ORIGINAL ARTICLE

Lower-Dose Zinc for Childhood Diarrhea — A Randomized, Multicenter Trial

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ABSTRACT

BACKGROUND

The World Health Organization recommends 20 mg of zinc per day for 10 to 14 days for children with acute diarrhea; in previous trials, this dosage decreased diarrhea but increased vomiting.

METHODS

We randomly assigned 4500 children in India and Tanzania who were 6 to 59 months of age and had acute diarrhea to receive 5 mg, 10 mg, or 20 mg of zinc sulfate for 14 days. The three primary outcomes were a diarrhea duration of more than 5 days and the number of stools (assessed in a noninferiority analysis) and the occurrence of vomiting (assessed in a superiority analysis) within 30 minutes after zinc administration.

RESULTS

The percentage of children with diarrhea for more than 5 days was 6.5% in the 20-mg group, 7.7% in the 10-mg group, and 7.2% in the 5-mg group. The difference between the 20-mg and 10-mg groups was 1.2 percentage points (upper boundary of the 98.75% confidence interval [CI], 3.3), and that between the 20-mg and 5-mg groups was 0.7 percentage points (upper boundary of the 98.75% CI, 2.8), both of which were below the noninferiority margin of 4 percentage points. The mean number of diarrheal stools was 10.7 in the 20-mg group, 10.9 in the 10-mg group, and 10.8 in 5-mg group. The difference between the 20-mg and 10-mg groups was 0.3 stools (upper boundary of the 98.75% CI, 1.0), and that between the 20-mg and 5-mg groups was 0.1 stools (upper boundary of the 98.75% CI, 0.8), both of which were below the noninferiority margin (2 stools). Vomiting within 30 minutes after administration occurred in 19.3%, 15.6%, and 13.7% of the patients in the 20-mg, 10-mg, and 5-mg groups, respectively; the risk was significantly lower in the 10-mg group than in the 20-mg group (relative risk, 0.81; 97.5% CI, 0.67 to 0.96) and in the 5-mg group than in the 20-mg group (relative risk, 0.71; 97.5% CI, 0.59 to 0.86). Lower doses were also associated with less vomiting beyond 30 minutes after administration.

CONCLUSIONS

Lower doses of zinc had noninferior efficacy for the treatment of diarrhea in children and were associated with less vomiting than the standard 20-mg dose. (Funded by the Bill and Melinda Gates Foundation; ZTDT ClinicalTrials.gov number, NCT03078842.)

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Although there has been a 90% decline in diarrhea-related deaths since the 1980s, diarrheal diseases remain a major public health problem. In 2018, approximately 500,000 children died from diarrhea. Most deaths from diarrhea among children could be avoided if children received high-quality case management with the care that has been recommended by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF); this care includes oral rehydration solutions and supplemental zinc.[1,2] The zinc recommendation is based on studies that have shown that administration of supplemental zinc results in a shorter duration of diarrhea, reduces the number of stools and stool output, reduces the risk of persistent diarrhea, and may reduce the risk of subsequent illness and increase weight gain.[3-8]

The recommended zinc dose (20 mg per day for 10 to 14 days) is based on assumptions of increased zinc losses during diarrhea and the need for additional zinc above the recommended dietary allowance for immune and gastrointestinal function.[9] Replication studies have generally used the 20-mg zinc dose without any further dose-ranging analyses. This dose substantially exceeds the recommended dietary allowance of zinc in infancy and early childhood (2 to 5 mg per day).[10]

Zinc given orally can cause vomiting because of its strong metallic taste and tendency to cause gastric irritation.[11] In a meta-analysis of 11 trials involving patients with acute diarrhea (4438 children in total),[4] patients who received supplemental zinc were significantly more likely to vomit after the initial dose of zinc than after the initial dose of placebo (12.7% vs. 7.6%; relative risk, 1.55; 95% confidence interval [CI], 1.30 to 1.84). In another review involving 12 trials (5189 children in total),[12] the risk of vomiting was significantly higher with zinc supplementation than with placebo (risk ratio, 1.59; 95% CI, 1.27 to 1.89).

Lower zinc doses, provided they are equally effective, might have the advantage of causing less vomiting than the current recommended dose. We therefore performed a randomized, double-blind, controlled trial comparing two lower doses of zinc with the recommended dose in low- and middle-income countries. We hypothesized that lower zinc doses (5 mg or 10 mg per day), as compared with the standard zinc dose (20 mg per day), would be noninferior with respect to treatment efficacy but superior with respect to the side-effect profile (i.e., vomiting).

METHODS

DESIGN

We have published the methods used in this trial previously,[13] and the protocol is available with the full text of this article at NEJM.org. The Zinc Therapeutic Dose Trial was an individually randomized, parallel-group, double-blind, controlled trial of three different doses of zinc among children in India and Tanzania who were 6 to 59 months of age.

To detect diarrhea, trial personnel screened children who presented with illness to outpatient health facilities. Patients were enrolled from periurban outpatient health facilities in India and Tanzania. The trial population was selected to reflect the general population of children presenting with diarrhea who receive ambulatory care in a primary health care setting. The patients were children who had had diarrhea (defined as three or more loose or watery stools in the past 24 hours) for less than 72 hours or dysentery (defined as diarrhea with visible blood), who were likely to stay within the study area for at least 2 months after enrollment, and whose caregivers provided written informed consent.

We excluded children who had severe acute malnutrition (weight-for-length or weight-for-height z score of less than −3 or presence of edema), severe dehydration not correctable within 4 to 6 hours, severe pneumonia (presence of fast breathing or chest in-drawing), or any of the following signs: inability to breast-feed or drink, lethargy or unconsciousness, convulsions, inability to eat without vomiting, clinically suspected bacterial sepsis, rapid diagnostic test–confirmed malaria, or other severe illness. Children who had previously been enrolled in the trial, who were currently enrolled in another study or trial, who had used zinc supplements during the 3 days before enrollment, or who had a sibling currently enrolled in the trial were also excluded.

INTERVENTIONS

Children were randomly assigned to receive one of three regimens: 5 mg, 10 mg, or 20 mg of

zinc administered once daily for 14 days. Study staff instructed caregivers to dissolve the dispersible tablet in 5 to 10 ml of water or breast milk immediately before administration. After receiving an initial dose under direct supervision of trial staff on the day of enrollment, children received zinc from their caregivers for 14 days in total. Zinc tablets were purchased from Laboratoires Pharmaceutiques Rodael, who manufactured the tablets and shipped them to the WHO for randomization and labeling before they were shipped to the study sites.

OUTCOMES

The primary efficacy outcomes were diarrhea lasting for more than 5 days and the number of loose or watery stools during the diarrhea episode after randomization. We defined diarrhea as the occurrence of three or more loose or watery stools per day. The primary safety outcome was the occurrence of vomiting within 30 minutes after administration of any zinc dose. This dose-related vomiting was measured by direct observation on day 1 and subsequently by caregiver report recorded in a daily diary. Caregivers also used the daily diary to record the zinc doses given, number of stools, and non–dose-related vomiting (>30 minutes after dose administration). This diary was reviewed by trained field workers at periodic home, clinic, or telephone visits on days 3, 5, 7, 10, and 15.

Secondary outcomes included diarrhea lasting longer than 3 days, the number of tablets consumed, caregiver reporting of favorable acceptability of zinc to the child, illness (diarrhea, fever, or respiratory symptoms) during the 60-day period after treatment initiation, growth (changes in weight, length, and mid–upper arm circumference) during the 60-day period after treatment initiation, and plasma zinc levels on days 1, 3, 7, 15, 21, and 30. To assess zinc levels during the follow-up period, two blood specimens were obtained from each participant: a randomly selected one third of participants at days 1 and 15, one third at days 3 and 21, and the remaining one third at days 7 and 30 after enrollment.

LABORATORY METHODS

Venous blood specimens (3 to 5 ml) were obtained with the use of a trace element–free syringe, transferred to zinc-free heparin tubes, and spun for 15 minutes, and plasma aliquots were stored in trace element–free tubes at −80°C until analysis.[14] Plasma specimens were analyzed for zinc status with the use of atomic absorption spectrometry (AAS 400, Perkin Elmer).

RANDOMIZATION AND BLINDING

Randomization was stratified according to country (India or Tanzania) and age (<24 months or ≥24 months) (four randomization lists). All three zinc tablets were identical in appearance, taste, and smell and were packaged in identical blister packs. Each pack was labeled only with a unique patient identification number according to a computer-generated permuted block randomization list with variable block size generated off site by a statistician who was not otherwise involved in the trial. The randomization code linking the unique identification number with the treatment group was broken after blinded analysis of all primary outcomes.

STANDARD OF CARE AND ETHICS

All enrolled children received standard of care for diarrhea management in accordance with WHO and UNICEF diarrhea case-management guidelines.[15] All caregivers signed written informed consent for their child's participation. The protocol was approved by the WHO Ethics Review Committee, the institutional review board of Boston Children's Hospital, the Tanzania Food and Drug Authority, the Tanzanian National Institute of Medical Research, the Muhimbili University of Health and Allied Sciences, Dar es Salaam, and the institutional ethics committee of Subharti Medical College and Hospital, Meerut, India. The data and safety monitoring board met twice during the trial and did not recommend any changes in the trial conduct. The authors vouch for the accuracy of the data and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

Assuming 1:1:1 random randomization, a 0.05 significance level (one-sided for the noninferiority tests for diarrhea duration and mean stool number and two-sided for the superiority test for vomiting), 90% power, and a 5% loss to follow-up, we calculated that 4500 patients were needed.[13] The assumptions used for sample-size calculation, including noninferiority and superiority

margins, are described in a separate article on methods (included in the Supplementary Appendix, available at NEJM.org).

All primary analyses used the intention-to-treat principle, and sensitivity analyses were performed with the use of a per-protocol approach for noninferiority outcomes.[16] The intention-to-treat analysis included all patients who underwent randomization and for whom assessable data were available, and the per-protocol analysis included patients for whom documentation showed that they had taken zinc for at least the first 5 days after randomization.

Children who did not have resolution of diarrhea, were lost to follow-up, died, or withdrew before day 5 were not included in the analysis of the first efficacy variable. Binomial generalized estimating equations with identity link were used to estimate the risk differences between the lower-dose groups and the standard-dose group.[17,18] The confidence intervals of these risk differences were compared with a prespecified noninferiority margin of 4 percentage points. We also constructed a Kaplan–Meier curve for the time to recovery from diarrhea in each group and used the log-rank test to test the differences.

Analysis of covariance was used to estimate the mean differences in the total number of loose or watery stools between the lower-dose groups and the standard-dose group and their confidence intervals. These confidence intervals were compared with a prespecified noninferiority margin of 2 loose or watery stools.

For the safety outcome of vomiting within 30 minutes after zinc administration, generalized estimating equations with the log link, binomial distribution, exchangeable correlation matrix, and robust estimators of variance were used to assess the relative risk of vomiting with lower doses as compared with standard doses and their confidence intervals.

We performed post hoc Bonferroni correction for the primary efficacy outcomes by providing 98.75% confidence intervals to account for multiple comparisons (duration of diarrhea and number of stools, 10 mg vs. 20 mg and 5 mg vs. 20 mg). Similar correction was applied to the primary safety outcome (vomiting) by providing 97.5% confidence intervals (10 mg vs. 20 mg and 5 mg vs. 20 mg).

We used a linear mixed-effects model to assess differences in plasma zinc response among the three groups. The model included treatment group, the day that the blood specimen was obtained, and an interaction term between these two variables. Relative risks or mean differences with their 95% confidence intervals were calculated for other secondary outcomes. They were not adjusted for multiple comparisons. Although the trial was not designed to draw conclusions about treatment-effect modification, prespecified exploratory subgroup analyses based on baseline characteristics were performed. Stratified risk differences and relative risks and their 95% confidence intervals are shown.

Statistical analyses were performed with Stata software, version 14 (StataCorp), SPSS software, version 25 (SPSS), and SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From January 2017 to February 2019, we screened 5676 children with diarrhea and enrolled 4500 children. One third of the children were randomly assigned to each treatment group (Fig. S1 in the Supplementary Appendix). Follow-up for primary outcomes was complete for approximately 98% of the enrolled children. For the primary outcome of diarrhea duration of more than 5 days, data were available for more than 98% of the patients (1480 of 1504 patients in the 5-mg group, 1480 of 1498 patients in the 10-mg group, and 1479 of 1498 patients in the 20-mg group); for the total number of stools, data were available for more than 99% (1496 of 1504, 1488 of 1498, and 1490 of 1498, respectively). Because the children were directly observed during the 30 minutes after the first dose, data were available for 100% of the patients for the primary outcome of vomiting within 30 minutes. For plasma zinc levels, the percentage of patients with data missing varied according to the day that the blood specimen was obtained and ranged from 13% to 26%.

Baseline characteristics were generally well balanced among the three groups (Table 1). The mean (±SD) ages of the children were 23.0±14.8 months in the 5-mg group, 22.7±14.6 months in the 10-mg group, and 23.2±15.3 months in the 20-mg group. The majority of children had no

Table 1. Baseline Characteristics of the Trial Population.*

Characteristic	5-mg Group (N=1504)	10-mg Group (N=1498)	20-mg Group (N=1498)
Study site — no. (%)			
India	753 (50.1)	749 (50.0)	748 (49.9)
Tanzania	751 (49.9)	749 (50.0)	750 (50.1)
Maternal and household characteristics			
Maternal age — yr†	26.7±5.0	26.8±5.0	26.9±5.0
Maternal education — yr‡	7.3±4.2	7.1±4.1	7.3±4.0
Household wealth above median — no./total no. (%)§	760/1499 (50.7)	738/1496 (49.3)	772/1496 (51.6)
Child characteristics			
Age at randomization — mo	23.0±14.8	22.7 ±14.6	23.2±15.3
Age group at randomization — no. (%)			
6 to <12 mo	412 (27.4)	410 (27.4)	434 (29.0)
12 to <24 mo	499 (33.2)	502 (33.5)	476 (31.8)
24 to <60 mo	593 (39.4)	586 (39.1)	588 (39.3)
Female sex — no. (%)	711 (47.3)	725 (48.4)	719 (48.0)
Breast-feeding on day before enrollment — no./total no. (%)	876/1499 (58.4)	857/1496 (57.3)	853/1495 (57.1)
Rotavirus vaccination — no./total no. (%)¶	749/1503 (49.8)	741/1498 (49.5)	748/1496 (50.0)
Duration of diarrhea before enrollment — no. (%)			
≤24 hr	58 (3.9)	48 (3.2)	59 (3.9)
25 to 48 hr	1259 (83.7)	1224 (81.7)	1231 (82.2)
49 to <72 hr	187 (12.4)	226 (15.1)	208 (13.9)
No. of loose or watery stools in the 24 hr before enrollment	5.7±2.0	5.7±2.1	5.7±2.1
Dysentery — no./total no. (%)	54/1503 (3.6)	62/1497 (4.1)	51/1497 (3.4)
Some dehydration — no. (%)‖	32 (2.1)	11 (0.7)	13 (0.9)
Axillary temperature >38°C — no. (%)	48 (3.2)	40 (2.7)	34 (2.3)
Cough or difficulty breathing — no. (%)	405 (26.9)	438 (29.2)	424 (28.3)
Observed respiratory rate >40 breaths/min — no. (%)	86/1503 (5.7)	84/1497 (5.6)	85/1497 (5.7)
Previous use of antibiotic agent — no. (%)	32/1499 (2.1)	38/1496 (2.5)	26/1496 (1.7)
z Score			
Length or height for age	−1.3±1.2	−1.3±1.1	−1.3±1.2
Weight for length or height	−0.7±1.0	−0.7±1.0	−0.7±1.0
Weight for age	−1.2±1.1	−1.2±1.0	−1.2±1.1
Mid–upper-arm circumference for age	−0.8±1.0	−0.8±1.0	−0.8±1.0
Zinc dose — mg/kg of body weight	0.53±0.13	1.07±0.25	2.14±0.54
Plasma zinc concentration — μg/dl**	71.5±23.4	74.9±23.9	74.0±27.1
Plasma zinc concentration <65 μg/dl — no./total no. (%)**	175/436 (40.1)	143/432 (33.1)	174/441 (39.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for plasma zinc to micromoles per liter, multiply by 0.1530.
† Data were missing for 13 patients in the 5-mg group, 8 patients in the 10-mg group, and 9 patients in the 20-mg group.
‡ Data were missing for 18 patients in the 5-mg group, 11 patients in the 10-mg group, and 16 patients in the 20-mg group.
§ A country-specific household wealth index was constructed by means of a principal components analysis of household ownership, household assets, drinking water source, and sanitation.
¶ More than 99% of Tanzanian children received at least one rotavirus vaccination, whereas less than 1% of children in India received at least one rotavirus vaccination.
‖ The World Health Organization Integrated Management of Childhood Illness (IMCI) definition of dehydration was used, which requires two of the following signs: restlessness and irritability, sunken eyes, thirst, eager drinking, and skin that goes back slowly when pinched.
** Plasma zinc concentrations were assessed in a random sample of 33.3% of patients at baseline at each site.

Table 2. Effect of Zinc Supplementation Dose on Diarrhea and Vomiting in Children with Acute Diarrhea.

Outcome	5-mg Group (N=1504)	10-mg Group (N=1498)	20-mg Group (N=1498)
Diarrhea-related outcomes			
Diarrhea >5 days, intention-to-treat analysis			
No./total no. (%)	106/1480 (7.2)	114/1480 (7.7)	96/1479 (6.5)
Risk difference (upper boundary of one-sided 98.75% CI) — percentage points*	0.7 (2.8)	1.2 (3.3)	Reference
One-sided P value for noninferiority†	<0.001	0.002	Reference
Diarrhea >5 days, per-protocol analysis			
No./total no. (%)	102/1431 (7.1)	109/1437 (7.6)	93/1440 (6.5)
Risk difference (upper boundary of one-sided 98.75% CI) — percentage points	0.7 (2.8)	1.1 (3.3)	Reference
Total loose or watery stools after enrollment, intention-to-treat analysis			
No. of patients with data	1496	1488	1490
Mean no. of stools	10.8±8.9	10.9±9.2	10.7±8.7
Mean difference (upper boundary of one-sided 98.75% CI) — no. of stools*	0.1 (0.8)	0.3 (1.0)	Reference
One-sided P value for noninferiority‡	<0.001	<0.001	
Total loose or watery stools after enrollment, per-protocol analysis			
No. of patients with data	1431	1437	1410
Mean no. of stools	10.8±8.9	11.0±9.3	10.6±8.2
Mean difference (upper boundary of one-sided 98.75% CI) — no. of stools	0.2 (0.9)	0.3 (1.1)	Reference
Vomiting-related outcomes			
Any vomiting over 14-day period within 30 min after dosing			
No./total no. (%)	206/1504 (13.7)	233/1498 (15.6)	289/1498 (19.3)
Relative risk (97.5% CI)§	0.71 (0.59–0.86)	0.81 (0.67–0.96)	Reference
Two-sided P value for superiority§	<0.001	0.01	
Any vomiting over 14-day period more than 30 min after dosing			
No./total no. (%)	301/1496 (20.1)	333/1488 (22.4)	403/1490 (27.0)
Relative risk (95% CI)	0.74 (0.65–0.85)	0.83 (0.73–0.94)	Reference

* A post hoc Bonferroni correction was applied to the primary efficacy outcomes to account for tests of the two efficacy outcomes and two treatment groups; 98.75% confidence intervals are shown, and a P value of less than 0.0125 was considered to indicate statistical significance (0.05 over four tests).
† The margin for noninferiority was 4 percentage points.
‡ The margin for noninferiority was 2 stools.
§ A post hoc Bonferroni correction was applied to the primary safety outcome to account for tests of the two treatment groups; 97.5% confidence intervals are shown, and a P value of less than 0.025 was considered to indicate statistical significance (0.05 over two tests).

dehydration at presentation, and the mean number of loose or watery stools in the 24 hours before enrollment was 5.7 in all three groups. Additional baseline characteristics are shown in Table S1. Baseline characteristics according to trial site are provided in Tables S2 and S3.

PRIMARY OUTCOMES

In the intention-to-treat analysis of the first primary efficacy outcome, the percentage of children who had diarrhea with a duration of more than 5 days was similar in the three groups (7.2% in the 5-mg group, 7.7% in the 10-mg group, and 6.5% in the 20-mg group) (Table 2). The risk in the 10-mg group was 1.2 percentage points higher than that in the 20-mg group (upper boundary of the one-sided 98.75% CI, 3.3), and the risk in the 5-mg group was 0.7 percentage points higher than that in the 20-mg group (upper boundary of the one-sided 98.75% CI,

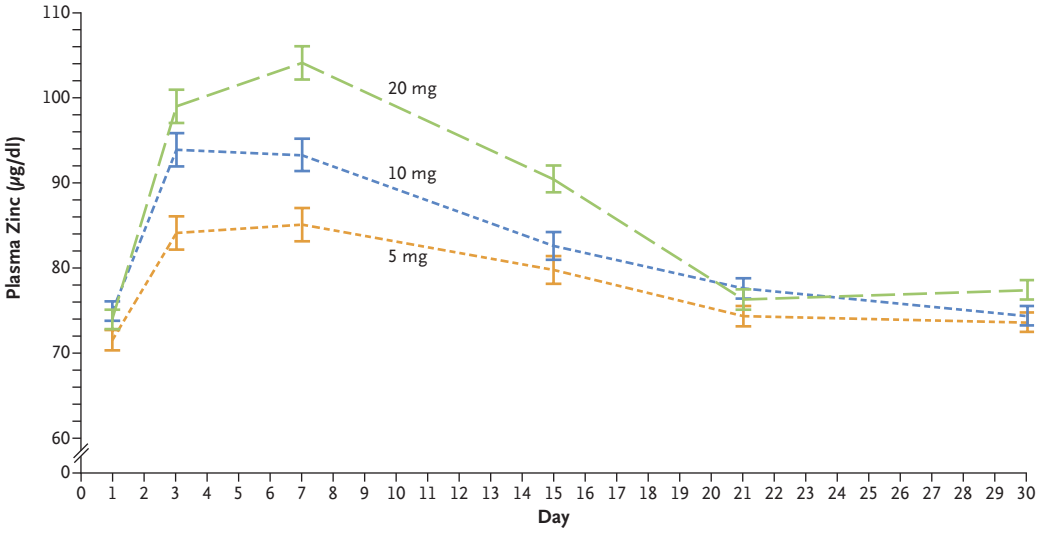

Figure 1. Modeled Plasma Zinc Concentrations.

Linear mixed-effects model estimates of the mean plasma zinc concentrations are shown; I bars indicate the SE. Plasma zinc testing was planned for 1500 patients at each of the pair of time points: day 1 (baseline) and day 15, days 3 and 21, and days 7 and 30. Plasma zinc concentrations were missing for 191 of 1500 patients (13%) on day 1, for 333 of 1500 (22%) on day 3, for 270 of 1500 (18%) on day 7, for 384 of 1500 (26%) on day 15, for 343 of 1500 (23%) on day 21, and for 247 of 1500 (16%) on day 30.

2.8). In both cases, the upper boundary of the confidence interval was lower than the prespecified 4-percentage-point noninferiority margin. Results from the per-protocol analyses were similar. Kaplan–Meier curves for the time to recovery from diarrhea are shown in Figure S4.

The intention-to-treat analysis of the second efficacy outcome showed that the mean number of loose or watery stools was similar in the three groups: 10.8±8.9 in the 5-mg group, 10.9±9.2 in the 10-mg group, and 10.7±8.7 in the 20-mg group (Table 2). The children assigned to the 10-mg group had a mean of 0.3 more loose stools (upper boundary of the one-sided 98.75% CI, 1.0) and children assigned to the 5-mg group had a mean of 0.1 more loose stools (upper boundary of the one-sided 98.75% CI, 0.8) than children in the 20-mg group. In both cases, the upper boundary of the 98.75% confidence interval was lower than the prespecified noninferiority margin of 2 stools. Results from per-protocol analyses were similar.

The effect of lower zinc doses on the risk of vomiting is shown in Table 2. Children in the 5-mg group had a 29% lower risk of vomiting within 30 minutes after zinc administration than children in the 20-mg group (relative risk, 0.71; 97.5% CI, 0.59 to 0.86). Children in the 10-mg group had a 19% lower risk of vomiting within 30 minutes after zinc administration than children in the 20-mg group (relative risk, 0.81; 97.5% CI, 0.67 to 0.96). Similar effects were seen for vomiting beyond 30 minutes after zinc administration (Table 2).

Results of subgroup analyses of the primary outcomes are shown in Tables S4, S5, and S6. The lower doses of zinc appeared to have larger beneficial effects on vomiting among patients in India than among those in Tanzania. Use of rotavirus vaccine also appeared to modify the effect size for vomiting, but this exposure was confounded with study site. The results of other subgroup analyses were unremarkable.

SECONDARY OUTCOMES

Figure 1 shows the mean and standard error of plasma zinc concentrations on day 1 (baseline), day 3, day 8, day 15, day 21, and day 30 in each treatment group. Plasma zinc concentrations were similar in the three groups at baseline but were lower in the 5-mg and 10-mg groups than in the 20-mg group on days 3, 7, and 14 after dosing. These differences were no longer seen on day 21 and day 30 (Table S7).

Results for secondary outcomes are shown in Table 3. The three groups had similar percentages of children with diarrhea, fever, or fast or difficult breathing at 30, 45, and 60 days of follow-up. Growth during the 60-day follow-up period and anthropometric status at the end of the follow-up period were also similar in the three groups, with the exception of the 5-mg group having a higher percentage of children with stunting than the 20-mg group at the end of follow-up. However, the observed differences in stunting between each lower-dose group and the 20-mg group were similar at baseline.

Adherence to the intervention was very high and similar in the three groups. Of the expected 14 pills, a mean of 13.5±2.1 pills was consumed by children in the 5-mg group, 13.7±1.7 by children in the 10-mg group, and 13.6±1.8 by children in the 20-mg group. More than 80% of the caregivers in each of the three groups (82.9% in the 5-mg group, 80.8% in the 10-mg group, and 81.1 in the 20-mg group) reported favorable acceptance of the treatment by their children.

DISCUSSION

In this large, multicenter clinical trial, lower doses of zinc (5 mg or 10 mg daily for 14 days) were noninferior to the standard dose of zinc (20 mg) in terms of duration of diarrhea and mean number of stools in children with acute diarrhea. Both the 5-mg and the 10-mg doses were superior to the 20-mg dose with respect to vomiting.

Vomiting is often a part of the acute diarrhea syndrome. Meta-analyses have shown a 50% higher risk of vomiting among children taking zinc supplements.[4,12] Efforts to scale up the use of zinc have highlighted the elevated risk of vomiting as a consideration in the rollout of such programs.[19] Reduced vomiting may improve food intake and alleviate parents' concerns about the severity of illness. In our trial, adherence to therapy was very high and did not differ significantly among the groups, despite the lower risk of vomiting associated with lower zinc doses. However, our study was an efficacy trial in which substantial efforts were made to achieve high adherence. Thus, our findings with respect to adherence might not be generalizable to program conditions.

We also found a potential effect modification according to site, in that children in India appeared to benefit more from lower zinc doses with respect to vomiting than did children in Tanzania. In addition to differing with respect to their country of origin and possibly other, unmeasured factors, the cohorts of children from the two countries included in the trial differed with respect to age (Tanzanian children were younger), nutritional status (Indian children were less well nourished), and rotavirus vaccine coverage (high in Tanzania and very low in India). Although we did not collect data on the underlying causes of diarrhea, it is possible that Indian children, because of the lack of a nationwide rotavirus immunization program, were more likely to have rotavirus as a cause of their symptoms.[20] In places where the rotavirus vaccine has been implemented, norovirus and sapovirus are common causes of childhood diarrhea.[21] Data on the potential differential effect of supplemental zinc according to the cause of diarrhea are limited.[22] Stratified analyses also suggested the possibility that children with stunting, who may be at higher risk for adverse effects of diarrheal diseases,[1,23] had greater benefit with respect to the risk of vomiting with the lower doses as compared with the 20-mg regimen.

The physiological basis for the effects of zinc supplementation on diarrheal diseases is not completely clear.[24] Possible mechanisms include correction of a nutrient deficiency, improvement of immune function,[25] or inhibition of cyclic AMP–mediated chloride secretion.[26] The doses we studied in the trial (5 mg and 10 mg daily) still exceed the recommended daily allowance for young children, and therefore it is plausible that they still work through these suggested mechanisms of action.

Strengths of our trial include its randomized, double-blind, multicenter design, large sample size, high rates of follow-up, location in countries in south Asia and sub-Saharan Africa, and recruitment of patients in outpatient facilities, where the majority of diarrhea is managed globally. Our trial addresses an important knowledge gap presented by the empirical use of the 20-mg zinc dose, which was recommended for global use without rigorous dose-finding trials.

Limitations of our trial include the reliance on caregiver reports for outcomes (although these were verified with frequent patient contact

Table 3. Effect of Zinc Supplementation Dose on Selected Secondary Outcomes.

Outcome	5-mg Group (N=1504)	Relative Risk or Mean Difference, 5 mg vs. 20 mg (95% CI)*	10-mg Group (N=1498)	Relative Risk or Mean Difference, 10 mg vs. 20 mg (95% CI)*	20-mg Group (N=1498)
Serious adverse event within 60 days — no. (%)	12 (0.8)	1.33 (0.56 to 3.14)	7 (0.5)	0.78 (0.29 to 2.08)	9 (0.6)
Diarrhea continuing beyond 3 days — no./total no. (%)†	333/1481 (22.5)	1.03 (0.90 to 1.18)	333/1481 (22.5)	1.03 (0.90 to 1.18)	323/1480 (21.8)
No. of tablets consumed during 14-day treatment period	13.53±2.05	−0.05 (−0.19 to 0.09)	13.65±1.71	0.06 (−0.06 to 0.19)	13.58±1.83
Diarrhea in the 14-day period before day 30 — no./total no. (%)	104/1433 (7.3)	0.90 (0.70 to 1.16)	104/1449 (7.2)	0.89 (0.69 to 1.15)	116/1437 (8.1)
Fever in the 14-day period before day 30 — no./total no. (%)	149/1433 (10.4)	1.12 (0.90 to 1.40)	139/1449 (9.6)	1.04 (0.83 to 1.30)	133/1437 (9.3)
Fast or difficult breathing in the 14-day period before day 30 — no./total no. (%)	8/1432 (0.6)	1.34 (0.47 to 3.84)	10/1449 (0.7)	1.65 (0.60 to 4.53)	6/1436 (0.4)
Ease in supplement administration reported by caregiver — no./total no. (%)	1187/1447 (82.0)	1.01 (0.97 to 1.04)	1174/1453 (80.8)	0.99 (0.96 to 1.03)	1182/1452 (81.4)
Anthropometric measures at day 60					
Change in z score for length or height for age‡	−0.11±0.34	−0.01 (−0.04 to 0.01)	−0.10±0.34	−0.005 (−0.03 to 0.02)	−0.10±0.33
Change in z score for weight for age§	0.10±0.35	0.02 (−0.007 to 0.05)	0.10±0.35	0.02 (−0.004 to 0.05)	0.08±0.35
Change in z score for weight for length or height¶	0.19±0.54	0.03 (−0.01 to 0.07)	0.18±0.55	0.03 (−0.01 to 0.07)	0.16±0.54
Change in z score for mid–upper arm circumference for age‖	0.21±0.40	0.02 (−0.008 to 0.05)	0.21±0.40	0.03 (−0.005 to 0.06)	0.18±0.41
Stunting — no./total no. (%)**	405/1354 (29.9)	1.16 (1.03 to 1.31)	386/1356 (28.5)	1.11 (0.98 to 1.25)	350/1357 (25.8)
Wasting — no./total no. (%)††	86/1354 (6.4)	0.85 (0.64 to 1.12)	102/1350 (7.6)	1.01 (0.77 to 1.31)	102/1360 (7.5)
Underweight — no./total no. (%)‡‡	284/1367 (20.8)	1.08 (0.93 to 1.26)	273/1370 (19.9)	1.04 (0.89 to 1.21)	262/1363 (19.2)
Favorable child acceptability reported by caregiver — no./total no. (%)	1199/1447 (82.9)	1.02 (0.99 to 1.06)	1174/1453 (80.8)	1.00 (0.96 to 1.03)	1177/1452 (81.1)
Reduction in diarrhea severity reported by caregiver — no./total no. (%)	1300/1446 (89.9)	1.00 (0.97 to 1.02)	1315/1453 (90.5)	1.00 (0.98 to 1.03)	1309/1453 (90.1)

* For outcomes analyzed as numbers and percentages of patients, the relative risk and 95% confidence interval are reported. For outcomes analyzed as means and SD, the difference in the mean and the 95% confidence interval are reported.
† Total numbers are the number of children at risk.
‡ Data were available for 1355 patients in the 5-mg group, for 1357 in the 10-mg group, and for 1357 in the 20-mg group.
§ Data were available for 1367 patients in the 5-mg group, for 1370 in the 10-mg group, and for 1363 in the 20-mg group.
¶ Data were available for 1354 patients in the 5-mg group, for 1350 in the 10-mg group, and for 1360 in the 20-mg group.
‖ Data were available for 1333 patients in the 5-mg group, for 1330 in the 10-mg group, and for 1346 in the 20-mg group.
** Stunting was defined as a z score for length or height for age of less than −2 SD.
†† Wasting was defined as a z score for weight for length or height of less than −2 SD.
‡‡ Underweight was defined as a z score for weight for age of less than −2 SD.

and daily recording of outcome information in the diary card). In addition, the modest rate of participation of children with severe diarrheal disease is likely to have contributed to lower-than-anticipated frequency of episodes lasting longer than 5 days. Our patients, however, are representative of those who present with diarrhea to first-level health facilities in low- and middle-income countries and are given oral rehydration solution and zinc treatment.

Despite evidence supporting the efficacy of supplemental zinc in improving outcomes in patients with diarrhea, as well as strong recommendations from policymakers, programmatic uptake of this component of diarrhea management has been slow to achieve high levels of coverage.[1,27] Evaluations of this limited coverage highlight the supply-side problems of insufficient financial and human capital and a weak global supply chain.[28] A renewed public health push will be needed to solve these problems and maximize the benefits of this intervention. Our findings may contribute to these programmatic efforts.

In our trial, we found that children with acute diarrhea receiving 5 mg or 10 mg per day of supplemental zinc had diarrhea outcomes similar to those in children receiving 20 mg but had less vomiting.

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