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ORIGINAL RESEARCH ARTICLE

Evaluation of the role of zinc supplementation in treatment of diarrhoea in paediatric patients: a randomized open-label study

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Abstract

Background Zinc deficiency has been associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function. Recently, oral zinc therapy has been added to the standard treatment of diarrhoea by the World Health Organization, as it can improve outcomes in paediatric patients with diarrhoea, especially those in developing countries.

Methodology A randomized open-label multicentre study was conducted in 100 paediatric patients with diarrhoea. Patients were randomized to the control group (received standard treatment for diarrhoea, such as oral rehydration solution [ORS], intravenous fluids, and antibiotics as required) or the zinc study group (received standard treatment plus oral zinc sulfate). Patients were followed up until recovery and collection of necessary data.

Results Of the 100 children enrolled in the study, 50 % were aged 1–5 years and 50 % were aged <1 year. In the overall population, children were treated with ORS (67 %), intravenous fluids (50 %) and antibiotics (77 %). The mean frequency of diarrhoea episodes was significantly ($p < 0.05$) lower in the zinc group than in the control group on day 4 of illness, but not on days 1, 2 and 3. All patients recovered on day 4 in the zinc group, while nine patients required treatment on day 5 in the control group ($p < 0.05$).

Conclusion In young children with diarrhoea, the addition of oral zinc supplementation to standard anti-diarrhoeal therapy may reduce the time to resolution of diarrhoea relative to standard treatment alone in developing countries.

Introduction

Diarrhoea is one of the most common illnesses responsible for morbidity and mortality in paediatric patients [1]. Worldwide, diarrhoeal diseases cause an estimated 1.5 billion episodes of morbidity and 1.5–2.5 million deaths annually among children aged <5 years [1]. In developing countries, the scenario is worse due to infections, malnutrition, poverty and illiteracy.

Acute diarrhoea remains a leading cause of childhood deaths despite the undeniable success of oral rehydration therapy [2]. Treatment of acute diarrhoea with oral rehydration solution (ORS) has become widespread, resulting in reduced mortality from dehydrating diarrhoea, but no decrease in the duration of episodes or their consequences, such as malnutrition [2]. Diarrhoeal episodes of longer duration (i.e. lasting for 2–4 weeks), commonly called persistent diarrhoea, have the greatest effect on the nutritional status of children [2, 3].

Two well documented determinants of diarrhoeal duration are low weight for age and decreased cell-mediated immunity [4]. An identified common determinant of both

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of these factors is zinc deficiency. Zinc deficiency is highly prevalent in children in developing countries. Inadequacy of dietary zinc intake is exacerbated by the net loss of zinc during diarrhoea. Provision of zinc during diarrhoea may, therefore, be a feasible strategy for both the treatment of diarrhoea and the prevention of subsequent morbidity and mortality [4, 5].

New revised recommendations formulated by the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend that acute diarrhoea is treated with zinc supplementation and low osmolarity ORS [6, 7]. Such treatment reduces the duration and severity of acute diarrhoea episodes, with zinc supplementation for 10–14 days also associated with reductions in the incidence of diarrhoea in the following 2–3 months [6–9].

The present study was undertaken to evaluate the role and effectiveness of the addition of zinc supplementation to standard therapy in the treatment of acute diarrhoea in young children.

Methodology

A randomized open-label study was conducted to evaluate the role and effectiveness of adding oral zinc supplementation to standard anti-diarrhoeal therapy in paediatric patients with acute diarrhoea. Approval for the study protocol was received from the 'Human Research Ethics Committee' before the commencement of the study. The nature and purpose of the study and risk/benefits related to the study were clearly explained to the parents/guardians of the participating children, and their written informed consent was obtained before their children were enrolled in the study.

A total of 100 paediatric patients (aged <12 years) of either gender attending the outpatient and/or inpatient departments of the three participating hospitals (a tertiary-care teaching rural hospital and two private hospitals) in Gujarat during the period from 1 January 2012 to 30 April 2012 and diagnosed as having diarrhoea by the paediatrician were eligible for inclusion in the study. Patients who were seriously ill and requiring intensive care unit admission or who were placed on ventilators or unable to communicate were excluded from the study.

As this was a multicentre study, the treatment protocol for diarrhoea was discussed among prescribers and uniformly followed throughout the study. The treatment protocol was based on WHO diarrhoea management guidelines [6, 10] and the guidelines of the Indian Academy of Pediatrics (IAP) [4].

Enrolled patients were divided randomly into two groups using a computer-generated random number table. Patients in the control group received standard treatment for diarrhoea (i.e. ORS, intravenous fluid and antibiotics) as required; patients in the study group received standard anti-diarrhoeal treatment as required plus oral zinc sulphate for 14 days (20 mg/day for patients aged >6 months and 10 mg/day for infants aged ≤6 months). All relevant background information (e.g. demographic characteristics and medical history) was collected by reviewing the case files and interviewing the parents of the patients. Patients were followed-up with regard to the frequency of episodes of diarrhoea until resolution of diarrhoea. Investigators were not part of the treating team and did not interfere with the treatment of patients at any stage of the study.

Data were presented as actual frequencies, percentages and mean standard deviation. For evaluations of the differences between the zinc and control groups Chi-square and independent *t* tests were applied. Data were analysed using SPSS version 14. *p* values of ≤0.05 were considered significant.

Results

A total of 100 young children with acute diarrhoea were enrolled (47 and 53 in the zinc and control groups, respectively). All enrolled children were aged ≤5 years. There were no significant between-group differences (BGDs) in demographic parameters (Table 1). Overall, half of the children were in the oldest age group (i.e. aged >1 to ≤5 years), most (64 %) were male, and the majority (62 %) weighed 6–12 kg (Table 1). There were also no significant BGDs in the proportion of patients using various anti-diarrhoeal treatments (i.e. ORS, intravenous fluids and antibiotics; Table 1). The number of episodes per day of diarrhoea was reported. As shown in Table 2, the mean frequency of daily diarrhoea episodes in the control and zinc treatment groups was not statistically significantly different on days 1, 2 and 3, but was significantly lower in the zinc group than in the control group on day 4 of illness (BGD 1.81 episodes; $p < 0.05$).

The number of patients with resolution of diarrhoea (defined as no episode of loose stool in a day) was recorded daily. There were no significant BGDs in this endpoint until day 3. All patients in the zinc group were recovered fully on day 4, whereas nine patients in the control group required continued treatment on day 5 (Table 2). Upon calculating time to recovery from diarrhoea/complete resolution of diarrhoea, a mean difference of 1.8 days was found between the control group and the zinc-treated group.

In subgroup analysis in the limited number of patients aged ≤6 months, no statistically significant difference was observed between the control and zinc groups with regard to the mean frequency of diarrhoea episodes on days 4 and

Table 1 Demographic parameters and use of anti-diarrhoeal therapies. Patients in the control group received standard anti-diarrhoeal treatment, and patients in the zinc group received oral zinc sulphate plus standard treatment

Parameter	Control ($n = 53$)	Zinc ($n = 47$)	Total ($n = 100$)
	No. of pts (%)	No. of pts (%)	% of pts
Age (months)			
1 to ≤6	9 (17.0)	5 (10.6)	14
>6 to ≤12	19 (36.9)	17 (36.2)	36
>12 to ≤60 (1–5 years)	25 (47.2)	25 (53.2)	50
Gender			
Male	32 (60.4)	32 (68.1)	64
Female	21 (39.6)	15 (31.9)	36
Body weight (kg)			
≤6	10 (18.9)	9 (19.2)	19
>6 to ≤12	32 (60.4)	30 (63.8)	62
>12 to ≤60	11 (20.8)	8 (17.0)	19
Use of anti-diarrhoeal therapies			
Intravenous fluids	25 (47.2)	25 (53.2)	50
Oral rehydration solution	40 (75.5)	27 (57.4)	67
Antibiotics	42 (79.2)	35 (75.5)	77

Table 2 Frequency of daily diarrhoea episodes and time to diarrhoea resolution. Patients in the control group ($n = 53$) received standard anti-diarrhoeal treatment; patients in the zinc group ($n = 43$) received oral zinc sulphate plus standard treatment

Day of illness	Mean frequency of diarrhoea episodes per day		No. (%) of pts with resolution of diarrhoea	
	Control	Zinc	Control	Zinc
Day 1	6.57	6.77	0	0
Day 2	4.70	4.21	10 (19.0)	11 (23.4)
Day 3	2.89	2.33	24 (45.3)	22 (46.8)
Day 4	3.00	1.19*	10 (18.9)	14 (29.8)
Day 5	2.18	0	9 (17.0)	0*

* $p < 0.05$ vs. control

5 (3.0 diarrhoea episodes in both groups). The mean frequency of diarrhoea in other age groups was 2.18 in the control group and 0 in the zinc group on day 5 of the treatment.

Discussion

Diarrhoeal illnesses have been identified as one of the leading causes of morbidity and mortality in paediatric patients all over the world, but especially in developing countries [1]. Poor water and sanitation supply, along with deficient nutrition, has worsened the scenario in middle- and low-income countries [4]. The utilization of appropriate guidelines on the clinical management of diarrhoea among the world's most vulnerable children, therefore, remain critical. Low-concentration ORS and zinc supplementation, at a dosage of 20 mg per day for 10–14 days in children aged >6 months, are two effective means of treating diarrhoea [6, 8, 10].

In this study, the frequency of diarrhoea episodes was significantly reduced on day 4 of illness in the zinc-treated group relative to the control group. A similar study conducted in Bangladesh by Baqui et al. [11] used a cluster randomized design to evaluate the effect on mortality and morbidity of providing daily zinc for 14 days to children with diarrhoea as part of the diarrhoea treatment programmes in the community. The intervention and the comparison clusters were both given ORS and advice on feeding during diarrhoea. The children in the zinc cluster had a shorter duration (hazard ratio 0.76; 95 % confidence interval [CI] 0.65–0.90) and lower incidence of diarrhoea (rate ratio 0.85; 95 % CI 0.76–0.96) than children in the comparison group. The children in the zinc cluster had a shorter duration and lower incidence of diarrhoea (rate ratio 0.85; 95 % CI 0.76–0.96) than children in the control group [11]. Bhatnagar et al. [12] observed that total stool output was reduced by 31 % (95 % CI 1–52) in zinc-treated children relative to the control group in their study.

In the present study, patients treated with zinc had earlier resolution of their diarrhoea than those in the control group ($p < 0.05$). Similar studies conducted in children with acute diarrhoea by Bahtnagar et al. [13] and the Zinc Investigators' Collaborative Group [9] have also shown a significant reduction in duration of diarrhoea after zinc supplementation in children. Bhan and Bhandari [14] observed that children who received elemental zinc 20 mg/day during acute diarrhoea had a 23 % reduction (95 % CI 12–23) in the risk of continued diarrhoea.

Measuring blood zinc levels could be the most absolute method of establishing the role of zinc in diarrhoea. During the study, blood zinc levels of ten patients with persistent diarrhoea (i.e. diarrhoea episodes lasting for 2–4 weeks) were measured and compared with those of ten healthy patients. Blood zinc levels in this study were significantly ($p < 0.05$) lower in patients with persistent diarrhoea than in normal healthy children (225.58 vs. 631.03 μg/dl). The sample size of ten was too small to make any conclusions, but the results suggest that zinc levels play a role in the pathogenesis of diarrhoea. Further larger studies that focus on the association between blood levels of zinc and the presence of persistent diarrhoea are required to support this result.

Zinc supplementation has been found to reduce the duration and severity of diarrhoeal episodes and likelihood of subsequent infections for 2–3 months [6, 10, 15, 16]. Zinc supplements are generally accepted by both children and caregivers and are effective regardless of the type of common zinc salt used (zinc sulfate, zinc acetate or zinc gluconate) [15, 17]. Supplementary zinc benefits children with diarrhoea because it is a vital micronutrient essential for protein synthesis, cell growth and differentiation, immune function, and intestinal transport of water and electrolytes. Zinc is also important for normal growth and development of children both with and without diarrhoea. Zinc deficiency is associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function [15]. Dietary deficiency of zinc is especially common in low-income countries because of a low dietary intake of zinc-rich foods (mainly foods of animal origin) or inadequate absorption caused by its binding to dietary fibre and phytates often found in cereals, nuts and legumes [15].

Although the benefits of zinc supplementation in the management of diarrhoea have been established, a number of barriers to the widespread implementation of this treatment strategy still remain. Currently, zinc is not used to treat most cases of diarrhoea because the known benefits of zinc supplementation are still not widely appreciated by physicians and healthcare workers in developing countries. There is a need to establish the optimal dosage and to investigate whether the same benefits of zinc supplementation are also applicable to children in middle- or high-income nations. There is also concern that high zinc intake may compete for absorption with other micronutrients, such as iron and calcium. This, in turn, can have unintended negative consequences for children's health and development. Studies are needed to help identify subpopulations that would benefit most in resource-limited settings and to ensure access to zinc supplementation, especially for those families whose children are most at risk of diarrhoea, but may not be able to afford treatments that include zinc supplements. However, zinc deficiency remains difficult to diagnose because measuring serum zinc levels is not necessarily accurate for this purpose. Currently, only a very small proportion of children in need have access to zinc supplementation.

Treatment of acute diarrhoea with zinc does not appear to reduce the duration or severity of the treated episode in children aged ≤6 months. Zinc supplementation did not show any benefit in reducing the frequency of diarrhoea episodes in children aged ≤6 months in our study, or in a systematic review by Lazzerini and Ronfani [16]. This contrasts with findings in children >6 months of age, in whom zinc given with ORS during an episode of acute diarrhoea has been shown to reduce the mean duration and severity of the treated episode [8, 17, 18].

An overview of other drugs used for the treatment of diarrhoea in our study indicated that ORS was prescribed in 75.5 % of patients in the control group and 57.4 % of patients in the zinc group. Ideally ORS should be prescribed to all patients with diarrhoea to prevent dehydration and its consequences. In a study conducted by Shimelis et al. [19], 39.3 % of patients receiving zinc received ORS, which is a lower rate than in our study. It is surprising that ORS is not widely prescribed by practitioners, despite a widespread campaign for the effectiveness of ORS in the prevention of dehydration in diarrhoeal diseases.

Intravenous fluids are required in patients who cannot take anything orally. In our study, intravenous fluids were received by 47.2 and 53.2 % of patients in the control and zinc groups, respectively, indicating that the need for parental fluid therapy to treat dehydration was quite high. Therefore, there is a need to educate patients and prescribers and encourage the use of ORS and limit the use of intravenous fluids [7, 20–22]. Most (77 %) patients in our study received antibiotics (79.2 and 74.5 % of patients in the control and zinc groups, respectively). In contrast, in the study by Shimelis et al. [19], only 16.1 % of patients received antibiotics. As it has been established that antibiotics have a very limited role in the treatment of functional diarrhoea and viral infective diarrhoea, the high rate of antibiotic prescribing observed in this study is alarming.

The limitations of the study include its small sample size and short duration. The effects of zinc supplementation on reductions in the use of antibiotics and intravenous fluids should be studied further in a larger trial.

In conclusion, in young children with diarrhoea, the addition of oral zinc supplementation to standard anti-diarrhoeal therapy may reduce the time to resolution of diarrhoea relative to standard treatment alone in developing countries. The applicability of these results to other countries is likely to depend on local zinc deficiency and population characteristics, such as the degree of malnutrition.

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