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Impact of zinc supplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea

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Objective: To assess the impact of zinc supplementation during acute diarrhoea on subsequent growth and morbidity in malnourished young children.
Design: Double blind randomized controlled clinical trial
Setting: International Centre for Diarrhoeal Disease Research, Bangladesh.
Subjects: Sixty-five children aged 3–24 months with acute diarrhoea for less than 3 d.
Intervention: Either elemental zinc (20 mg/d) in a multivitamin syrup or multivitamin syrup alone divided in three divided daily doses for a period of two weeks. Children were followed up weekly at home to assess subsequent growth and morbidity for a period of eight weeks.
Main outcome measures: Gain in length and body weight and reduction in diarrhoea and respiratory tract infection.
Results: During the follow-up, zinc supplemented children showed significantly greater cumulative length gain (18.9 mm *vs* 14.5 mm, $P < 0.03$) and comparable body weight gain than the children of the control group. Subsequent length gain was not correlated with initial height in the zinc-supplemented group ($r = 0.13$), $P = 0.5$), but was significantly correlated in the control group ($r = 0.6$, $P < 0.0007$). Zinc-supplemented and stunted children ($\leq 90\%$ length for age $n = 18$) experienced significantly fewer episodes of diarrhoea (0.07 *vs* 0.6, $P < 0.05$) and respiratory illness (1.0 *vs* 2.4, $P < 0.01$) compared to the control group. The underweight children ($\leq 71\%$ weight/age $n = 38$) receiving zinc-supplementation also had fewer episodes of diarrhoea (0.4 *vs* 1.0, $P < 0.04$) and shorter duration of diarrhoeal episodes (1.0 *vs* 3.0 d, $P < 0.04$) compared to their counterparts in the control group.
Conclusion: These results suggest that a short course of zinc supplementation to malnourished children during acute diarrhoea reduces growth-faltering and diarrhoeal and respiratory morbidity during subsequent two months.
Sponsorship: Wellcome Trust.
Descriptors: acute diarrhoea; zinc supplementation; subsequent; growth; morbidity

Introduction

Diarrhoea and malnutrition remain major health problems among children of developing countries. Although it has been well documented that diarrhoea is a major cause of malnutrition (Rowland *et al*, 1977; Tomkins, 1983) and malnourished children are at greater risk of infection and severe illness, the importance of micronutrient supplementation in the diarrhoea-malnutrition cycle has not been completely defined. Zinc is an essential trace element that is required for normal intestinal mucosal integrity, skeletal growth, sodium and water transport, and immune function. Malnourished children are often zinc deficient and marginal body zinc stores may be further depleted during diarrhoea through fecal zinc losses, which may be as high as 159 μg/kg/d (Castillo-Duran *et al*, 1988). Children in developing countries suffer from 3–4 episodes of acute diarrhoea yearly and each episode lasts an average of 3–4 days. This cycle of diarrhoea with lower dietary intake and fecal nutrient losses may substantially reduce the zinc stores which could result in growth-faltering and increased morbidity especially among the malnourished children. It has been shown that zinc supplementation during nutritional rehabilitation of the severely malnourished children results in rapid weight gain (Golden & Golden, 1981; Simmer K *et al*, 1988; Khanum S *et al*, 1988). Zinc deficiency is associated with depressed cell-mediated and humoral immunity and supplementation may enhance immune functions (Chandra & Au, 1980). In children of Bangladesh and Peru, depressed cell mediated immunity has been associated with higher diarrhoeal attack rates (Koster *et al*, 1987; Baqui *et al*, 1993). It is not yet known whether zinc replenishment in malnourished children during acute diarrhoea has the potential to reduce subsequent growth-faltering and morbidity.

We hypothesized that malnourished children who receive zinc supplementation during acute diarrhoeal episodes would be benefited with reduction in subsequent growth faltering and diarrhoeal and respiratory morbidity. Based on these assumption, we studied children who rec-eived zinc or placebo in a double-blind randomized trial for two weeks, to investigate the effect of zinc

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supplementation on growth and morbidity during subsequent two months.

Materials and methods

Population

Children aged 3–24 months with acute diarrhoea (AD) for less than 3 d and weight for age less than 76% of median NCHS (1976) standard were eligible to take part in this study. Weight for age and height for age percentage of median were used, as people of our country are more acquainted with this type classification of malnutrition. Weight for age less than 76% was used as cut-off point to avoid well nourished children to be included in the study, since well nourished usually do not have zinc or other micronutrient deficiency and zinc is believed to be more effective on zinc deficient children. As per Gomez classification up to 76% weight for age means second degree malnutrition. Irrespective of socio-economic status, all children, who fulfilled the inclusion criteria and attended the clinical research and service centre of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) were included into this study. Children who lived within a 20 km radius of the Centre and only urban and peri-urban children were included into this study. Rice is their staple food and seasonality do vary their food habit very much. Exclusion criteria included the presence of any severe systemic infection, temperature $> 38^{\circ}C$ and pedal oedema.

Methods

Written consent was obtained from the parents of all the children beforehand and the protocol was approved by the Ethical Review Committee of ICDDR,B. Diarrhoeal management was done according to standard practice of the treatment centre and was uniform for all the children. Briefly, severe dehydration was corrected within 4 h of admission according to the WHO guidelines with intravenous infusion of a poly-electrolyte solution (sodium 133 mmol/L, potassium 1 mmol/L, chloride 98 mmol/L and HCO_3 48 mmol/L), in case of some or mild dehydration, WHO/UNICEF recommended oral rehydration solution (sodium 90 mmol/L, pottasium 20 mmol/L, chloride 80 mmol/L and HCO_3 30 mmol/L) was administered. The detail of clinical management and outcome of these patients have been described elsewhere (Roy *et al*, 1996). Children were breastfed and a milk-cereal diet containing a small amount of dietary zinc (1.4 mg/L) was given during hospitalization. A double-blind randomized trial was conducted. Computer generated randomization was used. Block randomization was done using eight numbers in each block to ensure that after every eight patients equal numbers of patients have entered into each group. This procedrue was repeated for each set of eight patients. Children were randomly allocated to two groups. Each group received either 20 mg elemental zinc per day with multivitamins or multivitamins alone in a dose of twice the recommended dietary allowances in three divided doses for a period of two weeks. Study syrup was started immediately after sending baseline samples, that is blood and stool samples. At the hospitalization period, syrup was administered by nurse and after discharge it was administered by the mother of the child or the care taker of the child who was trained by our staff. The manufacturer of the syrup was ACME laboratories limited, Dkaka Bangladesh. The study syrup contained zinc (zinc acetate) 6.7 mg/5 ml in a multivitamin syrup. The composition of multivitamins were, vitamin A 3000 IU, B_1 1.2 mg, B_2 2.0 mg, B_6 0.06 mg nicotinamide 6.0 mg, calcium D pantothenate 6.0 mg per 5 ml. Multivitamins were given as all the children under study were moderately or severely malnourished and malnourished children are often found to be deficient in vitamins. Bad taste of the zinc were masked by the manufacturer as instructed by the investigators. After discharge from the diarrhoea treatment centre, compliance with daily intake of the syrup at home was monitored by checking the remaining portion of syrup by trained health workers at alternate day visits. Body weights of children were measured initially after correction of dehydration and repeated every morning between 9 and 10 am during their hospitalization using weighing scales of 20 g sensitivity (Toledo, USA). Weekly measurement of body weights was taken using weighing scales of 100 g sensitivity (Salter, UK). Supine length of a child was measured on admission and then at weekly interval for a period of eight weeks. Length was measured with a locally constructed length board with a precision of 1 mm. Four female Research Assistants were trained for two weeks on techniques of anthropometric measurements and data collection methods at field. Their intra-observation and inter-observation variation in anthropometric measurements were calculated and trained until they achieved an accepted level of 2% or less of co-efficient of variation. All instruments were standardized every morning before measurements. After two weeks of supplementation, children were followed up weekly for eight weeks. Stunting was defined as length for age less than or equal to 90% of median NCHS standard (NCHS, 1976). Underweight children were classified as weight for age less than or equal to 70% of the median NCHS standard. Morbidity data were collected from mothers by weekly recall method. A form was used to collect morbidity history of last 7 d by backwards methods. An episode of diarrhoea was defined as three or more loose, liquid, watery or mucoid stools during a 24 h period or any number of stools containing blood and mucous. A new diarrhoeal episode was defined when it was separated from the previous episode by at least a 48 h interval of passage of normal stool. If any episode continued into the subsequent week it was considered as the previous episode. During home visits, mothers were asked about the exact day of the beginning of any illness, its continuation and the day of recovery. Children not available on the scheduled date of follow-up were visited on the following day. Upper respiratory tract infection (URTI) was defined as presence of cough, nasal discharge and raised body temperature. Lower respiratory tract infection (LRTI) was defined by a respiratory rate of more than 50 per minute, difficulty in breathing, cough and body temperature above $38^{\circ}C$. All illness episodes were examined by investigators to confirm the diagnosis and institute necessary for standard medical care. Venous blood samples were taken at the beginning and at the end of the administration of the study syrup for two weeks. Morning blood specimens obtained by venipuncture were carefully collected with trace-element free plastic syringes and disposable stainless steel needles and were transferred into prewashed zinc-free plastic tubes. Glass tubes and plastic tubes were rendered trace-mineral free for collection and analysis of samples by overnight soaking in 50% nitric acid, rinsed three times with doubly deionized water and allowed to

drain dry. Serum zinc was estimated with an atomic absorption spectrophotometer (AAS, Perkin-Elmer Model 3100) and retinol was estimated by high-pressure liquid chromatography (HPLC, Waters 510, USA).

Statistical analysis

Data were transferred to coding sheets and analyses were performed using SPSS/PC$^+$ (SPSS Inc., USA) and NCHS statistical packages. In the case of normal distribution of data, group means were compared using Student's *t*-test. In case of non normal distribution, data was logarithmically transformed before using *t*-test. Statistical significance was accepted at a 5% probability level.

Results

The 32 children in the zinc and 35 children in the control group were comparable on admission with respect to age, sex, duration of diarrhoea before entry to the trial, nutritional status, serum zinc and retinol levels (Table 1). Two weeks after commencement of zinc supplementation, mean serum zinc level increased significantly in the zinc-supplemented subjects (13.0 *vs* 11.0 µmol/l, $P = 0.007$) whereas in the placebo group, it remained same (12.1 *vs* 12.1 µmol/l, $P = 0.98$) which has been reported elsewhere (Roy *et al*, 1996).

Seven per cent of the total children did not complete the study because of mitigation due to flood in the study area. These children were comparable in proportion between the groups and were comparable with their own treatment group in respect of age, nutritional status and severity of disease at the entry to the study.

The mean overall weight gain of the children were 14 g/kg/week from beginning of study until the end of two weeks of supplementation period a 11 g/kg/week during the subsequent eight weeks. There was no significant differences in mean weight gain between the zinc and control groups during the follow-up period. Unlike the gain in body weight, children receiving zinc supplementation during acute diarrhoea showed a 30% greater net length gain compared to the controls during the eight weeks follow-up period (18.9 *vs* 14.5 mm, $P < 0.05$, Figure 1).

The net gain in length was inversely correlated with initial length among the children not receiving zinc (r= 0.6, slope= 0.13, $p<0.0007$, Figure 2) whereas in the supplemented children, the net gain in length increased irrespective of any relationship with initial length r= 0.13, slope= 0.04, $p = 0.5$, Figure 3).

Table 1 Comparison of children receiving zinc and placebo for acute diarrhoea at the entry of follow-up (mean, 95% CI)

	Placebo ($n = 33$)	*Zinc* ($n = 32$)
Weight/age	68 (65.96, 70.04)	69 (66.92, 71.08)
Height/age	92 (90.98, 93.02)	92 (91.31, 92.69)
Weight/ht	81 (78.61, 83.39)	83 (81.27, 84.73)
MUAC (cm)	11.6 (11.26, 11.94)	11.5 (11.16, 11.84)
Sex (M/F)	18/15	16/16
Age (months)	11 (9.3, 12.70)	11 (9.62, 12.38)
Duration of diarrhoea (d)	2.6 (2.37, 2.83)	2.8 (2.49, 3.11)
Serum zinc (µmol/l)	12.6 (10.56, 14.64)	11.2 (10.16, 12.24)
Serum retinol (µmol/l)	0.52 (0.43, 0.62)	0.52 (0.44, 0.61)

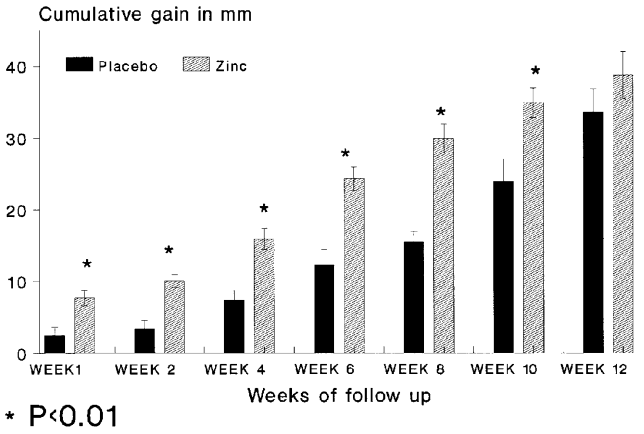

Figure 1 Impact of zinc supplementation on linear growth in children with acute diarrhoea (mean & s.e.m.).

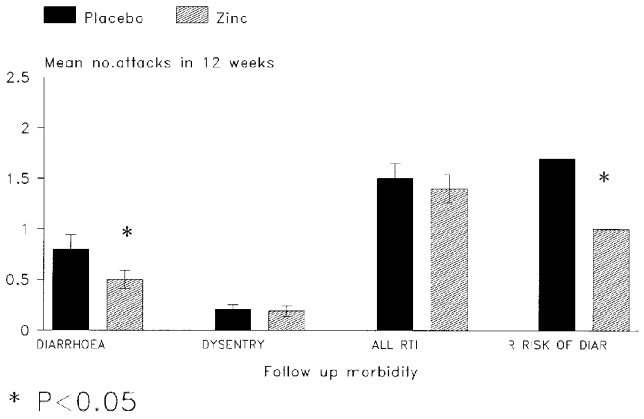

Figure 2

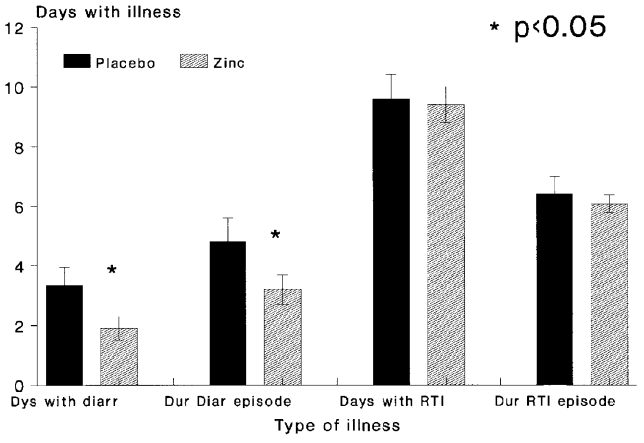

Figure 3

There was no difference in the morbidity pattern between the zinc supplemented and control children when entire groups were compared. However, among the lighter children (≤70% weight/age, basal serum zinc concentration, zinc group= 10.98 and placebo group-

Table 2 Effect of zinc supplementatin on diarrhoeal and respiratory illness among stunted (≤ 90% length/age) children during eight weeks of follow-up after acute diarrhoea (mean, 95% CI)

	Placebo $n = 16$	*Zinc supplementation* $n = 13$	*Statistical significance (P value)*
No. of all diarrhoea	0.6 (0.12, 1.08)	0.2 (0.00, 0.44)	0.1
Duration of diarrhoeal episodes (d)	2.3 (0.49, 4.11)	0.2 (0.00, 0.68)	0.03
No. of watery diarrhoea	0.6 (0.17, 1.03)	0.07 (0.00, 0.25)	0.05
Duration of watery diarrhoea (d)	2.1 (0.23, 3.97)	0.2 (0.00, 0.68)	0.05
No. of all respiratory tract infection	2.4 (1.55, 3.25)	1.0 (0.27, 1.73)	0.01
No. of lower respiratory tract infection (LRTI)	1.0 (0.57, 1.43)	0.3 (0.00, 0.54)	0.0009
Duration of LRTI episode (d)	4.2 (2.18, 6.22)	1.15 (0.00, 2.3)	0.01
No. of URTI episode	1.4 (0.81, 1.99)	0.7 (0.09, 1.3)	0.06
Duration of URTI (d)	6.4 (3.58, 9.22)	4.2 (0.33, 8.07)	0.2

Data were log transformed before using Student's *t*-test of significance.

$= 12.76\,\mu mol/L$), the mean (CI) number of diarrhoeal episodes was fewer 0.4 (0.13, 0.67) in the zinc supplemented children compared to control group 1.0 (0.55, 1.45) ($P = 0.04$). The number of mean (CI) episodes of watery diarrhoea were also fewer 0.2 (0.00, 0.42) in the zinc supplemented children compared to that in the placebo group 0.8 (0.43, 1.17) ($P < 0.02$). The mean (CI) duration of diarrhoeal episodes were significantly shorter in the zinc-supplemented group 1.0 (0.00, 2.44) days compared to that of the control group 3.0 (1.38, 4.62) days ($P < 0.04$). The effect of zinc supplementation on illness were more pronounced among the shorter children (≤ 90% length/age, basal serum zinc level, zinc group= 10.75 and placebo 15.0 μmol/L) in the zinc-supplemented group who has significantly fewer episodes of both water diarrhoea (mean 0.07 *vs* 0.6, $P < 0.05$) and respiratory tract infections (mean 1.0 *vs* 2.4, $P < 0.01$) compared to their counterparts in the control group (Table 2). These children also had a significantly shorter mean duration of diarrhoea (0.2 *vs* 2.1 d, $P = 0.05$) and respiratory tract infections (1.6 *vs* 4.2 d, $P < 0.01$).

Discussion

Our study examined the effects of zinc administered at the time of treatment of acute diarrhoea on subsequent growth and morbidity due to diarrhoea and respiratory illness. A pronounced effect of zinc supplementation was observed on linear growth, but no such effect was noticed on body weight. This is in contrast with the results of some studies of zinc supplementation during nutritional rehabilitation of severely malnourished children who were free from diarrhoea (Golden & Golden, 1981; Khanum *et al*, 1988). Walravens *et al* (1983) also reported that children provided with daily dose of 7.5 mg elemental zinc for six months had significant improvement of weight/age Z-score, but those children also received energy and protein-rich food.

Table 3 Effect on zinc supplementation on cumulative weight (g) of patients with acute diarrhoea during eight weeks follow-up (mean ± s.d.)

Weeks of follow-up	*Placebo*	*Zinc*	*Statistical significance*
Week 1	278 ± 338	308 ± 306	0.7
Week 2	344 ± 268	340 ± 274	0.9
Week 3	428 ± 304	383 ± 389	0.6
Week 4	531 ± 318	471 ± 445	0.5
Week 5	658 ± 351	579 ± 412	0.7
Week 6	672 ± 353	615 ± 445	0.6
Week 7	755 ± 361	702 ± 445	0.6
Week 8	793 ± 489	774 ± 531	0.9

There was no significant weight gain between the placebo and the supplemented groups during follow-up period.

During rapid catch-up growth of severely malnourished children, therapeutic goals include weight accrual which includes tissue synthesis and normalization of fluid and electrolytes. In the presence of adequate energy and protein in the diet, zinc would be utilized for lean tissue synthesis (Golden & Golden, 1981). In our study, an impact of zinc supplementation on body weight during follow up was not evident, perhaps due to one or more of the following reasons: (1) absence of a high-protein and high-energy diet at home, such as that given in rehabilitation studies as high intake of energy and protein intake is a prerequisite for optimal catch-up growth of malnourished children; (2) subjects of this study probably had lower absorption and retention of the supplemental zinc compared to the non diarrhoea state of malnourished children; and (3) in the absence of optimal dietary energy and protein, zinc might have been preferentially utilized for skeletal growth rather than for weight accrual. Additionally, in the absence of adequate energy and protein, zinc might be utilised for synthesis of labile proteins such as growth hormone (Chruvanky *et al*, 1982), immunoglobulins, enzymes, bone growth and bone mineralisation (Leek *et al*, 1984) rather than for lean tissue (muscle) synthesis. The dose of zinc was possibly too low to achieve a maximal supplementation effect. The study subjects received a rice and milk containing diet which was low in zinc (1.4 mg/l) during their relatively brief stay in the hospital. Yet they showed increase in body weight at the time of discharge which has been reported earlier (Roy *et al* 1997). The supplementation of zinc led to increased linear growth by improving the zinc store of the children. Deficit in height in growing children has been documented in a syndromic condition of mild zinc deficiency in both developing countries (Prasad, 1979), Denver (Hambridge *et al*, 1972), Yugoslavia (Buzina *et al*, 1980) and other areas. Zinc supplementation increased linear growth in a group of school children in Iran (Ronagy *et al*, 1974) and Denver (Buzina *et al*, 1980) USA. Recent results from a study of growth retarded Vietnamese children with 10 mg of daily zinc supplementation showed significant height gain over the five months of supplementation with rise in serum insulinlike growth factor level (IGF-1) (Ninh *et al*, 1996). The role of zinc on skeletal growth is not fully understood, but zinc is known to be essential for bone growth. In particular, bone-derived alkaline phosphatase is a zinc metalloenzyme which is dependent on body zinc status.

Growth-hormone deficient children showed significant increase in linear growth with zinc supplementation compared to treatment with growth hormone alone (Richards & Marshall, 1983). The active mediator of growth hormone, IGF-1 is dependent on zinc (Castro-Magana *et al*, 1981). The effect of zinc on bone growth in our subjects was further demonstrated by the differences in linear relationships between the initial height and the amount of net increase in height. In the supplemented group there was apparently no correlation between net skeletal growth and initial height, that is all supplemented children had maximised their catch-up growth with available zinc. But this was not the case for the unsupplemented children who showed a highly significant inverse linear relationship between net skeletal growth and initial height. The children of control group received no additional zinc, hence their growth was dependent on preexisting body reserves of zinc or dietary sources of zinc. During nutritional rehabilitation, it is observed that rate of catch-up growth is inversely proportional to initial nutritional deficit, as was observed in our control children.

In our study subject, neither diarrhoeal nor respiratory morbidity was different when the groups were compared as a whole, but zinc supplementation reduced the incidence of subsequent morbidity from diarrhoea and respiratory tract infections among the underweight and shorter children who tended to be more zinc deficient. Reduced morbidity in diarrhoea and preventive effect on new episodes have been reported with zinc supplementation where zinc supplementation was continued for a long period on daily dose (Sazawal *et al*, 1995). The interesting difference with our study was that our children were in more severe diarrhoea as they were hospitalised for treatment and zinc supplementation was only given during the diarrhoeal period, but our study documented additional benefits beyond the acute period. The effect of short term zinc supplementation were evident by promoting growth and reducing diarrhoeal and respiratory morbidity in most zinc deficient children, namely who were stunted. Zinc supplementation is known to improve immunity in malnourished children, although it would have been interesting to see the correlation, but we could not study that in our clinical study. Secretory IgA, an important defence mechanism against bacterial growth and colonisation, has been shown to be significantly increased in children supplemented with zinc during nutritional rehabilitation (Lethi, 1982; Castillo-Duran *et al*, 1987). Zinc deficiency is also associated with impaired cell-mediate immunity (CMI) with thymic atrophy whereas zinc supplementation increases thymic size (Golden *et al*, 1977) and improves delayed cutaneous hypersensitivity response in malnourished children (Golden *et al*, 1978). It also improves CMI in patients with syndromic zinc deficiency of acrodermatitis enteropathica (Oleske *et al*, 1979).

Protective effect of zinc for infectious diseases were reported earlier. Subjects given zinc prophylactically experienced fewer Rhinovirus infections (Al-Nakib *et al*, 1987). In Bangladesh, anergic children with depressed cell-mediated immunity associated with malnutrition experienced higher diarrhoeal attack rates compared with non-anergic children (Baqui *et al*, 1993). In a previous study in Chile, a significantly greater proportion of malnourished children not supplemented with zinc remained anergic compared to zinc-supplemented children (Castro-Magana *et al*, 1981). Our study supported the recent reports of the effect of zinc on reduction of morbidity of diarrhoea and respiratory infection in Mexico (Rosado *et al*, 1995) and Guatemala (Ruel *et al*, 1995).

Duration of subsequent illness was reduced in the zinc supplemented children who were shorter and lighter. There are several plausible causes for this observation which include a better mucosal function and fluid absorption, reduced bacterial adhesion and faster bacterial clearance from the epithelial surface in the supplemented children. Our earlier morphological studies with zinc have shown the earlier repair of small intestinal mucosa of young children suffering from acute or persistence diarrhoea (Roy *et al*, 1992). A recent study in India showed that zinc supplementation reduced severe diarrhoeal episodes and a 30% reduction of diarrhoea incidence in children (Sazawal *et al*, 1995). It is also possible that the zinc-supplemented children who had earlier recovery from diarrhoea might have a concomittant reduction in endogenous zinc loss through stool (Castillo-Duran *et al*, 1988) and additional zinc from supplement thus ensured their better zinc status which might have reflected in their higher serum zinc level after diarrhoea.

Conclusions

The results of our study indicate that short term zinc supplementation during acute diarrhoea reduces growth-faltering following diarrhoea as well as reduces subsequent diarrhoeal and respiratory morbidity in undernourished children for at least two months. Zinc supplementation should therefore be strongly considered in the child survival strategy including the treatment of acute diarrhoea in malnourished children.

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