obtained at enrollment, 24 hours after randomisation, and at recovery. The specimens were collected in zinc- and copper-free tubes, centrifuged, and the serum stored at −20°C. The zinc and copper concentrations in the specimens were analyzed using a flame furnace atomic absorption spectrophotometer (GBC Avanta, Dandenong, Victoria, Australia) using standard techniques and with SERONORM (Sero AS, Billingstad, Norway) as the reference (11). Serum electrolytes, hematocrit, and hemoglobin were determined using standard methods at enrollment and when indicated. Stool was collected in sterile vials with phosphate-buffered saline, and the detection of rotavirus was done by enzyme-linked immunosorbent assay using a commercially available kit (Premier Rotaclone, Meridian Bioscience Inc, Cincinnati, OH).

Ethics

The study was approved by the ethics committees of the study institutions and the Regional Committee for Medical Research Ethics of Western Norway. Informed written consent was obtained from the parent(s) using the standard norms of the institutional ethics committees.

Statistics and Data Analysis

All of the case report forms were checked daily by the supervisor before they were sent for double data entry using FoxPro for Windows (version 6.0, Microsoft Corporation, Redmond, WA) with inbuilt logic, range, and consistency checks. The 2 concurrent entries were compared using EpiInfo (version 3.4.3, Centers for Disease Control and Prevention, Atlanta, GA) and incorrect entries edited appropriately. We undertook an intention to treat analysis using STATA (version 10, StataCorp). Those lost to follow-up did not recover by 168 hours or in whom intervention was stopped for worsening of an associated clinical condition contributed data to the analyses until that time and were no longer given study ORS solutions. Stool output (grams) and ORS intakes (milliliters) are presented standardized by body weight and by time (hour); differences between the 2 groups for stool weight (gram per kilogram per hour) and ORS intake (milliliter per kilogram per hour) were calculated using the Wilcoxon rank sum test. The risk of episodes lasting longer than 72 hours since randomization, the need for unscheduled intravenous fluids, and the risk of vomiting in the initial 24 hours are presented as risk ratios (RRs) with their 95% confidence interval (CI). The Cox proportional hazards regression model was used to estimate the hazard ratios of time to recovery from diarrhea. The differences between the 2 groups for serum zinc are presented as difference in mean with the 95% CI. The efficacy of zinc-ORS on the primary outcomes was also analyzed in each randomization stratum (dehydration status, age) and by duration of diarrhea before enrollment.

RESULTS

Five thousand two hundred thirty-seven children ages 1 to 35 months with acute diarrhea of less than 7 days' duration attended the diarrhea treatment unit of the 2 hospitals during the study period. Of these, 2367 were boys, of whom we enrolled 500 (Fig. 1). The large number of exclusions was because of our strict inclusion criteria. Among those enrolled, 123 (25%) were younger than 6 months and 197 (39.4 %) were dehydrated. Only 3 children,

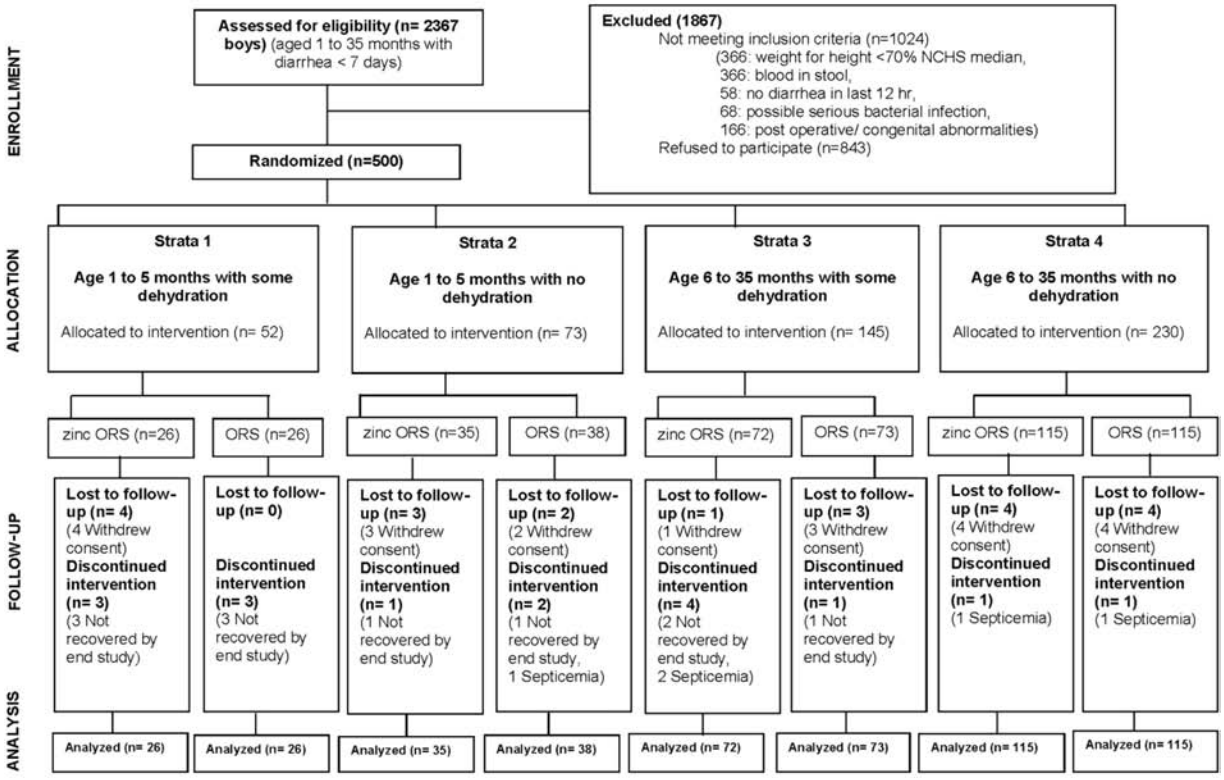

FIGURE 1. Flow of participants through each stage of randomized trial.

1 in the zinc-ORS and 2 in the ORS group, were enrolled after intravenous fluids were administered to correct severe dehydration. The overall loss to follow-up was 4.2%.

Baseline Characteristics

The 2 groups were comparable in admission characteristics (Table 2). Almost 75% of enrolled subjects were currently breastfed. The preadmission duration and severity of diarrhea were similar. Rotavirus was identified in about half (zinc-ORS 49.3% and ORS 47.3%) of the enrolled subjects. The mean (standard deviation [SD]) serum zinc concentrations (zinc-ORS 91.2 [29.1] vs ORS 88.9 [33.6] μg/dL) and the proportion of subjects with serum zinc <60 μg/dL were similar in the 2 groups (Table 2).

Effect of Zinc-ORS on Stool Output and Duration of Diarrhea

Adding 40 mg/L elemental zinc to ORS did not reduce the total (from time of randomization to time of recovery) stool output (median [interquartile range, IQR]; gram per kilogram per hour) (zinc-ORS 2.12 [0.9–3.76] vs ORS 1.78 (0.83–3.45; $P = 0.25$). There was no reduction in stool output in the initial 24 hours (zinc-ORS 2.46 [1.19–4.23] vs ORS 2.16 [1.12–3.97; $P = 0.33$]) after starting treatment (Table 3). Recovery from diarrhea was similar in children receiving zinc-ORS as compared with among those who got ORS, with a hazard ratio of 1.06 (95% CI 0.88–1.27) (Table 3). Zinc-ORS had no effect on either stool output or recovery from diarrhea in subgroups by hydration status, age, or duration of diarrhea at enrollment when compared with ORS (Table 4).

Effect of Zinc-ORS on the Risk of Prolonged (>72 hours) Diarrhea and the Need for Intravenous Fluids

The proportion of diarrheal episodes lasting longer than 72 hours (RR 0.94 [95% CI 0.69–1.30]) and the need for unscheduled intravenous fluids during the study (RR 0.80 [95% CI 0.45–1.43]) were the same in both groups (Table 3).

Effect of Zinc-ORS on Vomiting

Overall, more than 40% of the children in our study vomited at least once in the first 24 hours after enrollment and the proportions were similar (zinc-ORS 112 [45.1%] vs ORS 104 [41.3%]) in the 2 groups (Table 3).

Intakes of ORS and Zinc

Similar quantities (milliliter per kg per hour) of ORS were consumed by the 2 groups (median [IQR]: zinc-ORS 5.09 [2.21–7.79] vs ORS 4.65 [2.29–7.11, $P = 0.59$]) on days 1 and 2 after randomization ($P = 0.32$) (Table 3). In subjects who received zinc-ORS, the median (IQR) zinc intakes were 27 (16–46) mg on day 1, 15 (6–27) mg on day 2, and negligible thereafter. Only 68% of the subjects 6 months old or older received 100% or more of the WHO-recommended dose for diarrhea in the initial 24 hours; the number decreased further in the subsequent period and was only 1.7% on day 5 of the illness (Table 5). This was true for infants younger than 6 months as well (Table 5).

TABLE 2. Baseline (admission) characteristics by treatment groups: zinc-ORS and ORS

Admission characteristics	Zinc-ORS (n = 248)	ORS (n = 252)
Age, mo, mean (SD)	10.2 (6.5)	10.5 (6.5)
Age categorized, n (%)		
1 up to 6 mo	61 (24.6)	62 (24.6)
6 up to 12 mo	105 (42.3)	105 (41.7)
≥12 mo	82 (33.1)	85 (33.7)
Weight for height, % NCHS standard	84.1 (8.2)	84.3 (7.7)
Mothers' education, y, median (IQR)	5 (0, 9)	5 (0, 10)
Preadmission diarrheal duration, h		
Mean (SD)	53.1 (33.6)	49.9 (32.5)
≤24 h, n (%)	78 (31.5)	87 (34.5)
≤48 h, n (%)	148 (59.6)	164 (65.0)
No. stools in previous 24 h, mean (SD)	13.6 (7.2)	13.4 (6.5)
No. with some dehydration, n (%)	96 (38.7)	98 (38.9)
No. with severe dehydration, n (%)	1 (0.40)	2 (0.79)
No. with history of vomiting during this episode, n (%)	209 (84.3)	204 (80.9)
Duration of vomiting at enrollment, h, median (IQR)	24 (11, 48)	24 (7, 48)
No. with fast breathing, n (%)	2 (0.81)	2 (0.79)
No. taking breast milk, n (%)	189 (76.21)	188 (74.60)
Total leukocyte counts/mm^3 mean (SD)	11,049 (6113)	10,736 (4979)
Hematocrit, %, mean (SD)	31.6 (5.28)	30.8 (5.52)
No. stools positive for rotavirus, n (%)	99/201 (49.3)	88/186 (47.3)
No. stool culture positive for *Vibrio cholerae*, n (%)	0/206	4/198 (2.0)
Serum zinc, μg/dL, mean (SD)	91.2 (29.1)	88.9 (33.6)
No. with serum zinc <60, μg/dL	29 (12)	29 (12)

IQR = interquartile range; NCHS = National Center for Health Statistics; ORS = oral rehydration solution; SD = standard deviation.

TABLE 3. Effect of zinc mixed in ORS on clinical outcomes during diarrhea in 500 northern Indian children

	Zinc-ORS (n = 248)	ORS (n = 252)	P^*
Stool output	Median (IQR), ($g \cdot kg^{-1} \cdot h^{-1}$)		
Duration since enrollment, h			
0–24	2.46 (1.19–4.23)	2.16 (1.12–3.97)	0.33
0–48	2.14 (0.91–3.85)	1.75 (0.82–3.54)	0.28
0–recovery	2.12 (0.90–3.76)	1.78 (0.83–3.45)	0.25
	Median (IQR), h		HR[†] (95% CI)
Time to recovery	37 (19.7–69.5)	34.4 (18.5–69.7)	1.06 (0.88–1.27)
Duration of diarrhea since enrollment, h	No. children, n (%)		RR[‡] (95% CI)
>24	167 (67.3)	161 (63.9)	1.05 (0.93–1.19)
>48	103 (41.5)	101 (40.1)	1.02 (0.83–1.27)
>72	55 (22.2)	59 (23.4)	0.94 (0.69–1.30)
	No. children, n (%)		
Unscheduled IVF	19 (7.7)	24 (9.5)	0.80 (0.45–1.43)
Vomiting in first 24 h	112 (45.1)	104 (41.3)	1.09 (0.89–1.34)
ORS use rate	Median (IQR), ($mL \cdot kg^{-1} \cdot h^{-1}$)		
Duration since enrollment, h			P^*
0–24	5.09 (2.21–7.79)	4.65 (2.29–7.11)	0.59
0–48	3.69 (2.01–5.94)	3.39 (1.88–5.43)	0.32

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; IVF = intravenous fluids; ORS = oral rehydration solution; RR = risk ratio.
[*] Wilcoxon rank sum test.
[†] Hazard ratio >1 indicates a more protracted illness in the zinc-ORS recipients.
[‡] Relative risk <1 indicates a beneficial effect of zinc-ORS.

TABLE 4. Effects of zinc mixed in ORS on clinical outcomes in subgroups classified by stratification variables and features at enrollment

Subgroups	Zinc-ORS	ORS	P^*
Stool output	Median (IQR) ($g \cdot kg^{-1} \cdot h^{-1}$)		
Hydration at enrolment			
Dehydrated	2.95 (1.91–4.10)	2.33 (1.31–4.03)	0.06
Not dehydrated	1.35 (0.59–3.13)	1.35 (0.63–3.16)	0.89
Age at enrollment, mo			
≤6	3.03 (1.02–4.03)	3.16 (1.61–4.37)	0.32
>6	1.80 (0.85–3.29)	1.31 (0.71–2.90)	0.03
Duration of diarrhea at enrollment, h			
≤24	2.00 (0.99–3.47)	1.58 (0.76–3.60)	0.31
>24	2.14 (0.79–3.79)	1.87 (0.93–3.39)	0.46
Time to recovery	Median (IQR), h		HR[†] (95% CI)
Hydration at enrolment			
Dehydrated	53.0 (27.5–84.0)	41.3 (22.7–77.7)	1.25 (0.92–1.67)
Not dehydrated	29.9 (16.0–54.3)	30.1 (15.0–67.3)	0.95 (0.75–1.19)
Age at enrollment, mo			
≤6	46.8 (20.6–90.8)	58.3 (33.5–83.3)	0.99 (0.71–1.40)
>6	34.5 (19.7–62.7)	27.4 (15.8–63.5)	1.14 (0.92–1.41)
Duration of diarrhea at enrollment, h			
≤24	40.7 (19.8–72.0)	36.2 (17.5–78.8)	0.93 (0.67–1.27)
>24	36.2 (19.4–67.8)	33.3 (19.6–66.5)	1.15 (0.92–1.44)

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; ORS = oral rehydration solution.
[*] Wilcoxon rank sum test.
[†] Hazard ratio >1 indicates a more protracted illness in the zinc-ORS recipients.

TABLE 5. Amount of zinc received by children in the zinc-ORS group in a trial on the efficacy of zinc mixed in ORS in 500 northern Indian children

	Received 100% of recommended dose	Received 50% of recommended dose	Median IQR
6–35 mo (recommended dose is 20 mg elemental zinc/d)			
n = 182			
0–24 h	124 (68)	156 (85.7)	28 (15.3–49.7)
25–48 h	66 (36.5)	110 (60.8)	14.6 (5.5–27.3)
49–72 h	26 (14.4)	41 (22.7)	0 (0–9.5)
n = 179			
73–96 h	11 (6.1)	23 (12.8)	0 (0–0)
97–120 h	3 (1.7)	7 (3.9)	0 (0–0)
2–5 mo (recommended dose is 10 mg elemental zinc/d)			
n = 60			
0–24 h	50 (83.3)	56 (93.3)	26.2 (17.8–38.6)
n = 59			
25–48 h	39 (66)	48 (81.4)	16 (6.8–26.5)
n = 58			
49–72 h	22 (37.9)	24 (41.4)	0 (0–19.8)
73–96 h	14 (24.1)	17 (29.3)	0 (0–8.2)
n = 56			
97–120 h	11 (19.6)	11 (19.6)	0 (0–0)

IQR = interquartile range.

Effect of Zinc-ORS on Serum Zinc

The serum zinc was significantly higher in the zinc-ORS group 24 hours after randomization (difference in mean 5.8 [95% CI 0.43–11.17]) and at recovery (6.9 [95% CI 0.65–13.1]; Table 6).

DISCUSSION

A number of trials have documented faster recovery and reduced severity from zinc supplementation during acute diarrhea (3–7,12,13). This led to the WHO recommendation of supplemental zinc syrup or tablets (10 mg elemental zinc for infants younger than 6 months and 20 mg/day for children 6 months old or older) during acute diarrhea (4,8). Health system obstacles to widespread use of zinc during acute diarrhea include the need for zinc syrup or tablets to be made available at health facilities and prescribed by health care providers in addition to ORS. If zinc-containing ORS was found to be more effective than ORS, it could considerably simplify the logistics of incorporating zinc into national treatment guidelines for diarrhea in low- and middle-income countries. The purpose of this trial was to evaluate reduced-osmolarity ORS containing 40 mg/L of zinc in comparison with ORS without zinc among 1- to 35-month-old children hospitalized with acute diarrhea.

In this trial, adding zinc to ORS did not reduce total stool output or time to recovery. Also, the proportions of children who required intravenous fluids or had diarrhea that lasted >3 days were similar in the 2 groups. Despite modest increases in serum zinc concentration among children who received zinc-ORS when compared with children who received ORS, zinc-ORS did not result in improvements in stool output or duration of diarrhea, the clinical outcomes by which efficacy is most often measured (3–7). The daily dose of zinc that the WHO recommends for acute diarrhea was not achieved in most of the children in our zinc-ORS study arm beyond the first day of treatment, after which it was even lower. This is the most likely reason for the lack of effect.

TABLE 6. Serum zinc and copper in the 2 groups; zinc-ORS and ORS in a trial on the efficacy of zinc mixed in ORS in 500 northern Indian children

	Zinc-ORS (n = 248)	ORS (n = 252)	Difference in mean (95% CI, *P*)
Serum zinc	Mean (SD), μg/dL		
At randomization (baseline)	91.2 (29.1)	88.9 (33.6)	
24 h	89.8 (31.1)	83.9 (28.9)	5.8 (0.43–11.17, $P = 0.03$)
At recovery	91.3 (33.7)	84.5 (33.9)	6.9 (0.65–13.1, $P = 0.03$)
Serum copper	Mean (SD), μg/dL		
At randomization (baseline)	135.7 (31.9)	139.6 (31.2)	
24 h	120.8 (29.9)	124.5 (29.5)	−3.7 (−9.17 to 1.65)
At recovery	119.4 (28.1)	123.9 (27.4)	−4.5 (−9.72 to 0.72)

CI = confidence interval; ORS = oral rehydration solution; SD = standard deviation.

The results are different from an earlier community study (10). A number of differences can be noted between the 2 trials. First, the present study enrolled children with more severe diarrhea who were brought for hospitalization. Zinc losses in such children are likely to be larger and intake of zinc from zinc-ORS may be insufficient to compensate for these losses. Second, in nearly 50% of the subjects in the present study, rotavirus infection was the cause of diarrhea, whereas rotavirus has been reported as the cause in <25% of episodes of acute diarrhea in the community (14). Another difference was that the children in the present study were younger than the subjects in the community trial. A zinc-containing ORS has been reported to be beneficial when started within 24 hours of diarrhea in a small study in Italy (9). The intervention ORS used contained zinc as well as prebiotics and had a lower osmolarity (200 mOsm/L) than the control ORS (225 mOsm/L). The beneficial effect of the superhypotonic ORS could therefore be attributable to either of these 3 differences or a combination of them. The etiology of diarrhea differs with age—rotavirus diarrhea is more common among younger children (15–17). The effects of zinc-ORS may be influenced by the child's age, the severity and etiology of diarrhea, and the timing and amount of zinc from ORS. There was no beneficial effect of zinc even when the analysis was restricted to children older than 6 months (Table 4) or to children older than 12 months (data not shown). Zinc-ORS did not have an effect on stool or on the duration of diarrhea, even when it was started within the first 24 hours or among children dehydrated at enrollment who are likely to consume greater quantities of zinc-ORS. Zinc-ORS did not have any beneficial effects in subgroups by etiology of diarrhea (rotavirus positive and negative).

The limitation of the present study was that we did not include a third intervention group that received zinc as syrup or tablets. Zinc was not a part of standard recommended treatment for acute diarrhea when the proposal for the present study was written and when the necessary approvals were given. Meticulous measurement of primary study outcomes, stool weights, and time to recovery from diarrhea was performed. Every stool was weighed in a standardized manner, and ORS intakes were strictly supervised, restricting outcome misclassification to a minimum.

There were no adverse events associated with zinc-ORS. There were no differences in the clinical or biochemical parameters in the 2 groups. Stool output and time to recovery were similar between the 2 treatment groups when stratified by baseline zinc status (zinc normal and zinc deficient, data not shown) or pre-admission duration of diarrhea (Table 4). Zinc-ORS did not induce vomiting or reduce serum copper concentrations; the incidence of vomiting and mean serum copper concentrations were similar in the 2 groups at 24 hours and at recovery.

In conclusion, reduced-osmolarity ORS containing zinc was not superior to ORS alone in the management of acute diarrhea. The present WHO recommendation is to give zinc, as a syrup or dispersible tablet, for 10 to 14 days, in addition to reduced-osmolarity ORS, which may reduce subsequent diarrheal morbidity (18,19). Despite potential practical advantages of zinc-ORS, our results clearly demonstrate that the required therapeutic recommendations of oral zinc during diarrhea are not met when given mixed with ORS, and zinc-ORS does not reduce the severity or duration of acute watery diarrhea in children who are brought to hospitals with diarrhea. Zinc-ORS preparations are being introduced into the market in India. Attempts to market zinc-ORS using evidence from zinc (syrup/tablets) supplementation trials must therefore be discouraged and recommendations must clearly state that oral zinc separately from ORS is the only evidence-based zinc intervention for acute watery diarrhea.

Acknowledgments: We thank the medical and nursing staff of the 2 hospitals for their contribution and the patients and their parents. We acknowledge Mr Anil Kumar Sharma for quality assurance and staff supervision, and Mr Mukesh Juyal and Mr Dharmendra Sharma for secretarial and data management support, respectively. We are also thankful to Wallace Pharmaceuticals Pvt Ltd for preparing reduced-osmolarity ORS with and without zinc for the study.

REFERENCES

1. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull WHO* 2003;81:197–204.
2. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet* 2003;361:2226–34.
3. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr* 2000;72:1516–22.
4. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea. *J Health Popul Nutr* 2001;19:339–46.
5. Bhatnagar S, Bahl R, Sharma PK, et al. Zinc with oral rehydration therapy reduces stool output and duration of diarrhea in hospitalized children: a randomized controlled trial. *J Pediatr Gastroenterol Nutr* 2004;38:34–40.
6. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. *BMJ* 2002;325:1059.
7. Sazawal S, Black RE, Bhan MK, et al. Zinc supplementation in young children with acute diarrhea in India. *N Engl J Med* 1995;333:839–44.
8. *Implementing the New Recommendations on the Clinical Management of Diarrhoea. Guidelines for Policy Makers and Programme Managers.* Geneva: World Health Organization; 2006.
9. Passariello A, Terrin G, De Marco G, et al. Efficacy of a new hypotonic oral rehydration solution containing zinc and prebiotics in the treatment of childhood acute diarrhea: a randomized controlled trial. *J Pediatr* 2011;158:288–92.
10. Bahl R, Bhandari N, Saksena M, et al. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea. *J Pediatr* 2002;141:677–82.
11. Hambidge KM, King JC, Kern DL, et al. Pre-breakfast plasma zinc concentrations: the effect of previous meals. *J Trace Elem Electrolytes Health Dis* 1990;4:229–31.
12. Black RE. Zinc deficiency, infectious disease and mortality in the developing world. *J Nutr* 2003;133:1485S–9.
13. Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. *Aliment Pharmacol Ther* 2008; 28:713–23.
14. Samantaray JC, Mohapatra LN, Bhan MK, et al. Study of rotavirus diarrhea in a north Indian community. *Indian Pediatr* 1982;19:761–5.
15. Bhan MK, Kumar R, Khoshoo V, et al. Etiologic role of enterotoxigenic *Escherichia coli* & rotavirus in acute diarrhoea in Delhi children. *Indian J Med Res* 1987;85:604–7.
16. Bahl R, Ray P, Subodh S, et al. Incidence of severe rotavirus diarrhea in New Delhi, India, and G and P types of the infecting rotavirus strains. *J Infect Dis* 2005;192(suppl 1):S114–9.
17. Sharma S, Ray P, Gentsch JR, et al. Emergence of G12 rotavirus strains in Delhi, India, in 2000 to 2007. *J Clin Microbiol* 2008;46:1343–8.
18. Bhutta ZA, Black RE, Brown KH, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. *J Pediatr* 1999;135:689–97.
19. Rahman MM, Vermund SH, Wahed MA, et al. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. *BMJ* 2001;323:314–8.