

Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial

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Abstract

Objective To evaluate the effect on morbidity and mortality of providing daily zinc for 14 days to children with diarrhoea.

Design Cluster randomised comparison.

Setting Matlab field site of International Center for Diarrhoeal Disease Research, Bangladesh.

Participants 8070 children aged 3-59 months contributed 11 881 child years of observation during a two year period.

Intervention Children with diarrhoea in the intervention clusters were treated with zinc (20 mg per day for 14 days); all children with diarrhoea were treated with oral rehydration therapy.

Main outcome measures Duration of episode of diarrhoea, incidence of diarrhoea and acute lower respiratory infections, admission to hospital for diarrhoea or acute lower respiratory infections, and child mortality.

Results About 40% (399/1007) of diarrhoeal episodes were treated with zinc in the first four months of the trial; the rate rose to 67% (350/526) in month 5 and to >80% (364/434) in month 7 and was sustained at that level. Children in the intervention cluster received zinc for about seven days on average during each episode of diarrhoea. They had a shorter duration (hazard ratio 0.76, 95% confidence interval 0.65 to 0.90) and lower incidence of diarrhoea (rate ratio 0.85, 0.76 to 0.96) than children in the comparison group. Incidence of acute lower respiratory infection was reduced in the intervention group but not in the comparison group. Admission to hospital of children with diarrhoea was lower in the intervention group than in the comparison group (0.76, 0.59 to 0.98). Admission for acute lower respiratory infection was lower in the intervention group, but this was not statistically significant (0.81, 0.53 to 1.23). The rate of non-injury deaths in the intervention clusters was considerably lower (0.49, 0.25 to 0.94).

Conclusions The lower rates of child morbidity and mortality with zinc treatment represent substantial benefits from a simple and inexpensive intervention that can be incorporated in existing efforts to control diarrhoeal disease.

Introduction

Zinc deficiency is highly prevalent in children in developing countries.¹ Inadequacy of dietary zinc intake is exacerbated by the net loss of zinc during diarrhoea.² Zinc supplements given during diarrhoea reduce the duration and severity of treated episodes³ and, if given for 14 days during and after diarrhoea, can reduce the incidence of diarrhoea and acute lower respiratory infection in the subsequent two to three months.⁴ Provision of zinc during diarrhoea may thus be a feasible strategy for both treatment of diarrhoea and prevention of subsequent morbidity and mortality. The therapeutic trials of zinc supplementation conducted to date have been small and conducted in clinical settings. We aimed to evaluate the impact on morbidity and mortality of zinc treatment during diarrhoea in a realistic large scale public health programme.

Methods

Study design and population

We conducted this community based, prospective, cluster randomised controlled trial in the Matlab field area of the International Center for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). In 1998 infant mortality in the Matlab area was 60.6 per 1000 live births, and mortality in children aged 1-4 years was 5.2 per 1000 children. Diarrhoea accounted for about 12% of infant deaths and about a third of all deaths in children aged 1-4 years.⁵

Oral rehydration treatment and referral for patients with diarrhoea are provided in the villages by community health workers and by *Bari* mothers—community volunteers who distribute oral rehydration solution packets and provide advice to patients with diarrhoea. The community health workers also provide treatment and referral services for acute lower respiratory infection. On average, there is one community health worker for every 2000 people and one *Bari* mother for every 50 people. We selected for the study 30 service areas (clusters) of community health workers around Matlab treatment centre, each with about 200 children aged 3-47 months.

We initially enrolled children aged 3-47 months who were permanent residents of the study cluster

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Table 1 Effect of zinc on duration of diarrhoea by type of diarrhoea in a sample of episodes

| Type of diarrhoea | Intervention | | Comparison | | Hazards ratio* (95% CI) |
|-------------------|----------------|-----------------------------------|----------------|-----------------------------------|-------------------------|
| | No of episodes | Mean (SD) episode duration (days) | No of episodes | Mean (SD) episode duration (days) | |
| Non-dysenteric | 560 | 4.6 (3.6) | 582 | 5.8 (4.7) | 0.77 (0.64 to 0.92) |
| Dysentery | 60 | 6.0 (4.3) | 50 | 7.3 (4.2) | 0.62 (0.44 to 0.89) |
| All | 620 | 4.7 (3.7) | 632 | 5.9 (4.6) | 0.76 (0.65 to 0.90) |

*Adjusted for child's age, sex, and birth order, mother's education, and household homestead land size.

areas. We also included all babies as they became 3 months old and all babies in the age range of 3-59 months moving into the area during the period of the study, November 1998 to October 2000. Children with a mid-upper arm circumference of <110 mm were excluded and referred to the Matlab treatment centre for care. When study children became 60 months old they were excluded.

Intervention

The community health workers and *Bari* mothers in the intervention clusters taught the mothers how to use the zinc syrup. As soon as diarrhoea was reported, study children in the intervention villages were to receive 20 mg of elemental zinc as acetate each day for 14 days, regardless of the duration of the episode, in a once daily dose of 5 ml. The children in the intervention and comparison clusters received oral rehydration solution, and their mothers received advice on feeding during diarrhoea and on referral to the Matlab treatment centre, if needed.

Outcome definitions and follow up

Data collectors who were not involved in the implementation of the intervention made bi-monthly home visits (six monthly in the second year of the study) to collect data on morbidity from diarrhoea and acute lower respiratory infection and adherence to zinc treatment. Diarrhoea was defined as three or more loose, liquid, or watery stools or at least one loose stool containing blood in a 24 hour period. If the stool contained blood, the episode was classified as dysentery. Acute lower respiratory infection was diagnosed if the child had reported symptoms of cough, difficult breathing and rapid breathing, or chest in-drawing. Data on hospital admissions (diagnosis made by physician) were collected by surveillance in the Matlab treatment centre. Data on deaths in study children were collected by the health and demographic surveillance

system of ICDDR,B. Verbal autopsy was conducted with parents for all reported deaths.⁶

We used a Cox's hazards regression to assess the therapeutic effect of zinc on the duration of diarrhoeal episodes, and we estimated the effects of zinc treatment on other outcomes in two ways. Firstly, using children as the unit of analysis, we calculated rates, rate ratios, and 95% confidence intervals, adjusting for covariates with random effect Poisson regression. Secondly, we conducted a cluster level analysis in which we compared the mean rates in the intervention and comparison clusters adjusted for the distribution of selected characteristics of children.

Results

A total of 8070 children contributed 11 881 child years of observation (see bmj.com). The age distribution of children in the intervention cluster was similar to that in the comparison cluster. Significantly more boys were in the intervention clusters than the comparison clusters. The distribution of children's age and birth order, mothers' education, homestead land size, and baseline diarrhoea hospital admission rates were similar in the intervention and comparison clusters.

About 40% (399/1007) of episodes were treated with zinc in the first four months of the trial. Use of zinc increased to about 67% (350/526) of episodes by month 5 of the trial and to more than 80% (364/434) by month 7, and was sustained at that level. On average, intervention children received zinc for about seven days during each episode of diarrhoea.

The duration of diarrhoea in children from the intervention clusters was 24% shorter than that in the comparison group. The duration was significantly shorter for both non-dysenteric diarrhoea and dysentery (table 1).

The incidence of diarrhoea was 15% lower in the intervention clusters than in the comparison clusters (table 2). A slightly lower incidence of acute lower respiratory infection in the intervention clusters was evident by the end of the study, but the difference in rates between the intervention and comparison groups over the full study period was not significant. The intervention clusters had a much higher incidence of acute lower respiratory infection than the comparison clusters at the start, and this incidence declined significantly over the study period. No such trend was observed in the comparison clusters (figure). The trends in incidence of acute lower respiratory infection in the intervention and comparison clusters were significantly different ($P < 0.001$).

Children in the intervention clusters had a 24% lower diarrhoea related admission rate than children in the comparison clusters, which was a significant difference in the individual level analysis but not in the clus-

Table 2 Effect of zinc on incidence of diarrhoea and acute lower respiratory infection

| Disease | Intervention | Comparison | Rate ratio (95% CI)* | Difference in mean rates (95% CI)† |
|--|--------------|------------|----------------------|------------------------------------|
| Diarrhoea: | | | | |
| Periods observed | 20 699 | 21 089 | | |
| Periods with diarrhoea | 3 278 | 3 947 | | |
| Unadjusted incidence (%) | 15.8 | 18.7 | 0.85 (0.76 to 0.96) | 2.9 (0.8 to 5.1) |
| Acute lower respiratory infection: | | | | |
| Periods observed | 20 699 | 21 089 | | |
| Periods with acute lower respiratory infection | 1 543 | 1 700 | | |
| Unadjusted incidence (%) | 7.5 | 8.1 | 0.93 (0.78 to 1.10) | 0.7 (-0.7 to 2.0) |

*Based on individual level analysis using random effect Poisson regression model. Adjusted for child's age, sex, and birth order, mother's education, household homestead land size, baseline cluster level diarrhoea admission rates, and intra-cluster correlation.

†Based on cluster level *t* test analysis. Differences in mean rates expressed per 100 child years of observation. Adjusted for child's age, sex, and birth order, mother's education, household homestead land size, and baseline cluster level diarrhoea admission rates.

ter analysis. The admission rate for acute lower respiratory infection was also lower (by 19%) in the intervention clusters, but the difference was not statistically significant (table 3).

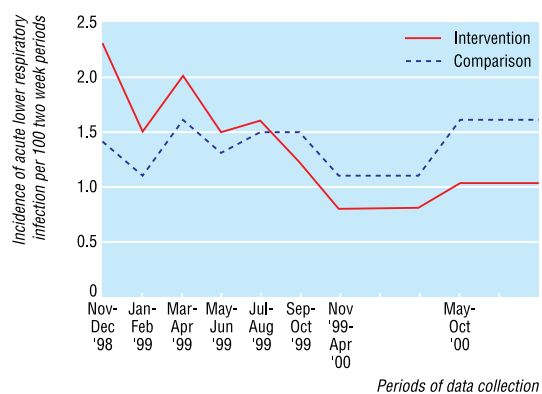
A total of 70 children died—33 in the intervention clusters and 37 in the comparison clusters. Thirty deaths were due to drowning, and the remaining 40 were not injury related. The non-injury death rate was 51% (95% confidence interval 6 to 75%) lower in the zinc intervention clusters than in the comparison clusters. The lower non-injury death rate in the intervention clusters was almost entirely due to fewer deaths from diarrhoea and acute lower respiratory infection. Diarrhoea and acute lower respiratory infection together accounted for 10 deaths in the intervention clusters and 20 deaths in the comparison clusters (see bmj.com).

Discussion

In our study population, children who received zinc supplementation during and after diarrhoea had 24% shorter duration of diarrhoea, 15% lower incidence of diarrhoea, and a trend suggesting fewer diarrhoea related hospital admissions. The reductions in duration of both non-dysenteric diarrhoea and dysentery were significant. The downward trend in the incidence of acute lower respiratory infection in the zinc treatment group, but not in the comparison group, and the 19% reduction in admissions for acute lower respiratory infection, although not statistically significant, also suggested a benefit of zinc.

The reduction in the duration of diarrhoeal episode is consistent with earlier studies.^{7,8} A meta-analysis of five studies of zinc treatment for acute diarrhoea found a summary estimate for reduction in duration of 16%.³ Possible mechanisms for the effect of zinc treatment on the duration of diarrhoea include improved absorption of water and electrolytes by the intestine,⁹ faster regeneration of gut epithelium,¹⁰ increased levels of enterocyte brush border enzymes,¹¹ and enhanced immune response,¹² leading to early clearance of diarrhoeal pathogens from the intestine.¹³

Several recent controlled trials have shown a preventive effect of routine zinc supplementation on the incidence of diarrhoea^{4,14,15} and acute lower respiratory infection.^{16,17} However, these studies pro-



Incidence of acute lower respiratory infection by area and study period

Table 3 Effect of zinc on diarrhoea related and acute lower respiratory infection related admission to hospital

| Disease | Intervention | Comparison | Rate ratio (95% CI)* | Difference in mean rates (95% CI)† |
|---|--------------|------------|----------------------|------------------------------------|
| Diarrhoea: | | | | |
| Child years observed | 5866 | 6015 | | |
| Admissions | 478 | 622 | | |
| Unadjusted admission rate | 8.15 | 10.34 | 0.76 (0.59 to 0.98) | 2.2 (-0.04 to 4.5) |
| Acute lower respiratory infection: | | | | |
| Child years observed | 5866 | 6015 | | |
| Admissions | 296 | 360 | | |
| Unadjusted admission rate | 5.05 | 5.99 | 0.81 (0.53 to 1.23) | 0.9 (-1.8 to 3.6) |

*Based on individual level analysis using random effect Poisson regression model. Adjusted for child's age, sex, and birth order, mother's education, household homestead land size, baseline cluster level diarrhoea admission rates, and intra-cluster correlation.

†Based on cluster level *t* test analysis. Differences in mean rates expressed per 100 child years of observation. Adjusted for child's age, sex, and birth order, mother's education, household homestead land size, and baseline cluster level diarrhoea admission rates.

What is already known on this topic

Zinc deficiency is highly prevalent in children in developing countries

Zinc supplements given during diarrhoea reduce the duration and severity of treated episodes

If given for 14 days during and after diarrhoea, zinc reduces the incidence of diarrhoea and pneumonia in the subsequent two to three months

What this study adds

Zinc used as a treatment for diarrhoea reduces mortality in children

Zinc reduces admissions to hospital for diarrhoea

The impact of zinc on mortality and morbidity can be achieved in a realistic large scale public health programme

vided daily zinc supplementation for a period of 6-12 months, which is often not feasible in large scale programmes.

The most important aspect of our study is that it shows for the first time a reduction in non-injury deaths from the use of zinc as a treatment for diarrhoea. About half the number of non-injury deaths occurred in the intervention clusters than in the comparison clusters. This difference was significant, even in the rigorous statistical analysis for the cluster level design, controlling for confounding variables. We believe, therefore, that the lower mortality can be attributed to zinc supplementation.

The intervention we evaluated is simple and inexpensive and can be incorporated into existing diarrhoeal disease control efforts. Further study is needed to determine whether zinc should be given as a supplement or can be incorporated into oral rehydration solution.

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Science commentary: What does zinc do?

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Adequate zinc intake is critical for health. Zinc deficiency affects cells of the immune system. It causes a reduction in the number B lymphocytes and T lymphocytes (CD4 lymphocytes in particular) through increased apoptosis and also reduces their functional capacity. The functions of the macrophage, another key immunological cell that engulfs and destroys bacteria, are also compromised. The production and potency of several cytokines, the central messengers of the immune system, are also perturbed by zinc deficiency. Many of these changes occur even in the early stages of deficiency.

Zinc plays a part in the maintenance of epithelial and tissue integrity through promoting cell growth and suppressing apoptosis and through its underappreciated role as an antioxidant, protecting against free radical damage during inflammatory responses. Thus, in the case of diarrhoea, multiple functions of zinc may help to maintain the integrity of the gut mucosa to reduce or prevent fluid loss. Notably, these responses can occur within 48 hours, much more rapidly than the direct effects of zinc on cellular development.

The recommended daily allowance is only 10 mg elemental zinc, but many people in both developing and industrialised countries do not have this in their diet.¹ Zinc deficiency is biochemically defined as a serum concentration of less than 9 µmol/l. However, serum zinc concentrations may not fully reflect the physiological zinc status in an individual, and individuals with apparently normal serum concentrations may benefit from daily zinc supplements.²

Benefits of supplementation

This is clearly illustrated in several randomised controlled trials of zinc supplementation. A meta-analysis indicated that daily zinc supplementation can reduce the incidence of pneumonia by 41% and

diarrhoea by 18%.³ A meta-analysis of trials of adjunctive zinc supplementation in children with diarrhoea reduced the duration of the illness by 24%.⁴ A trial of daily zinc supplementation in otherwise healthy children from New Guinea reduced the number of cases of malaria seen at a health clinic by 38%.⁵

There is also evidence that zinc supplementation could offer benefit to pregnant women and their babies.⁶ One study showed that prenatal zinc supplementation can increase birth weight,⁷ and another indicated reduced incidence of diarrhoea and other morbidities in the infants.⁸ Babies who are small for gestational age also seem to benefit from taking daily zinc supplementation. A trial in India found that babies who received zinc from 1 month onwards were 60% less likely to die during infancy.⁹ Lastly, several studies indicate a potential role for zinc and supplements that contain zinc in improving immune status¹⁰ and health in elderly people.¹¹ Zinc supplementation, therefore, seems to be particularly critical during periods of immune development or degeneration: early childhood, pregnancy, and later life.

Problems caused by too much zinc

Taking too much daily zinc could also be a problem because, although it is not toxic, high doses can impair copper absorption. This can lead to copper deficiency with immunosuppression and other subtle and apparent adverse effects, especially for the mother and fetus during pregnancy.¹² For this reason, doses more than twice the recommended daily allowance are not recommended and prenatal zinc supplements should contain copper,¹³ especially in populations with low mineral intakes.

1 Gibson RS, Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some