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Zinc Supplementation for the Treatment of Diarrhea in Infants in Pakistan, India and Ethiopia

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ABSTRACT

Objective: This randomized, placebo-controlled trial was designed to assess the safety and efficacy of 10-mg zinc supplementation for the treatment of acute diarrhea in infants.

Patients and Methods: A total of 1110 infants age 28 days to 5 months with acute diarrhea were enrolled and randomized to receive either zinc (n = 554) or placebo (n = 556) for 14 days. Diarrhea history, anthropometric status, breast-feeding status and socioeconomic indicators were assessed at baseline. The homes of all infants were visited every 3 days until the diarrhea episode was over. The number of stools, presence of blood and additional illnesses were recorded daily.

Results: The geometric mean duration of the diarrhea episode was 0.21 days longer among infants receiving zinc versus those receiving placebo, but this was not statistically significant and no difference was observed after controlling for sex, exclusive breast-feeding and length for age *z* score. There were no differences in any subgroup (ie, sex, baseline length for age *z* score, exclusive breast-feeding or site after controlling for the remaining subgroup variables). There were no differences in reported stool frequency or among the proportion of episodes lasting longer than 7 days. Rates of vomiting were similar in the zinc and placebo groups.

Conclusions: Young infants do not appear to benefit from zinc supplementation for the treatment of diarrhea. ***JPGN 43: 357–363, 2006.*** **Key Words:** Zinc supplementation—Diarrhea—Infants—Randomized controlled trial. © 2006 Lippincott Williams & Wilkins

INTRODUCTION

Diarrhea remains a leading cause of death in children younger than 5 years around the world. A recent report estimated nearly 2 million children die every year from diarrhea, of which more than half of the episodes are exacerbated by undernutrition (1). Although young infants have fewer episodes of diarrhea per year than older infants and children, they more quickly develop dehydration and have higher rates of case fatality than older children; diarrhea remains a leading cause of death in nonbreast-fed infants (2,3).

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Zinc supplementation for the treatment of diarrhea has been proven safe and effective in numerous studies in children 6 to 59 months of age (4,5). Zinc has been shown to decrease the duration of the episode in both acute and persistent diarrhea (5). Zinc treatment has also been shown to decrease the severity of the diarrhea episode by decreasing the number of stools per day (6–8), the volume of stools per day (9–11) and the number of episodes lasting beyond 7 days (6,12).

Although there is now a global recommendation by World Health Organization (WHO) and UNICEF for zinc supplementation for the treatment of all diarrhea in children younger than 5 years (13), there has been only one study that specifically assessed the efficacy of zinc supplementation in infants 1 to 6 months of age (14). In this study, 275 male infants were randomized to receive 5-mg zinc, 20-mg zinc or placebo daily during hospitalization for acute watery diarrhea. There were no differences in duration or severity of the episode between the children supplemented with zinc (either 5 or 20 mg) or placebo. The results are different from those in older children and even those in infants younger than 12 months; however, few of these trials included infants younger than 6 months.

Exclusively and predominantly breast-fed infants younger than 6 months may have a higher zinc intake

than infants who are receiving complementary foods (15). Therefore, infants with diarrhea may respond differently to zinc supplementation depending on their breast-feeding status. It is also likely that low birth weight infants have poorer zinc stores at birth than larger, more developed infants (16). In addition, there have been studies linking small size at birth with a higher incidence of diarrhea and respiratory infections (17,18). Thus, it may be hypothesized that zinc supplements for diarrhea may have more of an effect in low birth weight infants.

We conducted a randomized, placebo-controlled trial to assess the efficacy and safety of zinc supplementation in infants younger than 6 months in Pakistan, India and Ethiopia—3 countries with high diarrhea morbidity and high infant mortality (19–21). In addition, we sought to characterize any variation in effect of zinc supplementation by breast-feeding status before the diarrhea episode and by the infant's anthropometric status.

PATIENTS AND METHODS

Study Population

From October 2003 to February 2005, we enrolled 1110 infants with acute watery diarrhea from urban, low socioeconomic neighborhoods of Karachi, Pakistan; New Delhi, India; and Addis Ababa, Ethiopia. We hypothesized that infants receiving zinc would recover from diarrhea 1 day sooner than infants receiving placebo. The sample size was calculated to detect a 1-day difference in mean duration of diarrhea between zinc and placebo groups, assuming a 10% loss to follow-up, 80% power and a 2-sided alpha of 0.05. We used a sample size of 1122 to detect the 1-day difference after stratification by exclusive breast-feeding status and low length for age *z* (LAZ) score; this assumed that 30% of infants would be exclusively breast-fed and 30% would be <-1 LAZ. Because we were not able to obtain accurate birth weights, LAZ score was used to approximate small size at birth.

Infants 1 to 5 months of age with acute diarrhea (<72 hours) were recruited from those seeking care at the study clinics set up within neighborhoods and those referred for care from household visits by field workers. Infants were screened by study physicians and excluded for one or more of the following: (1) severe malnutrition (<-3 *z* score weight for age), (2) signs of pneumonia if younger than 2 months (cough and difficult or fast breathing with a respiratory rate of >60 breaths/min), (3) signs of severe pneumonia if 2 to 5 months of age (cough or difficult or fast breathing and chest indrawing, nasal flaring or grunting), (4) required hospitalization (an overnight stay at a healthcare facility) for any reason, (5) known major congenital malformation, (6) any other serious preexisting medical condition, (7) lived out of or planned to move out of the study area within the following 3 months or (8) previously enrolled in the study.

All parents/guardians of eligible infants were informed of the purpose of the study, expected procedures and potential risks and benefits. Written permission was obtained from the parent/guardian. The written consent and all study procedures were approved by the Johns Hopkins Bloomberg School of Public Health's Committee on Human Research, the Addis Ababa University Faculty of Medicine's Research and Publication Committee, the Aga Khan University's Ethical Review Committee, and the Society for Applied Studies' Ethical Review Committee.

Enrolled infants were assessed for history of the diarrhea episode including all clinical symptoms and treatments, history of other illnesses and medications given in the past month, breast-feeding status and sociodemographic indicators. The length of episode (hours), severity (number of stools in past 24 hours) and presence/absence of blood were recorded. In Pakistan, length of the episode was recorded as greater than or less than 72 hours. Weight was measured on an infant scale and recorded to the nearest 100 g. Length was measured using an infant length board and was recorded to the nearest 0.1 cm. Breast-feeding status was assessed by asking about the frequency of breast-feeding in the 24 hours before diarrhea, if any, and the intake of any other liquids and foods in the baby's diet for the week before the episode of diarrhea and since the episode of diarrhea began.

Upon enrollment, infants were assigned chronological study IDs corresponding to a prelabeled blister pack of either zinc or placebo tablets. Individual block randomization of block size 8 was done by study site for all blister packs of zinc and placebo. The randomization scheme was assigned in Geneva and kept secure until the completion of data collection and initial analysis. All members of the study teams were kept blinded throughout the study.

Each infant was assessed for signs of dehydration using WHO guidelines (22). Dehydration, if any, was corrected with oral rehydration solution (ORS) as per the WHO guidelines (22). After dehydration was corrected, the study doctor/nurse demonstrated to the parent/guardian how to disperse 1 tablet in a spoonful of either expressed breast milk or ORS and supervised as the mother gave her baby the first tablet. The parent/guardian was then instructed to give the infant 1 dispersed tablet each day for 14 days. (The dispersed tablet will be hereafter referred to as tablet.) Two packets of ORS were given to the parent/guardian with instructions to continue ORS use until the diarrhea episode ceased. Each parent/guardian was counseled regarding the importance of exclusive breast-feeding, continued and increased feeding throughout the diarrhea episode, giving adequate fluids and when to seek additional medical care. She was then advised that a trained data collector would be visiting her home to assess the progress of the diarrhea episode and monitor growth. In cases where the location of the home could not be adequately described, the mother was accompanied home to map the location.

All enrolled infants were followed up 3 days after the baseline assessment by a trained data collector. If, for any reason, the visit was not possible due to holiday or absence of the parent or infant, the follow-up visit was repeated within 24 hours or the original visit date. The follow-up visit assessed the progress of the index diarrhea episode (number of stools per day and presence/absence of blood in the stool), the adherence to ORS and the zinc/placebo treatment tablets by asking the mother if she had given the tablet on each day and then visual assessment of the zinc/placebo blister pack, and daily assessment of vomiting or any other adverse reaction. Any additional treatment or care seeking was also recorded. Referrals were made for any infant with a worsening diarrhea or any danger signs as recommended by WHO (22). The follow-up visits continued every 3 days until the baby had passed less than 3

watery stools per 24 hours for at least 48 hours and until the mother confirmed the diarrhea had ended. On the last 3-day follow-up visit, the weight and length of the infant were measured and the mother was advised to continue to give the baby 1 tablet per day until all 14 tablets were finished. Any infant with diarrhea lasting more than 9 days was referred to the healthcare facility for additional clinical assessment.

Statistical Methods

Data entry was done in a customized double-entry system. The analysis was conducted using STATA 8.0 statistical software (23). Baseline characteristics were assessed for all enrolled infants. Sex, age, duration and severity of diarrhea upon enrollment, breast-feeding status, maternal literacy, household size and access to a toilet were compared by zinc and placebo groups for all infants and by country. Breast-feeding categories were adapted from current published guidelines of breast-feeding definitions (24). Any differences in proportions between zinc and placebo groups were assessed using Pearson χ^2 test. Any differences in means between zinc and placebo groups were assessed using the Student t test. Infants who withdrew from the study during the 3-day follow-up period were excluded from the analysis, and all analyses were based on "intention-to-treat."

The main outcome variables were duration and severity of diarrhea. The duration (days of diarrhea) was assessed as a continuous variable. To normalize the distribution of diarrheal duration, a log transformation was used. For severity, the mean number of stools per day of diarrhea was measured as a continuous variable and the proportion of episodes greater than 7 days as a dichotomous variable. Subsequent to the overall comparisons between the zinc and placebo groups data were stratified by site, age (<3 months vs 3–5.99 months), sex, breast-feeding status (exclusive vs nonexclusive) and length for age at enrollment (≤−1 LAZ vs >−1 LAZ). Stratified analyses by exclusive breast-feeding and baseline LAZ score were done as per the original primary study design. Stratification by site and age were done for descriptive purposes. Stratification by sex was done to account for the baseline differences in the proportion of boys and girls in each randomization group. Differences in the

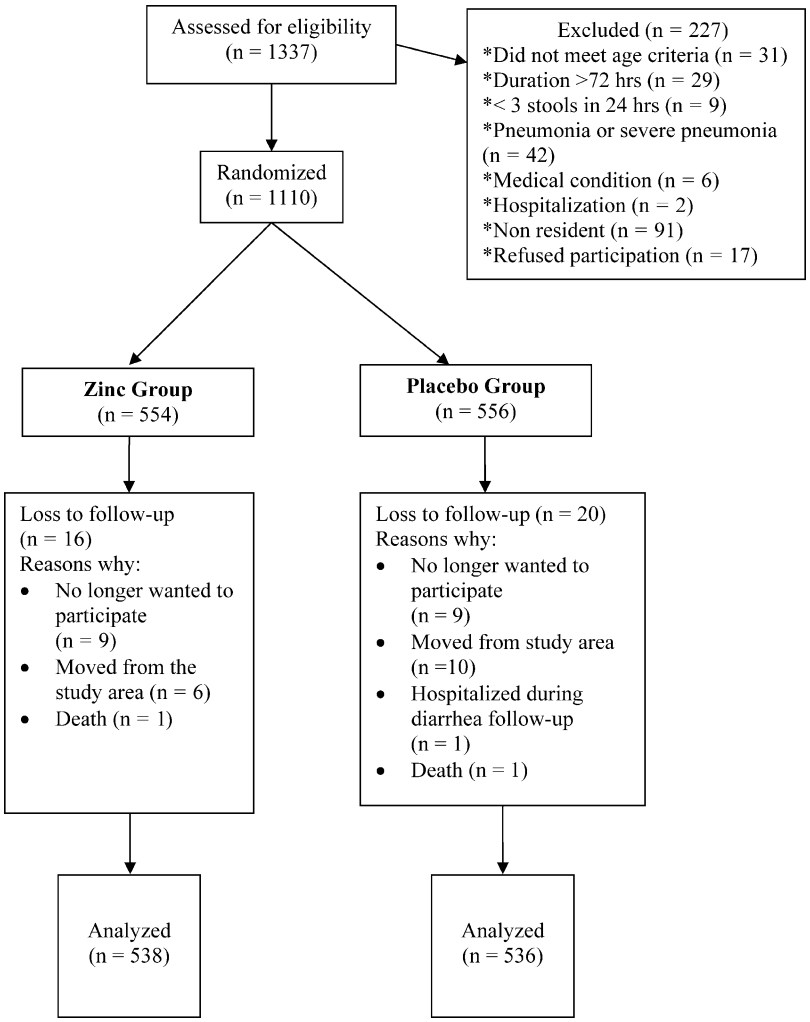

FIG. 1. Trial profile.

TABLE 1. *Baseline characteristics by site and supplementation group**

Selected baseline characteristics at enrollment	All sites		Pakistan		India		Ethiopia	
	Zinc (n = 554)	Placebo (n = 556)	Zinc (n = 281)	Placebo (n = 279)	Zinc (n = 186)	Placebo (n = 187)	Zinc (n = 87)	Placebo (n = 90)
Male, %	49.8†	56.8	49.1	56.3	45.2	53.5	62.1	65.6
Mean age, d	97.8 ± 43.0	99.2 ± 41.5	89.1 ± 39.8	89.1 ± 38.2	102.3 ± 44.2	103.6 ± 42.5	117.1 ± 43.0	121.4 ± 39.0
Mean weight, g	5285 ± 1282	5267 ± 1181	5218 ± 1223	5199 ± 1087	5035 ± 1212	4970 ± 1079	6138 ± 1343	6096 ± 1296
Mean length of diarrhea upon enrollment, h	NA	NA	NA	NA	34.6 ± 16.0	37.9 ± 17.4	52.2 ± 20.0	52.9 ± 19.8
Mean number of loose or watery stools	6.7 ± 3.8	6.6 ± 3.4	5.8 ± 2.2	5.8 ± 2.1	9.2 ± 5.0	8.6 ± 4.4	4.2 ± 1.0‡	4.7 ± 1.5
Percent exclusively breast-fed§	29.8†	24.3	46.3	39.1	10.2	9.0	18.4†	10.0
Percent of mothers who are able to read and write	49.3	45.5	29.9	22.9	66.7	64.2	77.3	76.7
Median number of persons in household	6 (2,50)	6 (2,32)	8 (3,50)	8 (3,32)	6 (3,16)	6 (3,19)	4 (2,10)	4 (2,13)
Percent of households with a private latrine or toilet	73.0	70.6	98.6	97.8	57.0	52.9	25.0	22.5

*Data are presented as percents, mean ± standard deviation or median (range).
†Differences in proportions between zinc and placebo group are statistically significant by Pearson χ^2 test ($P < 0.05$).
‡Differences in means between zinc and placebo group are statistically significant by Student t test analysis ($P < 0.05$).
§Exclusively breast-fed is defined as receiving only breast milk in the week before the diarrhea episode.
NA indicates not applicable.

geometric mean duration were assessed using a nonparametric ANOVA, differences in geometric mean stools per day were assessed using a Student t test and differences in proportion of infants with diarrhea greater than 7 days were assessed by Pearson χ^2 test. Generalized gamma multivariate regressions were then carried out to control for sex, exclusive breast-feeding and LAZ score for the comparison of zinc versus placebo effects among all infants and stratified subgroups analyses. Adjustments were made for sex because of the imbalance in distribution between zinc and placebo and for exclusive breast-feeding status and baseline LAZ because both may be directly related to the infant's baseline zinc status and thus may alter the effect of zinc on diarrhea morbidity. For the categorical variable of duration lasting more than 7 days, Mantel-Haentzel adjusted odds ratios were performed to adjust for sex, exclusive breast-feeding, LAZ scores and site. All statistical differences were assessed at the 95% significance level or above.

Safety was assessed by comparing the rates of vomiting. Vomiting was defined as the full ingestion of the tablet and regurgitation within 5 minutes. The proportion of infants who vomited 1 or more tablets during the supplementation period was calculated. These rates were compared by supplementation group for all infants and within each site. The differences between proportions were assessed using Pearson χ^2 test.

RESULTS

A total of 1337 infants with diarrhea were screened for enrollment in this intervention study; 1110 met all inclusion and exclusion criteria and were enrolled (Fig. 1). Enrollment varied by site, that is, in Pakistan, 560; India, 373; and Ethiopia 177. Fifty percent of the infants received zinc supplements and 50% received placebo. Infants receiving placebo were more likely to be male (56.8%) than infants receiving zinc (49.8%). Infants receiving zinc were more likely to be exclusively breast-fed (29.8%) than infants receiving placebo (24.3%). Infants were similar with regard to other baseline characteristics (Table 1). More than 90% of all infants were receiving some breast milk before the episode of diarrhea, but only 27% of infants were receiving only breast milk (Table 2). Blood

TABLE 2. *Prevalence of exclusive breast-feeding before the diarrhea episode by country**

Breast-feeding categories†	All, %	Pakistan, %	India, %	Ethiopia, %
Exclusively breast-fed	27.0	42.7	9.7	14.1
Partially breast-fed with water	21.1	21.8	26.8	6.8
Partially breast-fed with other liquids (juice, tea, cow's milk)	27.4	19.3	35.1	36.7
Partially breast-fed with foods	16.4	11.6	21.7	20.3
Not breast-fed	8.1	4.6	6.7	22.0

*Totals do not add to 100% due to rounding.
†Breast-feeding category determined by the mother's report of feeding practices in the week before the diarrhea episode.

TABLE 3. *Effect of zinc supplementation on diarrhea duration and severity**

	All infants		Pakistan		India		Ethiopia	
	Zinc (n = 538)	Placebo (n = 536)	Zinc (n = 273)	Placebo (n = 270)	Zinc (n = 185)	Placebo (n = 183)	Zinc (n = 80)	Placebo (n = 83)
Geometric mean duration of episode, d	3.80†‡ (1.84, 7.85)	3.59 (1.82, 7.10)	3.66 (2.04, 6.58)	3.53 (2.07, 6.02)	3.62 (1.40, 9.36)	3.17 (1.31, 7.62)	4.87 (3.08, 7.00)	5.02 (3.11, 8.09)
Median duration, d	4 (1, 24)	4 (1, 22)	3 (1, 24)	3 (1, 22)	4 (1, 24)	3 (1, 20)	5 (1, 9)	5 (1, 17)
Mean stools per day, number	5.0 ± 2.3	5.0 ± 2.4	4.9 ± 1.8	4.9 ± 1.8	5.6 ± 3.1	5.6 ± 3.4	4.0 ± 0.8	4.0 ± 0.6
Proportion of episodes >7 d	25.1 (21.5, 29.0)	20.3 (17.0, 24.0)	20.5 (15.8, 25.8)	14.4 (10.5, 19.2)	30.8 (24.2, 38.0)	23.5 (17.6, 30.3)	27.5 (18.1, 38.6)	32.5 (22.6, 43.7)

*Data reported as follows: Geometric mean (−1 SD, +1 SD), median (range), mean (± SD) and proportion (95% confidence interval).
†Zinc versus placebo: ANOVA analysis of the log-transformed data ($P = 0.1762$).
‡Zinc versus placebo: Generalized gamma regression controlling for sex, breast-feeding status and LAZ score ($P = 0.225$).

was present in 1.7% of the episodes at baseline; there were no differences in dysentery rates between supplementation groups. Thirty-six infants, 16 in the zinc group and 20 in the placebo group, withdrew from the study during the first 3-day follow-up period and were excluded from the analysis. Compliance was high for both groups; 95.8% of infants receiving zinc and 95.6% of infants receiving placebo consumed at least 10 tablets, and 85.6% of infants receiving zinc and 84.4% of infants receiving placebo consumed 1 tablet a day until all 14 tablets were finished.

The duration of diarrhea was 0.21 days longer among infants receiving zinc compared to those receiving placebo when geometric means were compared, but this

TABLE 4. *Effect of zinc supplementation on diarrhea duration and severity stratified by breast-feeding status, anthropometric status, sex and age*

	n	Zinc	n	Placebo
Geometric mean duration of episode*				
All	538	3.80†‡ (1.84, 7.85)	536	3.59 (1.82, 7.10)
Exclusively breast-fed§	163	3.91 (2.09, 7.32)	129	3.91 (2.22, 6.89)
Nonexclusively breast-fed	375	3.76 (1.75, 8.07)	407	3.49 (1.71, 7.12)
<−1 LAZ	242	3.91 (1.92, 7.98)	246	3.55 (1.76, 7.18)
>−1 LAZ	296	3.72 (1.78, 7.75)	290	3.62 (1.87, 7.03)
Male	264	3.85 (1.92, 7.11)	304	3.54 (1.84, 6.80)
Female	274	3.76 (1.77, 7.99)	232	3.66 (1.78, 7.50)
<3 mo of age	254	3.67 (1.82, 7.41)	239	3.44 (1.76, 6.74)
3–5.99 mo of age	284	3.92 (1.86, 8.62)	297	3.71 (1.86, 7.39)
Mean number of stools per day				
All	538	5.0 ± 2.3	536	5.0 ± 2.4
Exclusively breast-fed§	163	4.9 ± 2.3	129	5.1 ± 2.2
Nonexclusively breast-fed	375	5.0 ± 2.3	407	5.0 ± 2.5
<−1 LAZ	242	5.0 ± 2.1	246	5.1 ± 2.6
>−1 LAZ	296	5.0 ± 2.4	290	4.9 ± 2.2
Male	264	4.9 ± 2.2	304	4.9 ± 2.3
Female	274	5.1 ± 2.4	232	5.1 ± 2.6
<3 mo of age	254	5.1 ± 2.2	239	5.1 ± 2.6
3–5.99 mo of age	284	5.0 ± 2.4	297	5.0 ± 2.3
Proportion of episodes >7 days				
All	538	25.1 (21.5, 29.0)	536	20.3 (17.0, 24.0)
Exclusively breast-fed§	163	25.1 (18.7, 32.5)	129	18.6 (12.3, 26.4)
Nonexclusively breast-fed	375	25.1 (20.7, 29.8)	407	20.9 (17.0, 25.2)
<−1 LAZ	246	23.6 (18.4, 29.4)	246	21.1 (16.2, 26.8)
>−1 LAZ	290	26.4 (21.4, 31.8)	290	19.7 (15.2, 24.7)
Male	264	23.1 (18.2, 28.7)	304	19.1 (14.8, 24.0)
Female	274	27.0 (21.8, 32.7)	232	22.0 (16.7, 27.9)
<3 mo of age	254	22.4 (17.5, 28.1)	239	17.6 (13.0, 23.0)
3–5.99 mo of age	284	27.5 (22.4, 33.0)	297	22.6 (17.9, 27.7)

*Data reported as geometric mean (−1 SD, +1 SD).
†Zinc versus placebo: ANOVA of the log-transformed data ($P = 0.1762$).
‡Zinc versus placebo: Generalized gamma regression controlling for breast-feeding status, LAZ score and sex ($P = 0.225$).
§Exclusive breast-feeding is defined as feeding with only breast milk in the week before the diarrhea episode.

was not statistically significant (Table 3). No difference was observed after controlling for sex, breast-feeding status and LAZ score of the infant in the generalized gamma regression. There were no differences between supplementation groups in duration of diarrhea, number of stools per day or the proportion lasting more than 7 days among all infants or when stratified by site.

There were no differences in the geometric mean duration of the episode observed in subgroups stratified by baseline breast-feeding status, LAZ score, sex or age (Table 4). There were no differences in the mean number of stools per day overall or in any stratified analysis and no differences in the proportion of episodes that continued 7 days or more.

Vomiting rates were similar between zinc-supplemented (8.7%) infants and those receiving placebo (6.2%). There was only one hospitalization for receipt of intravenous fluids during the 3-day follow-up period of the study; this occurred in the placebo group. Two infants in Ethiopia died during the second and third 3-day follow-up. One was receiving zinc and one receiving placebo.

DISCUSSION

We assessed the efficacy of 10-mg/d zinc supplementation among infants younger than 6 months in 3 countries where there are high rates of zinc deficiency. A national nutrition survey, recently completed in Pakistan, found that 37.1% of children younger than 5 years had a serum zinc concentration <60 μg/dL (25). In India and Ethiopia, previous trials of long-term daily zinc supplementation have documented positive effects of zinc supplementation among young infants and children (26,27). Stunting rates, a recommended indicator for high rates of zinc deficiency among children younger than 5 years, are high in all 3 countries (28), and diarrhea is frequent in children younger than 5 years (19–21).

Although we sought to enroll equally in all sites, the rates of infant diarrhea at the study sites were significantly lower than expected in Ethiopia. To meet the desired sample size, it was necessary to enroll more infants in Pakistan to compensate for the slower enrollment in Ethiopia. Stringent uniform enrollment criteria were used across all sites; therefore, this variation should not affect the interpretation of the results.

Only one other study has assessed the efficacy of zinc supplementation (5 mg or 20 mg) for the treatment of diarrhea in this age group (14). Our infants were slightly younger than the infants enrolled by Brooks et al. (3.2 mo vs 4.0 mo) and had a higher prevalence of exclusive breast-feeding (27.0% vs 6.9%). Brooks et al. observed a nonsignificant benefit of zinc supplementation for 5 mg/d, but not 20 mg/d, on the duration or severity of the diarrheal episode. We observed a nonsignificant increase in duration among infants receiving zinc compared to those who received placebo. These results differ substantially from results observed among older infants and children where zinc supplementation has been shown to decrease the duration of the diarrhea episode by 15% on any given day (5) and decrease the number of stools per day by as much as 76% (8).

This study was powered to assess differences within subgroup analyses by breast-feeding status and baseline LAZ score. There was no difference when stratified by breast-feeding status. Breast milk typically provides adequate zinc during the first 6 months of life, and the addition of complementary foods with low zinc and/or high phytate content would be expected to decrease the infant's zinc status. Even in countries where maternal zinc intake is low, infants receive adequate zinc in the breast milk until approximately 6 months of age (29,30). Thus, it was expected that infants who were not exclusively breast-fed would benefit more from zinc supplementation given during diarrhea; however, these infants may have not had enough time to develop zinc deficiency. It is also possible that those infants who were predominantly, if not exclusively breast-fed, had zinc intakes that were similar to those who were exclusively breast-fed despite their dietary pattern. We did not have sufficient infants in a nonbreast-fed group to do a clearer comparison. We did not collect serum samples from the infants in this study; thus, we are not able to categorize zinc deficiency based on serum zinc status.

There was no difference between supplementation groups when stratified by LAZ score. The mean LAZ at enrollment for these children was -0.91 z, and 47% were <-1 LAZ. Because it was not possible to ascertain accurate birth weights from babies in these communities, we used LAZ score to best approximate size at birth. At this age, the low LAZ scores likely represent infants born small for gestational age, as compared to older infants where stunting is often a result of long-term undernutrition. Despite their small stature, inadequate zinc stores do not appear to be a limiting clinical problem for these infants.

There are possible explanations for the benefit of zinc treatment of diarrhea in older children but not in young infants. The effects of zinc may differ by pathogen, and the relative importance of different pathogens varies by age. For example, zinc has been shown to inhibit ion secretion induced by cholera toxin but not by *Escherichia coli* heat-stable toxin (31). The effect of zinc on recovery from diarrhea due to rotavirus or other pathogens that predominate in the study age group is unknown. Another possible difference between young infants and older children is the mechanisms of immune protection. Young infants derive substantial protection from immune factors in breast milk, whereas older children must rely on acquired immunity and rapid response to infection at the onset of diarrhea. Plausibly then, the immunocompromise that is associated with zinc deficiency may have greater consequences in an age group that relies on active rather than on passive immune factors in recovery from illness.

More than 25% of the infants enrolled in this study were ill in the month before the index episode of diarrhea. Because of the difficulty in achieving accurate reporting of illness severity, duration and treatments, it is difficult to assess the impact, if any, that prior illnesses may have on the episode of diarrhea. The reported use of antibiotics for this episode was less than 5%, yet a large percentage of parents reported "unknown" treatments. It is difficult to accurately categorize medications given before enrollment and conclude what effect, if any, other drugs given immediately before enrollment might have had on the effect of zinc treatment in these young infants.

Although these data do not show that zinc supplementation decreases the duration or severity of the diarrhea episode in infants younger than 6 months, they do show that zinc is safe in young infants. Rates of vomiting were clinically low in both groups, and there were no serious adverse events attributable to zinc supplementation. The importance of ORS and continued feeding, especially breast-feeding for the treatment of diarrhea, should continue to be emphasized for community- and clinic-based treatment, especially in young infants where zinc may not be as effective as in older children. The current WHO/UNICEF recommendations for the treatment of diarrhea suggest zinc supplementation in addition to ORS and continued feeding for all children younger than 5 years (13). These data suggest that WHO should consider reevaluating this policy for infants younger than 6 months.

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