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Zinc Treatment for 5 or 10 Days Is Equally Efficacious in Preventing Diarrhea in the Subsequent 3 Months among Bangladeshi Children[1–4]

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Abstract

We conducted a randomized, double-blind placebo controlled, community trial in rural Bangladesh in children 4–59 mo of age to compare the efficacy of a 5- and 10-d course of zinc therapy on the incidence and duration of diarrhea over the subsequent 90-d follow-up after initial treatment for an acute childhood diarrheal (ACD) episode. Children (n = 1622) with ACD were randomly allocated to either 5 or 10 d of zinc treatment. Female field workers visited each child daily, supervised the administration of zinc, recorded the duration of current episode, and the occurrence and duration of diarrhea over the subsequent 3 mo. The incidence of diarrhea over the 90 d of follow-up did not differ between the 5-d (1.08 ± 1.38 episodes) and 10-d (1.02 ± 1.35 episodes) groups (P = 0.35). Children in both groups experienced a comparable duration of diarrheal episodes (3.1 ± 5.6 d vs. 2.9 ± 5.6 d, 5-d vs. 10-d, respectively; P = 0.64) with a mean difference between groups within the defined range of equivalence. Time to onset of the first episode and the proportion children experiencing diarrhea during the 90-d follow-up also did not differ between groups. These findings suggest that among Bangladeshi children, a 5-d zinc treatment for ACD is as efficacious as 10 d in preventing diarrhea in the subsequent 3 mo. J. Nutr. 141: 312–315, 2011.

Introduction

Diarrhea continues to be a major cause of mortality and morbidity in young children in developing countries (1). Although the mortality due to diarrhea has been substantially reduced in recent years, its morbidity burden has remained almost unaltered (2). In settings where diarrhea takes its greatest toll, zinc deficiency also coexists as a major nutritional deficiency (3,4). Dietary inadequacy is mainly attributable to inadequate intake of zinc (5) resulting from low consumption of animal products rich in zinc and dependence on less bioavailable plant sources with high phytate content (6–8). Also, abnormal loss of zinc in the stool during diarrheal episodes often exacerbates zinc deficiency (9). Zinc treatment trials in young children in populations where zinc deficiency is likely to be prevalent have shown substantial reductions in the duration of the treated episode and the incidence of diarrhea over the subsequent 3 mo (10,11). As a result, WHO/UNICEF diarrhea management guidelines have been revised to include 10–14 d of zinc treatment as an adjunct therapy during acute childhood diarrhea (ACD) (12). National scale-up campaigns are now underway in several countries where zinc treatment has been adopted as policy, including the first such campaign in Bangladesh (13).

The recommended duration of therapy is longer than the duration of most acute diarrheal episodes, which typically resolve within 3–5 d (14). Mothers usually stop medications once the diarrhea resolves, resulting in nonadherence with a full course of treatment. Even with intensive campaigns and motivations, a zinc study in rural Bangladesh achieved a compliance of 7 of the intended 14 d (10). Similar lower compliance to zinc treatment has also been reported in recent impact monitoring of National Scale Up of Zinc for Childhood Diarrhea in Bangladesh (15).

The purpose of this investigation was to determine whether a 5-d short course of zinc treatment would offer equivalent preventive benefits to 10 d of treatment in terms of decreased subsequent episodes and decreased subsequent duration of

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[3] This trial was registered at www.clinicaltrials.gov as NCT00325247.
[4] Supplemental Figure 1 is available with the online posting of this paper at jn.nutrition.org.
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episodes. We hypothesized that a 5-d course of 20 mg/d elemental zinc would be as efficacious as a 10-d treatment.

Participants and Methods

Study design. This was a double-blind, community-based, randomized trial carried out from February 2005 to May 2006.

Study population and randomization. This study was conducted in 13 villages in the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) field site of Matlab, a rural subdistrict of Chandpur district in Bangladesh. Infants and young children aged 4–59 mo with diarrhea identified during daily home visits by trained study female field workers (FFW) were eligible for entry into the study. If the diarrhea was <48 h duration, the child had not received antibiotic or zinc for the current episode, and there were no signs of severe dehydration, the child met the eligibility criteria and the mother was asked whether she would consent to her child participating in the study. The FFW explained to the mother that her child would receive a 5- or 10-d course of zinc treatment. Informed written consent was then obtained. Children were randomized individually to a double-blind, supervised administration of either 5 or 10 d of zinc treatment of 20 mg daily elemental zinc in a dispersible tablet formulation. Those who were randomized to 5 d of treatment received an inert, indistinguishable, dispersible tablet as a placebo for the second 5 d to complete a total 10-d course. Randomization applied permuted blocks of 6 and was carried out by a scientist not directly involved in the study. Investigators remained unaware of the treatment assignment until the analysis was complete. The study was approved by the Research Review Committee and Ethical Review Committee of ICDDR,B.

Conduct of study. FFW visited each child under her surveillance daily for 10 d and ensured zinc administration in the home. They remained with the child for one-half hour after zinc administration and recorded whether the child spitted, vomited, or regurgitated during that period. Zinc and placebo tablets were supplied in similar blister packs manufactured by a French company (Nutriset). Starting from d 15, children were followed daily at home for 90-d period so that diarrheal morbidity could be recorded. FFW were local residents with a minimum of a grade 10 education. After recruitment, they received 1 wk of intensive training on routine surveillance, completing study forms and questionnaires, and taking anthropometric measurement. Each FFW was assigned to a specific village. The number of children under surveillance varied from 60 to 110/FFW. During daily routine visits, FFW asked the mother or caretaker whether the child had a loose motion during the previous 24 h. If the child passed ≥3 liquid or loose stools during the previous 24 h, this was recorded as an episode. The FFW then further interviewed the mother or caretaker about the number and consistency of stool and related symptoms. A diarrhea episode was considered resolved if the child remained diarrhea free for 3 consecutive days. If the child moved within the study area to another FFW's surveillance area, the record of the child along with zinc tablets were transferred to the respective FFW.

Sample size estimation. This study was primarily designed to test the hypothesis that a 5-d course of zinc treatment would be as efficacious as a 10-d course in preventing diarrhea over the 3 mo following treatment of an episode. We assumed a 15% reduction in the incidence of repeat in both groups. Previous studies in the same area reported that the probability of having a second episode in 3 mo would be 0.425 (16) and the difference (δ) between treatment groups would not exceed 12%. We calculated that the number of children with diarrhea needed to be followed would be 2050 (1025/group) (17).

Data management and analysis. All data forms and questionnaires were checked daily by field supervisors and edited before the data were entered using MS Access, with built-in checks for consistency and validity. Incidence of diarrhea and total time spent with diarrhea during the 90-d observation period were compared by Student's *t* test. The mean difference in incidence between treatment groups and its 95% CI were calculated to confirm that the difference did not exceed the defined limit of equivalence irrespective of the significance in the Student's *t* test. Additionally, during the 90-d observation period, whether the 2 treatment regimens differ in terms of time to onset of the next episode of diarrhea after initial treatment was tested by comparing the survival function and the significance using the log rank test. The comparability of the protective efficacy over the 90-d period between treatment groups was tested by comparing the proportion of children who experienced diarrhea. $P < 0.05$ was considered significant.

Results

A total of 1681 children with diarrhea were identified, of which 1656 were randomized to 10 d (n = 835) or 5 d (n = 821) zinc treatment with a subsequent 5 d of placebo. Excluded were 6 children with bloody diarrhea, 16 with diarrhea for longer than 48 h, and 3 who had received an antibiotic for diarrhea. Of the randomized children, 1622 had complete data through 90 d of follow-up; the remaining 34 children were lost to follow-up (**Supplemental Fig. 1**). The main reason for the loss to follow-up after enrollment was having moved out of the study area (n = 28) or withdrawal of consent to continue with the study (n = 6).

Children in both the 10- and 5-d treatment groups had a mean age of 26 mo and were comparable in sex, nutritional variables, maternal education, family size, drinking water source, and defecation practices (**Table 1**). Adherence to treatment was 99% for the first 5 d for both groups and 97% for the second 5 d.

During the 90-d follow-up, the mean number of repeat episodes did not differ between the 5-d (1.08 ± 1.38 episodes) and 10-d (1.02 ± 1.35 episodes) groups. The number of days of diarrhea was also similar in the 5-d (3.1 ± 5.6 d) and 10-d (2.9 ± 5.6 d) groups. Over the 90-d observation period, the day of onset of the first repeat episode did not differ between groups. The proportion of children who had at least 1 episode of diarrhea during the 90-d observation period did not differ between 5-d (54%) and 10-d (52%) zinc treatment groups (P = 0.39). This difference of 2% is well below the upper limit of equivalence (**Fig. 1**).

The mean duration of the treated episode did not differ between the 5-d (3.5 ± 2.8 d) and 10-d (3.3 ± 2.7 d) zinc treatment groups (P = 0.08). The proportion of prolonged (≥7 d) and persistent diarrhea episodes (≥14 d) did not vary between the 5-d (19 vs. 16%; $P < 0.08$) and 10-d (12 vs. 10%; P = 0.14) groups.

TABLE 1 Selected characteristics of the study participants who received either 5- or 10-d zinc treatment during acute diarrheal episode[1]

	Zinc treatment group	
Characteristic	5 d, n = 803	10 d, n = 819
Age, *mo*	25.6 ± 16.2	25.6 ± 16.2
Z-scores		
Weight for height	−0.73 ± 1.0	−0.66 ± 1.0
Height for age	−2.17 ± 1.2	−2.11 ± 1.1
Weight for age	−1.78 ± 1.0	−1.68 ± 1.0
Maternal education, *y*	5.8 ± 2.7	6.1 ± 2.7
Family size, *n*	6.1 ± 2.3	6.0 ± 2.2
Sex (male), %	50.8	48.7
Tube-well (drinking water), %	98.4	97.9
Sanitary latrine, %	21.8	19.7

[1] Values are means ± SD or percent.

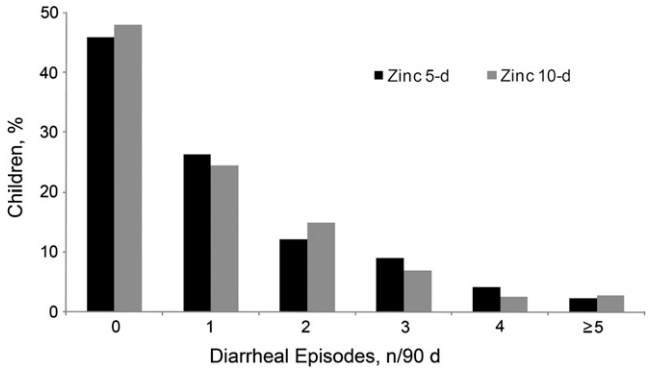

FIGURE 1 Distribution of children by number of episodes of diarrhea over the 90-d observation period after initial treatment with zinc for 5 (n = 803) or 10 d (n = 819).

The frequency of vomiting within one-half an hour of zinc administration did not differ significantly between the 2 groups during the first 5 d of treatment (**Fig. 2**). However, during the second 5 d, the proportion of children vomiting was significantly higher in the 10-d Zn group than in the 5-d Zn group that received placebo during the second 5 d. Regurgitation occurred in <1% of children and did not differ significantly between 10- and 5-d zinc groups.

Discussion

Our study tested the efficacy of a 5-d compared with 10-d zinc treatment of ACD on incidence of diarrhea over the subsequent 3 mo and demonstrated that the shorter course is as efficacious as the longer course in preventing diarrhea. To our knowledge, this is the first study to test a 5-d duration of zinc treatment in ACD and to compare its preventive efficacy with a 10-d treatment over 3 mo post-treatment. Before discussing the findings, strengths and limitations may be worthwhile to mention.

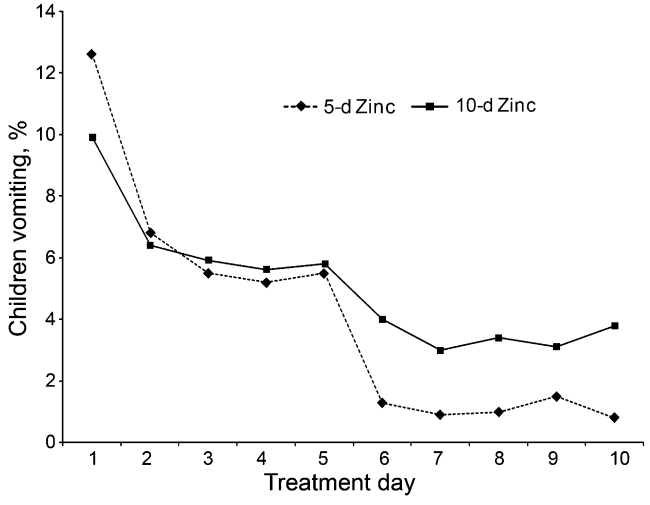

FIGURE 2 Incidence of vomiting within one-half hour after the administration of a zinc tablet to children for 5 (n = 803) or 10 d (n = 819). The 5-d zinc group received the placebo from d 6 to 10. Groups differed from d 6 to 10, $P < 0.01$.

The major strengths of our study include a priori hypothesis regarding treatment effect, daily surveillance of all eligible children daily by the FFW, supervised administration of the assigned treatment, and daily follow-up during the subsequent 90-d period. We did not include any group without zinc, which may be viewed as a limitation of the study. However, zinc is already proven to be efficacious in shortening the duration of acute episode and in preventing diarrhea in the subsequent 3 mo postsupplementation (10,12). Because the current policy of the government of Bangladesh is to provide zinc to all children with diarrhea, it would not have been ethically permissible to deprive children with diarrhea from zinc treatment. However, having no such absolute control group did not limit our ability to test the study hypothesis of relative efficacy of 5-d compared with 10-d zinc treatment in preventing diarrhea over the 90-d follow-up period.

We observed that study children on average suffered just over 1 episode of diarrhea during the 3-mo observation period. Because our study covered all seasons of the year, it might not be too unrealistic to extrapolate this finding to estimate the annual incidence. This finding suggests that children under 5 y old in that area may suffer an estimated 4 episodes/y, which is consistent with an earlier report from this area (16). Our findings represent a more accurate depiction of these children and are unlikely to be biased due to underreporting, because mothers often do not report very trivial diarrheal episodes of a short duration such as diarrhea lasting for 1 or 2 d when diarrheal history is collected using a longer recall period. Our data are based on daily surveillance, which potentially had the ability to detect those mild episodes. An earlier study in Bangladesh documented that weekly recall underestimated severe diarrheal episodes by over 20% and by 40% in less severe diarrheal episodes (18).

Zinc is a soluble trace element and requires daily intake to maintain a steady state, because there is no specialized storage mechanism in the body (19). Because zinc is mostly intracellular and is involved in the catalytic and structural function of more 300 enzymes, replenishment in deficient children with zinc supplementation is likely to increase intracellular storage (20,21). Zinc supplementation during diarrhea helps with quicker recovery from acute episodes and prevention of diarrhea in the following months through its effect on the immune system (22), regeneration of gut epithelium and improved appetite (23,24), and enhancement of absorption (25). These immediate functional improvements and future preventive benefits may be equally achieved irrespective of zinc treatment duration of 5 or 10 d during diarrhea.

Vomiting is often reported as a known side effect of zinc and the increased risk of vomiting has been reported to be associated with zinc treatment (26–28). Our study also showed a clear link between zinc and excess vomiting, although the proportion of children who vomited was lower in our study than reported by Larson et al. (27). This difference was probably due to the difference in observation time, which was one-half an hour in our study compared with 1 h in the other study. Incidence of vomiting in the zinc group continued at the same rate as the first 5 d until the end of treatment, while those who received placebo from d 6 stopped vomiting almost as soon as they were given placebo. Therefore, a shorter course may also be desirable to avoid unnecessary vomiting in young children.

Findings of this study may also have important implications for the treatment cost that potentially may result from nonadherence to treatment, which is known to occur as soon as diarrhea resolves. Because the 5-d treatment seems to be as efficacious as the 10-d course, if a 5-d course of zinc treatment is

recommended instead of 10-d course, this would simply result in 50% less treatment cost, a great savings on the health care cost, largely of poorer households where diarrhea occurs most (29,30). Under-five children constitute ~12% of the Bangladesh population, which translates into 15 million children who are at risk of diarrhea. Each child under 5 y old in Bangladesh, on average, suffers ~4 episodes/y, which translates into ~60 million diarrheal episodes would require zinc treatment each year. Therefore, a 5-d course means a substantial reduction of cost of treatment as well as a potential reduction of noncompliance, which often results as the duration of treatment gets longer.

We conclude that a 5-d zinc treatment in ACD is as efficacious as 10-d therapy in preventing in the subsequent 3 mo in rural the Bangladeshi setting. However, these findings need to be confirmed in other settings, and large-scale effectiveness study are needed to assess the preventive efficacy in a less-controlled environment.

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Literature Cited

1. Parashar UD, Bresee JS, Glass RI. The global burden of diarrhoeal disease in children. Bull World Health Organ. 2003;81:236.
2. Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. Bull World Health Organ. 2003;81:197–204.
3. Sarker SA, Rahman MM, Ali A, Hossain S, Alam AN. Prolonged depression of serum zinc concentration in children following post-measles diarrhoea. Hum Nutr Clin Nutr. 1985;39:411–7.
4. Hambidge KM. Zinc and diarrhoea. Acta Paediatr Suppl. 1992;381:82–6.
5. Ferguson EL, Gibson RS, Opare-Obisaw C, Ounpuu S, Thompson LU, Lehrfeld J. The zinc nutriture of preschool children living in two African countries. J Nutr. 1993;123:1487–96.
6. Oberleas D, Harland BF. Phytate content of foods: effect on dietary zinc bioavailability. J Am Diet Assoc. 1981;79:433–6.
7. Wise A. Phytate and zinc bioavailability. Int J Food Sci Nutr. 1995; 46:53–63.
8. International Zinc Nutrition Consultative Group. Assessment of the risk of zinc deficiency in population and options for its control (technical document). Hotz C, Brown KH, editors. Food Nutr Bull. 2004;25 (1 Supp 2):94–204.
9. Al-Sonboli N, Gurgel RQ, Shenkin A, Hart CA, Cuevas LE. Zinc supplementation in Brazilian children with acute diarrhoea. Ann Trop Paediatr. 2003;23:3–8.
10. Baqui AH, Black RE, Arifeen SE, Yunus M, Chakraborty J, Ahmed S, Vaughan JP. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ. 2002;325:1059.
11. Sazawal S, Black RE, Bhan MK, Bhandari N, Sinha A, Jalla S. Zinc supplementation in young children with acute in India. N Engl J Med. 1995;333:839–44.
12. UNICEF and WHO. Clinical management of acute diarrhoea: WHO/ UNICEF joint statement. Geneva: WHO; 2004.
13. International Centre for Diarrhoeal Disease Research, Bangladesh. SUZY News: newsletter of the 'Scaling Up Zinc for Young children with diarrhoea in Bangladesh' (SUZY) Project. Dhaka (Bangladesh): ICDDR. B; 2006.
14. Alam MB, Ahmed FU, Rahman ME. Misuse of drugs in acute diarrhoea in under-five children. Bangladesh Med Res Counc Bull. 1998;24: 27–31.
15. Larson CP, Saha UR, Nazrul H. Impact monitoring of the national scale up of zinc treatment for childhood in Bangladesh: repeat ecologic surveys. PLoS Med. 2009;6:e1000175.
16. Baqui AH, Black RE, Sack RB, Yunus MD, Siddique AK, Chowdhury HR. Epidemiological and clinical characteristics of acute and persistent diarrhoea in rural Bangladeshi children. Acta Paediatr Suppl. 1992; 381:15–21.
17. Blackwelder WC. Proving the null hypothesis in clinical trials. Control Clin Trials. 1982;3:345–53.
18. Alam N, Henry FJ, Rahaman MM. Reporting errors in one-week diarrhoea recall surveys: experience from a prospective study in rural Bangladesh. Int J Epidemiol. 1989;18:697–700.
19. Rink L, Gabriel P. Zinc and the immune system. Proc Nutr Soc. 2000; 59:541–52.
20. Tapiero H, Tew KD. Trace elements in human physiology and pathology: zinc and metallothioneins. Biomed Pharmacother. 2003; 57:399–411.
21. Coleman JE. Zinc proteins: enzymes, storage proteins, transcription factors, and replication proteins. Annu Rev Biochem. 1992;61:897–946.
22. Fraker PJ, King LE, Laakko T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr. 2000;130: S1399–406.
23. Krebs NF, Hambidge KM, Walravens PA. Increased food intake of young children receiving a zinc supplement. Am J Dis Child. 1984;138: 270–3.
24. Umeta M, West CE, Haidar J, Deurenberg P, Hautvast JG. Zinc supplementation and stunted infants in Ethiopia: a randomised controlled trial. Lancet. 2000;355:2021–6.
25. Rodriguez P, Darmon N, Chappuis P, Candalh C, Blaton MA, Bouchaud C, Heyman M. Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc. Gut. 1996;39:416–22.
26. Winch PJ, Gilroy KE, Doumbia S, Patterson AE, Daou Z, Coulibaly S, Swedberg E, Black RE, Fontine O. Prescription and administration of a 14-day regimen of zinc treatment for childhood in Mali. Am J Trop Med Hyg. 2006;74:880–3.
27. Larson CP, Hoque AB, Larson CP, Khan AM, Saha UR. Initiation of zinc treatment for acute childhood diarrhoea and risk for vomiting or regurgitation: a randomized, double-blind, placebo-controlled trial. J Health Popul Nutr. 2005;23:311–9.
28. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database Syst Rev. 2008;CD005436.
29. Hillis SD, Miranda CM, McCann M, Bender D, Weigle K. Day care center attendance and l morbidity in Colombia. Pediatrics. 1992;90: 582–8.
30. Mahalanabis D, Faruque AS, Islam A, Hoque SS. Maternal education and family income as determinants of severe disease following acute diarrhoea in children: a case control study. J Biosoc Sci. 1996;28:129–39.