Therapeutic and preventive effects of zinc on serious childhood infectious diseases in developing countries¹–³

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ABSTRACT    In children in developing countries, zinc deficiency may be common and associated with immune impairment and increased risk of serious infectious diseases such as diarrhea, pneumonia, and malaria. Studies have evaluated the therapeutic effects of zinc supplementation during acute or persistent diarrhea. In studies of acute diarrhea, the illness duration has been found to be 9–23% shorter in zinc-supplemented than in control children. Diarrhea was also less severe in zinc-supplemented children. In studies of persistent diarrhea, the effect sizes were similar but were often not statistically significant, perhaps because of the small number of children participating in these studies. Trials that provided continuous daily zinc supplementation for 5–15 mo evaluated effects on the incidence of diarrhea and in some studies acute lower respiratory infections and malaria. The reduction in the incidence of diarrhea in the zinc-supplemented group in these studies ranged from 8% to 45%. A study that gave 2 wk of zinc supplementation found preventive effects against diarrhea for the 3 mo of surveillance. More limited data also suggest that the incidence of acute lower respiratory infection and clinical attacks of malaria may also be reduced by zinc supplementation. If these results are confirmed by meta-analysis of the existing trials and additional research, improvement of zinc nutriture should become a priority intervention to reduce the high burden of serious infectious disease in children in developing countries. Am J Clin Nutr 1998;68(suppl):476S–9S.

KEY WORDS  Zinc, zinc deficiency, zinc supplementation, diarrhea, lower respiratory infection, malaria, morbidity, children, India, Bangladesh, Gambia, Indonesia, Pakistan, Peru, Vietnam, Mexico, Guatemala, Papua New Guinea

INTRODUCTION

Zinc deficiency may be widespread among children in developing countries (1), along with high rates of serious infectious diseases such as diarrhea, pneumonia, and malaria (2, 3). Because zinc deficiency has been associated with diarrhea (4–7) and impaired immunity (8–10), recent studies have evaluated possible therapeutic or preventive roles for supplemental zinc. These studies were conducted in a variety of settings in children who were not known to be zinc deficient, but who had degrees of undernutrition typically found in developing countries. A review of these studies provides preliminary evidence that zinc deficiency is related to the incidence or outcome of serious childhood infectious diseases and that zinc can have therapeutic or preventive benefits.

THERAPEUTIC EFFECTS OF ZINC ON DIARRHEA

The first study on the therapeutic use of oral zinc on acute diarrhea was conducted by Sachdev et al (11) in India in children between the ages of 6 and 18 mo (average age 9 mo). This hospital-based inpatient study excluded children who were <60% of weight-for-age in comparison with an international reference population. The study provided 40 mg elemental Zn/d as the sulfate for 25 children in the experimental group and compared them with another 25 children receiving placebo. Overall, this study found a nonsignificant 9% reduction in the duration of diarrhea. It further showed that in children defined as having low concentrations of rectal mucosal zinc there was a significant 33% reduction in diarrheal duration. This study also found a reduction in diarrheal severity; children in the zinc-supplemented group had an 18% lower diarrheal stool frequency. Zinc-supplemented children in the lower-tissue-zinc subgroup had a significant 33% lower stool frequency compared with those having a higher tissue zinc.

Another study in India was conducted as a community-based trial of acute diarrhea (12). Children 6–35 mo of age (average age 6 mo) were enrolled, and only children with malnutrition severe enough to require hospitalization were excluded. Children in both the zinc and control groups were given vitamins A, B, D, and E and children in the experimental group received 20 mg Zn/d as gluconate. This was a large study comparing 456 children in the experimental group with 481 children in the control group. The study observed a 23% reduction (95% CI: 12%, 32%) in the duration of the diarrheal episode. Furthermore, the severity of diarrhea, as indicated by the number of watery stools, was reduced by 39% (95% CI: 6%, 70%). The reductions in duration and severity of diarrhea were greater in children with stunting than in those with normal growth.

A study in Bangladesh enrolled children 3–24 mo of age who had acute diarrhea and weights-for-age less than the 76th percentile of the National Center for Health Statistics (NCHS)
median (13). Children were kept in the hospital until diarrhea stopped. Vitamins A, B, D, and C were given to both groups and 20 mg Zn/d as acetate was given daily to the experimental group. In this small study with 37 children per group, there was a non-significant 14% reduction in the duration of diarrhea in the zinc-supplemented children. The subgroup of children with lower plasma zinc concentrations (< 14 µmol/L) had a significant 22% reduction in diarrheal duration. Children who had poorer nutritional status also tended to have greater reductions in episode duration than did children with better nutritional status. This study, the only one to date to measure stool output in hospitalized children, also found that zinc-supplemented children had 36% lower stool outputs than nonsupplemented children. Similar reductions of 32% and 38% in subgroups with lower initial plasma zinc concentrations and poorer nutritional status, respectively, were significant.

An additional study from Bangladesh in 6–24-mo-old children was conducted in a community in which experimental groups received either 14 or 40 mg Zn/d as acetate; the experimental groups and control group all received vitamins A and C. This study with >340 children with acute diarrhea per group found a significant 20% reduction in episode duration (D Mahalanabis, personal communication, 1997). In Indonesia, a very large community-based study was conducted in children <36 mo of age using 4–5 mg Zn·kg⁻¹·d⁻¹ as acetate (n = 1165) compared with placebo (n = 1114). This study found a significant 11% reduction in diarrheal duration (A Hidayat, personal communication, 1997).

Studies in India (12), Bangladesh (13), and Indonesia (A Hidayat, personal communication, 1997) also found that acute diarrheal episodes in zinc-supplemented children were less likely to last >7 d. These longer duration episodes occurred 25–43% (all P<0.05) less often in zinc-supplemented children than in control children in these 3 studies.

Diarrheal episodes of ≥14 d are defined as persistent diarrhea by the World Health Organization (14). Such episodes are associated with higher mortality and greater adverse growth effects than acute diarrhea, making them of particular importance in developing countries (15). Several studies examined the therapeutic effects of zinc on persistent diarrhea. Again, the first study on this topic was conducted by Sachdev et al in India (16). This was a hospital-based inpatient study of children 6–18 mo of age (average age 9 mo). This study excluded children with severe malnutrition (<60% of weight-for-age). Children in the experimental group received 40 mg Zn as sulfate and the control group received placebo. This study had only 20 children per group, so the 19% shorter duration in the zinc-supplemented group than in the controls was not significant.

A therapeutic study of persistent diarrhea in Bangladesh was conducted in 3–24-mo-old (average age: 8 mo) children who were hospitalized for the period of illness (13). Both the experimental and control groups received vitamins A, B, D, and E and the experimental group received 5 mg Zn·kg⁻¹·d⁻¹ as acetate (=30 mg/d). There were 95 children initially enrolled in each group, but sizable numbers were lost during follow-up and could not be included in the analysis. Overall, the duration of these episodes was 9% shorter in the zinc-supplemented children than in the control children. The duration of diarrhea was 25% shorter (significant) in the subgroup of children who had poorer nutritional status at the time of enrollment than in children with better nutritional status.

Two additional treatment studies in persistent diarrhea have been completed, but the results are not yet published. In Pakistan, children 6–36 mo of age (average age: 12 mo) with weight for age ≥2 z (ie, 2 SDs below the reference median) were included in an inpatient study. Both the experimental and control groups received vitamins A, B, C, and D, while the experimental group received 3 mg Zn·kg⁻¹·d⁻¹ as sulfate (=20 mg/d). Preliminary results of this study presented at the Zinc for Child Health Symposium (Z Bhutta, personal communication, 1997) indicated no significant difference in duration of diarrheal episodes overall, but a trend toward shorter episodes in children with lower plasma zinc concentrations at enrollment. A study in Peru done in a perurban community enrolled children 6–36 mo of age (average age: 18 mo) (M Penny, personal communication, 1997). Children with persistent diarrhea received either 20 mg Zn/d as gluconate or placebo. The 22% shorter duration of episodes in the zinc-supplemented group was not significant, nor was a 32% shorter duration in children with lower initial plasma zinc concentrations.

**PREVENTIVE EFFECTS OF ZINC SUPPLEMENTATION ON DIARRHEAL DISEASES**

Several studies were published recently showing a preventive effect of routine oral zinc supplementation on diarrheal diseases; other studies are completed, but not yet published. These studies had a variety of outcomes from which some will be selected to enhance comparison among the studies. In some cases additional analyses, beyond what was in the initial publication, were provided by study investigators for the purpose of this review.

Two different types of study designs were used. First, illness follow-up studies provided supplements for 2 wk to 6 mo after episodes of acute or persistent diarrhea. Second, community-based studies provided supplements or control preparations to all children in a study community, and were not initiated from an illness episode. These studies were conducted for 5–15 mo.

In India, Sazawal et al (17) conducted a preventive community-based study in children 6–41 mo of age (average age: 19 mo) after acute diarrhea. Supplementation and surveillance continued for 6 mo. All children received vitamins A, B, D, and E and the experimental group received 10 mg Zn/d as gluconate. This was a large study evaluating 286 and 293 children in the zinc and control groups, respectively. Compared with children not given zinc, diarrheal incidence was 8% lower in zinc-supplemented children and 17% lower in the subgroup of children with lower initial plasma zinc concentrations at enrollment. There was a strong age relation with the efficacy of zinc supplementation in this study, with zinc-supplemented children >12 mo of age showing a significant 27% lower incidence of diarrhea and zinc-supplemented children 6–11 mo of age showing no reduction. This study also found the zinc-supplemented children to have a 21% lower incidence of persistent diarrhea and 14% lower incidence of dysentery than nonsupplemented children (18). In children with lower baseline zinc concentrations, the zinc-supplemented group had a 73% lower incidence of persistent diarrhea, and in children >11 mo old the zinc group had 43% less persistent diarrhea, both of which were significant. Zinc supplementation also resulted in a 38% lower incidence of dysentery in boys; there was no effect on dysentery in girls.

A community-based study in Vietnam enrolled children 4–41 mo of age (average age: 20 mo) who were <2 z weight-for-age
and height-for-age compared with the NCHS reference (19). Children were assigned randomly to receive either 10 mg Zn/d as sulfate or placebo. The publication from this study reported a 3-fold decrease in diarrhea in the zinc-supplemented group. Reanalyzed data provided by the principal investigator using simpler methods to compare the effect on diarrheal incidence with that found in the other studies showed a significant 45% reduction in diarrheal incidence in the zinc-supplemented children (NX Ninh, personal communication, 1997).

Two community-based trials from Latin America were published recently. In Mexico, children 18–36 mo of age (average age: 29 mo) were studied with supplementation and surveillance for 12 mo (20). Children were assigned randomly to receive 20 mg Zn/d as methionate or placebo. Children in the zinc-supplemented group had a significant 35% lower incidence of diarrhea than the children in the placebo group. In Guatemala, children 6–17 mo of age (average age 14 mo) participated in a supplementation trial for 6 mo, receiving 10 mg Zn/d as sulfate or placebo (21). Children in the zinc-supplemented group had a significant 22% lower incidence of diarrhea during the period of surveillance than unsupplemented children.

Other studies in Bangladesh, Papua New Guinea, and Peru also found lower diarrheal incidence in the zinc-supplemented group, with statistical significance depending in large part on the size of the study. The study in Bangladesh is noteworthy in its observation that children with persistent diarrheal disease who were given zinc supplements for 2 wk had a significant 38% lower incidence of diarrhea during the 3-mo period after recovery from the enrollment episode (SK Roy, personal communication, 1997). This may suggest that shorter term zinc supplementation during and shortly after diarrheal illnesses may help the child recover from excess zinc losses from diarrhea and return to more normal zinc nutrition during the convalescent period. One study done in Gambia provided 70 mg zinc as gluconate twice per week or placebo (22). This study found that children in the zinc-supplemented group had a slightly higher, nonsignificant incidence of diarrhea than the placebo group.

PREVENTIVE EFFECTS OF ZINC ON ACUTE LOWER RESPIRATORY INFECTIONS

Few studies published to date have examined the effect of zinc supplementation on acute lower respiratory infections or pneumonia. A study in India found a reduction of 45% (95% CI: 10%, 67%) in the incidence of acute lower respiratory infections in zinc-supplemented children compared with the control children (23). The study from Vietnam reported a 2.5-fold decrease in respiratory infections, but these were predominantly upper respiratory illnesses (19). The study in Mexico found a small and nonsignificant reduction in respiratory disease episodes, but again, nearly all of these illnesses were of the upper respiratory tract (20). Other studies in Bangladesh have likewise found reductions in all respiratory diseases, but did not have sufficient numbers of acute lower respiratory infections to evaluate this outcome (13).

PREVENTIVE EFFECTS OF ZINC ON MALARIA

In a community-based trial with zinc supplementation twice weekly in Gambia, clinic visits for malaria were evaluated as a study outcome (22). The children participating in this trial were in their second and third years of life; the basis for the diagnosis of malaria was not provided in the study. Zinc-supplemented children had 32% fewer clinic visits for malaria than unsupplemented children, a finding of borderline significance.

A trial in Papua New Guinea assessing the effects of zinc supplementation on malarial morbidity was completed recently (A Shanks, personal communication, 1997). Children 6–60 mo of age were enrolled in a placebo-controlled trial of 10 mg Zn as gluconate provided 6 d/wk for 10 mo. Zinc-supplemented children had 29% fewer health center visits and 38% fewer reported fevers. Most importantly, there were 40% fewer fevers associated with Plasmodium falciparum parasitemia, 32% fewer malaria-attributed fevers, with parasite densities >5000/μL. There were also 36% fewer fevers with parasite densities >50000/μL, a density indicating severe disease. Zinc supplementation had no effect on densities of P. vivax parasitemia.

CONCLUSIONS

The evidence reviewed here regarding the therapeutic or preventive effects of zinc supplementation is based on a substantial number of randomized controlled trials in which the sole experimental variable was administration of zinc. This type of study provides the most convincing causal inference on the benefits of zinc. The trials were rigorously conducted and analyzed, further adding to the credibility of the findings. Studies were conducted in 10 countries of Asia and Latin America, and the consistency of the findings suggests that the results may apply to much of the developing world. An obvious limitation is that only 1 study was conducted in Africa, and this study had an unusual design with twice weekly zinc dosing. This extensive body of studies deserves more comprehensive assessment. A meta-analysis of the therapeutic and preventive trials is underway. Cooperation among the study investigators in this analysis will permit better estimates of the effects overall and in important subgroups, eg, based on age, nutritional status, or plasma zinc status.

Children in developing countries appear to benefit from zinc supplementation during acute diarrhea, with a reduction in episode duration and severity. The effect on illness duration is also seen in the reduction in the proportion of acute diarrheal episodes that last >7 d. The therapeutic effect of zinc supplementation on persistent diarrhea appears to be of a magnitude similar to that found in acute diarrhea. A more definitive statement on this must await the publication of the trials that were conducted in Bangladesh, Pakistan, and Peru, and perhaps additional research.

Routine zinc supplementation in children in developing countries also appears to reduce the incidence of acute diarrhea and possibly also the incidence of persistent diarrhea and dysentery, at least in some subgroups. Zinc supplementation may also reduce the incidence of acute lower respiratory infections, but with one exception, studies have been of insufficient size or inappropriate design to evaluate the effects on these infrequent severe illnesses. The study from India suggesting a large effect on acute lower respiratory infections needs to be confirmed in other settings. Two studies, especially the recent one in Papua New Guinea, suggest that zinc supplementation reduces the incidence of clinical attacks of malaria in children. This finding also needs to be confirmed. Possible therapeutic effects of zinc in pneumonia and malaria also need to be evaluated.

The magnitude of the therapeutic and the preventive effects of zinc on serious childhood infectious diseases appears to compare
favorably with other health interventions being implemented in developing countries to improve child health and survival (24, 25). Given the findings to date that zinc supplementation reduces the incidence and severity of serious childhood infectious diseases, one could hypothesize that it could also reduce child mortality. Further research on the benefits of zinc supplementation, including reduction of mortality and on means to improve zinc nutriture in children in developing countries, are urgently needed.

REFERENCES