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Zinc and childhood infectious disease morbidity and mortality

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Zinc is an essential mineral and deficiency results in abnormal immune function and higher rates of infectious diseases. Randomized controlled trials of zinc supplementation have been conducted in children in developing countries to determine effects on infectious disease morbidity and mortality. Zinc-supplemented children have been found to have lower rates of diarrhea, pneumonia and malaria in comparison with children not given zinc. Zinc used as an adjunct to fluid and dietary management of acute and persistent diarrhea has been found to reduce diarrheal duration and severity. Preliminary evidence suggests that zinc supplementation in children in poor developing country settings may also reduce infant mortality, but larger trials are needed to address this important issue. Preventive and therapeutic interventions should be implemented in developing countries where zinc deficiency is likely to be prevalent.

Diarrhea: Malaria: Malnutrition: Pneumonia: Zinc

Introduction

Zinc is an essential mineral, critical to human metabolism, growth and immune function (Aggett & Comerford, 1995). With zinc deficiency epithelial barriers are compromised and many components of the immune system malfunction (Shankar & Prasad, 1998). This decrease in immunological competence may lead to a higher risk of infectious diseases or a greater severity of illnesses. Such an association of zinc deficiency with infectious disease morbidity, observed in clinical and field studies (Prasad, 1985; Bahl *et al.* 1998), has been shown to be a causal relationship through randomized controlled trials of zinc in prevention of disease. Trials of zinc in the treatment of diarrhea provide evidence of benefit on episode outcomes, as well. The benefits demonstrated in these trials, along with biological measures, such as plasma or tissue zinc, or dietary intake assessments, suggest that zinc deficiency is prevalent in children in developing countries and has important effects on morbidity and possibly mortality.

For this review, all published and unpublished randomized controlled trials of oral zinc supplementation in preschool children in developing countries were sought by systematic researching of bibliographic databases, by references from publications and by contacts with funding agencies and experts in the field. Special efforts were made to identify unpublished reports to avoid the possible bias of using published reports, which are possibly more likely to have positive findings. The selection criteria for the review included double-blind trials containing at least one half of the United States Recommended Daily Allowance of zinc (5 mg/d in infants and 10 mg/d in children 1–4 years old). The prevention trials included in this review were those that provided the oral zinc supplements and conducted concurrent household-level morbidity assessments for at least 4 weeks. The therapeutic trials included in this review were those that gave the supplement as an adjunct to fluid and dietary therapy in acute ($<$14d pre-enrolment duration) or persistent ($\geq$14d pre-enrolment duration) diarrhea. From the search twenty-six trials were identified, eight were prevention trials, and five each were therapeutic trials in acute and persistent diarrhea.

The included studies are reviewed providing the effect size and statistical significance from the original publication or in some cases from a pooled analysis. The pooled analysis was performed with seven of the eight prevention trials, three of five acute diarrhea treatment trials and four of five persistent diarrhea treatment trials. The other four trials either did not have original data available for analysis (two) or were not provided by the investigators (two).

The pooled analysis of prevention trials was performed with the Confidence Profile Method (Eddy *et al.* 1992*a*) using FAST*PRO Software, Version 1.8 (Eddy *et al.* 1992*b*). A joint posterior probability distribution was estimated with a random effects hierarchical model (Bryk *et al.* 1989) and Odds Ratio with 95 % Confidence Intervals calculated for each and overall study. For the pooled analysis of therapeutic trials on duration of diarrhea Cox survival regression models were used, stratified by individual trial, with continuation of the episode after enrolment modeled as the dependent variable and treatment groups and pre-enrolment duration as independent variables. These models permitted calculation of the Relative Hazard for continuation of the episode (time until diarrhea

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Table 1. Trials evaluating the preventive effects of zinc supplementation on diarrhea or pneumonia

Country	Authors	Number in zinc group	Number in control group	Child-Years		Enrolment		Zinc. suppl.	Control suppl.	Effect of zinc on diarrheal incidence	Effect of zinc on pneumonia incidence
				Zinc	Control	Age (mo)	Other criteria				
Vietnam	Ninh *et al.* 1996	73	73	30·8	30·8	4–36	Weight for age and height for age $< -2z$**	10 mg as sulfate	Placebo	44 % lower*	44 % lower*
India	Sazawal *et al.* 1997, Sazawal *et al.* 1998	286	293	122·9	124·8	6–35	Recovered from acute diarrhea	10 mg as gluconate; Vit. A,B,D,E	Vit. A,B,D,E	8 % lower	43 % lower*
Mexico	Rosado *et al.* 1997	97	97	116·0	117·1	18–36	–	20 mg as methionate; half with iron	Placebo; half with iron	37 % lower*	–
Guatemala	Ruel *et al.* 1997	45	44	23·2	22·9	6–9	–	10 mg as sulfate	Placebo	18 % lower*	–
Jamaica	Meeks-Gardner *et al.* 1998	31	30	7·1	6·2	6–24	Weight for age $< -2z$**	5 mg as sulfate; Vit. A,B,C,D	Vit. A,B,C,D	8 % lower	88 % lower
Peru	Penny *et al.* reported in Zinc Investigators' Collaborative Group, 1999	80	79	36·1	37·4	6–35	Recovered from persistent diarrhea	10 mg as gluconate	Placebo	12 % lower*	15 % lower
Papua New Guinea	Shankar *et al.* reported in Zinc Investigators' Collaborative Group, 1999	136	138	75·3	80·7	6–60	–	10 mg as gluconate	Placebo	12 % lower	–

* Statistically significant effect.
** z = standard deviation score.

ceased) with its 95 % Confidence Interval (Cox & Oakes, 1984; Allison 1995; Delong *et al.* 1994). The control group was coded as 1 and zinc group as 0, and a Relative Hazard of <1 was a beneficial effect consistent with the beneficial effect expressed by the Odds Ratio. The dependent outcomes of treatment failure or death in persistent diarrhea were analyzed using logistic regression models stratified by trial, with treatment group, subgroup categories and potential interaction terms as independent variables to calculate the Odds Ratio and 95 % Confidence Intervals (Matthews & Farewell, 1988).

Zinc supplementation effects on prevention of infectious diseases

Zinc deficiency has been associated with higher rates of infectious diseases, including skin infections, diarrhea, respiratory infections, and malaria, as well as with delayed wound healing (Prasad, 1985; Bahl *et al.* 1998; Black, 1998). With regard to outcomes in children in developing countries, the best studied have been diarrhea and lower respiratory tract infections, although limited information on malaria is also available. Due to the difficulty in assessing zinc status of children in a population, most of the information on the role of zinc deficiency in the risk of infectious disease is available from randomized controlled trials of zinc supplementation. In these trials when zinc is the only experimental variable, there is direct causal evidence that additional zinc can result in a lower rate of infectious diseases.

Seven trials of zinc supplementation provide information on outcomes of diarrhea and four of these include information on pneumonia (Table 1). These trials were done in preschool children who were representative of poor developing country populations, and in two of the studies more poorly nourished children were selected for enrolment into the trial. These trials were done in seven different countries representing a wide range of development and nutritional status of the population. The results with regard to diarrheal incidence are consistent in showing that zinc-supplemented children have lower rates of diarrhea than those of the control children. Individually, in most of these studies statistically significant differences were found in diarrheal incidence and a pooled analysis showed that the overall incidence of diarrhea in zinc-supplemented children was 18 % (95 % CI 7 %, 28 %) less than in unsupplemented children (Zinc Investigators' Collaborative Group, 1999). Since it also appears that zinc supplements reduce the duration of diarrhea (Sazawal *et al.* 1995), it is not surprising that the overall effect in the pooled analysis on the prevalence of diarrhea was greater than the effect on incidence, i.e. 25 % (95 % CI 12 %, 37 %) lower prevalence of diarrhea in the zinc-supplemented children (Zinc Investigators' Collaborative Group, 1999). While children in these trials who were in their second or later year of life (*v.* infants), had lower plasma zinc concentrations, were wasted or were female had a tendency to have greater effects of zinc supplementation, the comparison of effects between these subgroups of children did not show statistically significant differences (Zinc Investigators' Collaborative Group, 1999).

Table 2. Trials evaluating the therapeutic effects of zinc supplementation on acute diarrhea

Country	Authors	Diarrheal duration on enrolment	Number in zinc group	Number in control group	Enrolment		Zinc. suppl.	Control suppl.	Effect of zinc on episode duration	Effect of zinc on diarrhea episodes	Effect of zinc on episode severity
					Age (mo.)	Nutritional criteria					
India	Sachdev *et al.* 1988	<4d	25	25	6–18	Excluded mod.–sev. malnutrition	20 mg as sulfate	Placebo	9 % shorter episodes	–	18 % lower stool frequency
India	Sazawal *et al.* 1995	<7d	456	481	6–35	Excluded sev. malnutrition	20 mg as gluconate Vit. A, B, D, E	Vit. A, B, D, E	21 % reduced probability of continuing diarrhea*	15 % fewer	39 % fewer watery stools*
Bangladesh	Roy *et al.* 1997	<3d	57	54	3–24	Included if weight for age <76th percentile	20 mg as acetate; Vit. A,B,D,E	Vit. A,B,D,E	14 % reduced probability of continuing diarrhea	23 % fewer*	28 % lower stool output
Bangladesh	Faruque *et al.* 1999	<4d	343	341	6–23	Excluded sev. malnutrition	14 or 40 mg as acetate; Vit. C; half Vit. A	Vit. C; half Vit. A	20 % reduced probability of continuing diarrhea*	43 % fewer*	–
Indonesia	Hidayat *et al.* 1998	<7d	739	659	3–25	None	4–5 mg/kg as acetate	Placebo	11 % shorter episodes*	28 % fewer	–

* Statistically significant effect.

Fewer studies provide information on the effects of zinc supplementation on the incidence of pneumonia and the original data from these trials have been examined in the pooled analysis (Zinc Investigators' Collaborative Group, 1999) (Table 1). The four studies available consistently show that zinc-supplemented children have lower rates of pneumonia and two of these studies showed sizeable and statistically significant effects individually. The other two studies had smaller numbers of subjects and the differences did not reach statistical significance. In an overall pooled analysis, there was a 41 % (95 % CI 17 %, 59 %) lower rate of pneumonia in zinc-supplemented children (Zinc Investigators' Collaborative Group, 1999).

Only two randomized controlled trials provide information on the effects of zinc supplementation on clinical attacks of malaria. In Gambian children with a twice-weekly 70 mg zinc supplement, there was 30 % reduction in clinic visits due to malaria, which was of only borderline statistical significance in this small study (Bates *et al.* 1993). In a larger trial with daily zinc supplementation using 10 mg of zinc gluconate in Papua New Guinea, there was a significant reduction of 40 % in clinic-based *Plasmodium falciparum* malaria rates and a higher efficacy (70 %) for clinical attacks with parasite densities of more than 100 000:l (Shankar *et al.* in press).

Therapeutic effects of zinc during diarrhea

The therapeutic effects of zinc supplements during diarrhea have been investigated in five trials in acute diarrhea and five additional trials in persistent diarrhea. These studies reveal consistent benefits of zinc supplementation. In the acute diarrhea studies (Table 2) zinc supplementation generally resulted in shorter diarrheal episodes and a reduced likelihood that the episode would continue for more than 7 days after enrolment in the study. Not all of the apparent effects were statistically significant, but some of the small studies had low statistical power. A pooled analysis of zinc supplementation in acute diarrhea trials for which original data could be obtained (Sazawal *et al.* 1995; Roy *et al.* 1997; Hidayat *et al.* 1998) revealed an overall 15 % (95 % CI 5 %, 24 %) lower probability of continuing diarrhea in the supplemented group (Zinc Investigators' Collaborative Group, 2000). Several studies also reported reductions in episode severity, as measured by frequency of watery stools or measured stool output. (Sachdev *et al.* 1988; Sazawal *et al.* 1995; Roy *et al.* 1997)

The five trials addressing the effect of zinc supplementation in persistent diarrhea likewise showed benefits with zinc supplementation (Table 3). Generally, the studies revealed that supplementation was associated with a shorter episode duration and the pooled analysis with four trials (Roy *et al.* 1998; Penny *et al.* 1999; Bhutta *et al.* 1999; Khatun 1998) indicated that children in these trials had 24 % (95 % CI 9 %, 37 %) lower probability of continuing diarrhea, if they received the zinc supplement (Zinc Investigators' Collaborative Group, 2000). There was also a suggestion of reduced episode severity in one trial (Sachdev *et al.* 1990), but not in the second (Bhutta *et al.* 1999). Importantly in some trials, large reductions in the rate of treatment failure or death were reported. Overall in

Table 3. Trials evaluating the therapeutic effects of zinc supplementation on persistent diarrhea

Country	Authors	Diarrheal duration on enrolment	Number in zinc group	Number in control group	Enrolment		Zinc. suppl.	Control suppl.	Effect of zinc on episode duration	Effect of zinc on episode severity	Effect on treatment failure or death
					Age (mo.)	Nutritional criteria					
India	Sachdev *et al.* 1990	<14d	20	20	6–18	Excluded mod. – sev. malnutrition	20 mg as accetate	Placebo	19 % shorter episodes	21 % less stool frequency	–
Bangladesh	Roy *et al.* 1998	<14d	95	95	3–24	None	20 mg as acetate;	Vit. A,B,D	15·3 % reduced probability of continuing diarrhea	–	63 % reduction*
Peru	Penny *et al.* 1999	≥14d	139	136	6–35	One	20 mg as gluconate	Placebo	18 % reduced probability of continuing diarrhea	–	19 % reduction
Pakistan	Bhutta *et al.* 1999	>14d	43	44	6–36	Weight for age ≤ −2z**	3 mg/kg as sulfate Vit. A,B,D,E	Vit. A,B,D,E	2 % reduced probability of continuing diarrhea	No effect	58 % increase
Bangladesh	Khatun 1998	>14d	44	44	6–24	Weight for age <76th percentile	20 mg as acetate; Vit. B,C,D	Vit. B,C,D	55 % reduced probability of continuing diarrhea*	–	75 % reduction*

* Statistically significant effect.
** z = standard deviation score.

the pooled analysis, there was a 42 % (95 % CI 10 %, 63 %) reduced rate of treatment failure or death in children given zinc supplements. For this outcome the trials were significantly heterogeneous ($P = 0{\cdot}04$), which was mainly due to the results in the study in Pakistan.

Effect of zinc supplementation on child mortality

Pneumonia and diarrhea are the two most common causes of death in children in developing countries and malaria also contributes substantially in many settings. With the large and consistent effects of zinc supplementation on the incidence and in some cases severity of these infectious diseases, one might hypothesize an effect on child mortality. None of the studies of zinc supplementation conducted to date have been of substantial size to fully address the effects on mortality. One study recently completed in India does provide preliminary evidence that zinc-supplemented infants have a lower rate of overall mortality (Sazawal *et al.* 1999). In this trial among 1250 small for gestational age infants, studied from 1 to 9 months of age there was 67 % reduction in mortality in zinc-supplemented infants. Supplementation with selected other vitamins and minerals, including iron, was not associated with a significant reduction in mortality in this four-cell factorial design trial.

Conclusions

There is now evidence that zinc supplementation can prevent episodes of diarrhea and pneumonia, as well as possibly malaria, and can improve the outcome of acute and persistent diarrhea. It will be important to confirm these findings, especially those for pneumonia and malaria, for which results from diverse settings are limited. Additionally, it will be important to evaluate the effects of zinc supplementation on child mortality in potentially vulnerable developing country populations. Plans are underway to conduct such trials in at least three settings, i.e. India, Nepal and Zanzibar; these studies should start within the next year. However it appears that there is ample evidence to move forward to explore public health applications, using zinc either preventively in children or therapeutically for diarrhea. For the preventive uses of zinc, there is a need to evaluate various ways to improve the zinc nutriture of children in developing countries. These include improving the dietary sources and availability of zinc, fortifying foods with zinc, and supplementation programs. Therapeutic uses of zinc in diarrhea should be studied in regard to feasible modes of delivery. For both preventive and therapeutic applications the cost-effectiveness should be assessed and compared with alternative interventions.

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