Impact of zinc supplementation in children with acute diarrhea in Turkey

Perran Boran, Gulnur Tokuc, Elif Vagas, Sedat Oktem & Mujgan K Gokduman

Dr Lutfi Kirdar Kartal Research and Training Hospital

Corresponding author:
Perran Boran
Akin sok Hatboyu Cikmazi
Ortac apt 13/12, Sasinbakkal
Istanbul 34740
Turkey
Telephone: 90 532 7127756
Fax: 90 216 4110877
Email: drperran@yahoo.com

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Abstract

Objective: Zinc deficiency is prevalent in children in developing countries. Supplemental zinc provides therapeutic benefits in diarrhea. Our aim was to evaluate the effect of daily zinc supplementation for 14 days on diarrhea duration, severity and morbidity in children.

Methods: In a randomized, open label non-placebo controlled trial; we assessed the efficacy of providing zinc sulfate to 6 to 60 months old children with acute diarrhea for 2 weeks followed by 3 months of morbidity surveillance. Children were randomly assigned to zinc (n=150) and control (n=130) groups and received daily 15mg-30 mg elemental zinc. The trial outcomes included diarrheal duration, severity, incidence and prevalence.

Results: Supplemented children had a significant improvement in plasma zinc levels by day 14 of therapy. Zinc deficiency was observed in 2.6% of the treatment and 3.3% of the control group. The mean duration of diarrhea after starting the supplement was 3.02 ± 2 days in the zinc group and 3.67 ± 3.2 days in the control group. There was no significant differences in the diarrhea duration by treatment group (p>0.05). The number of stools after starting the supplement on day 1 was 5.8 ± 3.7 and 5.1 ± 3.9, on day 2 was 2.9 ± 1.6 and 3.0 ± 2.2 and on day 3 was 1.8 ± 1.1 and 1.6 ± 0.9 in the zinc group and control group respectively. There was no significant effect was found on the incidence and prevalence of diarrhea in the zinc supplemented group as compared with the control group.

Conclusion: Our data indicate that supplementing children with acute diarrhea in Turkey with 3 RDA of elemental zinc during 14 days neither improved diarrhea duration nor severity, despite significant increments in plasma zinc.
Introduction

Worldwide, diarrheal diseases are a leading cause of pediatric morbidity and mortality, with 1.5 billion episodes and 1.5-2.5 million deaths estimated to occur annually among children aged below 5 years.[1][2] In our country, in 1986, an estimated 30 thousand deaths/year occurred, and in 1992, the estimated annual deaths declined to 10 thousand/year. [3][4][5] Although the total number of deaths has been reduced substantially, still diarrhea accounts for about 6% of all deaths in children aged below 5 years.[3][4][5]

In 1992, Center for Disease Control (CDC) prepared the first national guidelines for managing childhood diarrhea and data have emerged regarding diarrhea treatment, including importance of zinc supplementation.[6] Multiple reports, all from the developing countries, have linked diarrhea and abnormal zinc status, including increased stool zinc loss, negative zinc balance, and reduced tissue levels of zinc.[7][8] It is thought that zinc deficiency might play a role in childhood diarrhea and zinc supplementation might be of benefit either for improved outcomes or as prophylaxis against diarrhea. Possible mechanisms for the effect of zinc treatment on diarrhea include; improved absorption of water and electrolytes by the intestine, faster regeneration of gut epithelium, increased levels of enterocyte brush border enzymes, and enhanced immune response, leading to early clearance of diarrheal pathogens from the intestine.[9][10][11]

In the randomized controlled trials of zinc supplementation that evaluated prevention of diarrhea, significantly lower incidence of diarrhea occurred in the zinc group than in the controls.[12][13][14][15] A pooled analysis that includes most of these trials revealed 18% less diarrhea in the zinc supplemented children.[16] Furthermore zinc supplements given for 14 days during and after diarrhea, can reduce the incidence of diarrhea in the subsequent two to three months.[17] World Health Organization (WHO) has recommended, zinc to be used in the treatment of persistent diarrhea, which makes trials on persistent diarrhea no longer appropriate.[18]

We aimed to evaluate the impact of zinc supplementation on acute diarrhea severity, duration and assess three months of morbidity surveillance after supplementation was given.

Materials and methods

We carried out a home based, prospective randomized open label non-placebo controlled trial in 280 children aged 6-60 months, during April 2004 to January 2005.

The study protocol was approved by the respective institutional ethics committees at the Dr. Lutfi Kirdar Kartal Research and Training hospital. Eligible children were included after informed consents were taken from at least one of the parents.

Children with acute diarrhea (<14 days pre-enrollment duration) were recruited for the study from the pediatric emergency and outpatient clinic. Exclusion criteria included refusal of consent, malnutrition, medical conditions requiring hospitalization, having received anti-diarrhea medications and antibiotics.
Children were randomly assigned to one of two groups. Block randomization was done using eight numbers in each block to ensure that equal numbers of patients have entered each group after every eight patients. Diarrhea was managed according to WHO guidelines.[19] The study group received a zinc syrup in a dose of 3 Recommended Dietary Allowances (RDA) once daily (15 mg zinc to 6 to 12 months old children and 30 mg to 12 to 60 months old children) as zinc sulfate for a total of 14 days and the control group received oral rehydration salts solution (ORS) only. The RDA for infants is 5 mg elemental zinc/day, and for children 1 to 4 years old is 10 mg/day.[20] Any vomiting or nausea, other possible side effects, the amount of supplement taken was recorded by the mother. Children were examined by the physician daily at the hospital until the diarrhea episode had ceased and then followed up every 7 days by phone calls by the residents. During each hospital visit, study physician asked about the child’s health, including the number and characteristics of all stools passed and use of the supplement each day since the last visit. Children were referred to the study physician for reexamination if they had recurrent diarrhea or evidence of other infection during the study period.

Assessment of nutritional status was performed using weight for height (WFH), height for age (HFA), and weight for age (WFA) z scores. Values for each nutritional index were converted into standard deviation (z) scores according to 2000 CDC growth charts. Apparently healthy children who recovered from the diarrhea episode within 2 weeks of supplementation had effects on morbidity, assessed by surveillance for a subsequent 3 months without further supplementation.

At enrollment and on day 15, non-fasting venous blood was drawn into zinc-free heparinized tubes between 9 AM and 4 PM. Plasma were stored at -20°C until analysis. Plasma specimens were analyzed for zinc using atomic absorption spectrophotometer technique.[21]

Diarrhea was defined as 3 or more loose stools in a 24 hour period. An episode of diarrhea was defined as at least 1 day of diarrhea, with the final day of the episode being the last day meeting the diarrhea definition followed by at least 48 hours without diarrhea. Two consecutive days free from disease were regarded as resolution of previous diarrheal illness. Relapse was defined as a new episode of diarrhea during the study period. Serum zinc concentrations were considered low if they were below 60µg/dl. The trial outcomes included diarrhea duration, severity, incidence and prevalence (the number of new episodes of the illness and of days with the illness, respectively, per total days of observation).

Based on information from previous studies,[22] a sample size of 130 children per group was calculated to be adequate to detect a 35% difference in the duration of the current episode of diarrhea after starting the treatment.

Statistical analyses were completed by using SPSS 10.0 and significance was set at 5%. Analysis of variance and Chi-Square tests were used to assess differences among groups. The possible covariates included age, sex, nutritional status, initial stool frequency and initial plasma zinc concentration. We estimated the therapeutic effect of zinc on the incidence and prevalence of diarrhea episodes by calculating Odds ratio and 95% confidence intervals. The odds ratios were obtained by using logistic regression.
Results

The children in the 2 groups were comparable for a number of baseline characteristics, including age, child feeding practices, nutritional status, maternal literacy, family size and socioeconomic characteristics. Responses to the socioeconomic survey indicated that about 90% of the mothers were housekeepers, 90% of the mothers were between 18-35 years of age, family income was above the minimum wage in 60%, and family size was under five in 84%. No significant differences were noted between two groups (p>0.05). 5 patients in the zinc group and 10 patients in the control group are lost to follow up and the final analysis was performed in the remaining patients. Table 1 details the admission characteristics of the two groups.

Table 1. Baseline characteristics of children enrolled in the zinc and control groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Zinc group (n=150)</th>
<th>Control group (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)</td>
<td>69/81</td>
<td>56/74</td>
</tr>
<tr>
<td>Age (months)</td>
<td>27.7 ± 15.2</td>
<td>24.3 ± 13.1</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2500 gr</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>&gt;2500 gr</td>
<td>136</td>
<td>121</td>
</tr>
<tr>
<td>Breast feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>102</td>
<td>79</td>
</tr>
<tr>
<td>Initial weight (kg)</td>
<td>13.5 ± 3.75</td>
<td>12.06 ± 2.76</td>
</tr>
<tr>
<td>Initial length (cm)</td>
<td>89.8 ± 12.4</td>
<td>85.7 ± 10.01</td>
</tr>
<tr>
<td>Weight-for-age z score</td>
<td>1.69 ± 0.82</td>
<td>1.58 ± 0.75</td>
</tr>
<tr>
<td>Height-for-age z score</td>
<td>1.74 ± 0.75</td>
<td>1.65 ± 0.8</td>
</tr>
<tr>
<td>Weight-for-height z score</td>
<td>1.98 ± 0.1</td>
<td>1.87 ± 0.3</td>
</tr>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>87</td>
<td>64</td>
</tr>
<tr>
<td>6-9</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>&gt;10</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Preenrollment diarrhea duration (days)</td>
<td>2.2 ± 1.3</td>
<td>2.7 ± 3.3</td>
</tr>
</tbody>
</table>

The mean plasma zinc at baseline and end of study were 109.6 ± 22.6 µg/dl and 132.7 ± 35.8 µg/dl in the zinc and 102.9 ± 32.3 µg/dl and 101.8 ± 23.7 µg/dl in the control groups respectively (figure 1). 2.6% of the children had plasma zinc concentration below 60µg/dl in the zinc group, and 3.3% of the children had plasma zinc concentration below 60µg/dl in the control group. The plasma zinc concentration was significantly higher at the end of the study in the zinc supplemented group (p<0.05). The difference in plasma zinc between end of study and baseline concentrations was also substantially higher in the zinc group as compared with the control group (p<0.05).

Five children (4.3%), all in the zinc group, reported vomiting immediately after the supplement was given on each day during the first week of supplementation. If the patient
vomited in 10 minutes after the supplementation, the dose has been repeated. The reported data revealed no other side effects than vomiting.

The mean duration of diarrhea after starting the supplement was 3.02 ± 2 days in the zinc group and 3.67 ± 3.2 days in the control group. There was no significant differences in the diarrhea duration by treatment group (p>0.05). Evaluation of the outcomes for the subgroup with low admission plasma zinc levels (<60 µg/dl), and who had the greater number of stools (>10 stools per day versus 6-9, 3-5 stools per day) also did not reveal any significant differences (p>0.05).

The number of stools after starting the supplement on day 1 was 5.8 ± 3.7 and 5.1 ± 3.9, on day 2 was 2.9 ± 1.6 and 3.0 ± 2.2 and on day 3 was 1.8 ± 1.1 and 1.6 ± 0.9 in the zinc group and control group respectively (figure 2). There was no significant differences in the diarrhea severity by treatment group (p>0.05).

Approximately one fifth of the children in the zinc group (30/150) and control group (25/130) in this study no longer had diarrhea as early as the first day of illness. 14.5% of the children in the zinc, 13.5 % of the children in the control group had a relapse of diarrhea during the follow up period. No significant effects was found on the incidence (odds ratio [OR]: 1.34; 95% confidence interval (CI): 0.68-2.65) and prevalence of diarrhea (odds ratio [OR]: 1.06; 95% CI: 0.92-1.22) in the zinc supplemented group as compared with the control group.

Discussion

Zinc deficiency, a prevalent condition of children in developing countries, places children at increased risk of infectious diseases in developing countries. The major effect during supplementation trials with zinc has been shown on diarrhea related morbidity.[12][13][14][15] Although WHO has recommended zinc to be used in the treatment of persistent diarrhea, more information is needed on the use of zinc supplementation in acute diarrhea in different settings.

In addition to the preventive trials in which zinc was given on a routine, usually daily for an extended period of time, there are other trials in which zinc was provided as an adjunct to therapy for acute and persistent diarrhea. The preventive trials are consistent in showing that zinc supplemented children have lower rates of diarrhea than control children.[14] [22] [23] The trials evaluating therapeutic effects of zinc for diarrhea, demonstrate the zinc-supplemented children have shorter duration episodes, lower number of stools or stool volume and reduction in treatment failure or death.[8] [12] [24]

In this study, most children were able to adequately absorb oral zinc sulfate with an increase in plasma levels. Evidence that they were successfully absorbed is provided by the plasma concentration of zinc which rose significantly in zinc supplemented groups by day 15 of therapy. However, in contrast to previous studies, our data suggest, supplementing healthy children with acute diarrhea during 14 days, neither improved diarrhea recovery nor had an impact on morbidity surveillance for a subsequent 3 months without further supplementation. It must be recognized however, that this trial was conducted in ambulatory, apparently healthy children without malnutrition, and who have not been hospitalized. Previous trials were conducted with malnourished children having more severe diarrhea who reside in typical developing country settings where the prevalence of subclinical zinc deficiency almost
The trials also employed children that were selected with at least a moderate degree of undernutrition, who were stunted. Important factors resulting in such a controversy other than zinc and malnutrition status may be differences of therapeutic approach like supplementation of zinc for longer periods of time and supplementation of multivitamins including zinc. The beneficial effect could be the result of a synergistic effect contained in the multivitamin supplements.

In our study, only 2.6% of the children had plasma zinc concentration below 60µg/dl in the zinc group, and 3.3% of the children had plasma zinc concentration below 60µg/dl in the control group. Estimates of the prevalence of zinc deficiency in our country vary between 15.7% and 24% according to different studies.[25][26] It has been mainly searched among children with malnutrition and having chronic diarrhea. In a study by Cetin et al, zinc deficiency was seen in 64% of 42 hospitalized acute diarrhea cases but this high incidence could not be explained by the researchers themselves.[27] A recently published trial from Turkey by Polat et al, found a reduction in severity and duration of diarrhea but in a group of malnourished children who are also at risk for zinc deficiency as in developing countries.[28]

The previous analysis shows trends that children with lower plasma zinc concentrations have greater effects of zinc supplementation.[14][16][17] The low prevalence of zinc deficiency in our study could be a reasonable explanation for the failure of zinc therapy. It is likely that initial zinc status influences the response to therapy and benefits of zinc supplementation may be limited to individuals or populations in which preexisting zinc deficiency is likely. In the present study, data analysis was done between low plasma zinc group and normal zinc group, and analysis did not reveal any significant differences (p>0.05). The differences in diarrheal duration and severity were not statistically significant, possibly because the small sample size of the subgroup with low zinc levels was so small to detect a statistically significant difference.

Furthermore, this low percentage of zinc deficiency found in the present study can be explained by the hypothesis that 3.02 ± 2 days as the mean duration of diarrhea after starting the supplement, is such a short time for increased intestinal losses of zinc and appearance of zinc deficiency in a healthy child.

Approximately one fifth of the children in the zinc group (30/150) in our study no longer had diarrhea as early as the first day of treatment. This rapid recovery from diarrhea on the first day of intervention complicates the interpretation of the study because it seems unlikely that zinc could have influenced the clinical outcomes in such a short period of time. Indeed, a previous supplementation trial among children with acute diarrhea showed that there was only a small, non-significant reduction in the risk of continuing diarrhea during days 1 to 3 of zinc treatment, whereas there was a statistically significant 38% reduction in the risk of ongoing illness in zinc treated children after the third day of therapy.[12]

According to the recommendations made by the pharmaceutical industry, zinc supplements already have widespread use in outpatient diarrhea cases. Zinc supplementation is carried out as an adjunct therapy in acute diarrhea in many units. There may be some adverse effects of zinc supplements given to the well-nourished children with normal serum level of zinc, and the consequences may not be immediate rather delayed. Iron deficiency anemia is the most common nutritional deficiency in the developing world and is a particular problem in preschool children. Significant interaction of zinc absorption with copper and iron has been described and zinc supplementation alone may aggravate deficiencies of other minerals.[29]
Measures of iron and copper status would have been helpful in this study; but we had none. Furthermore Ruel et al, found that both the incidence and prevalence of respiratory infection were higher in children who received zinc supplementation.[23] Schlesinger et al, have shown that zinc supplementation inhibits phagocytic and fungicidal activity in malnourished infants.[30] In studies of assessing the effect of zinc supplementation on the developmental levels of infants, Hamadani et al, found that the mental development index scores of the zinc-treated group were slightly but significantly lower than those of the placebo group[31] and suggested zinc supplementation during pregnancy in mother’s diets had a negative effect on mental development in their children at 13 months of age.[32]

In conclusion, our data indicate that supplementing children with acute diarrhea in Turkey with 3 RDA /day of elemental zinc during 14 days neither improved diarrhea recovery nor morbidity, despite significant increments in plasma zinc concentrations. We believe that the adverse effects of zinc supplementation should be weighed against the beneficial effect of zinc in reducing diarrhea. Specific recommendations regarding the use of zinc supplementation in acute diarrhea should await additional population based studies assessing the role of zinc supplementation in the treatment of children with acute diarrhea.
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What is already known on this topic

Zinc deficiency, a prevalent condition of children in developing countries, places children at increased risk of infectious diseases in developing countries.

The major effect during supplementation trials with zinc has been shown on diarrhea related morbidity.

Zinc supplements given for 14 days during and after diarrhea reduce the duration and severity of treated diarrhea episodes and can reduce the incidence of diarrhea in the subsequent two to three months.

What this study adds

Supplementing healthy children with acute diarrhea in Turkey with 3 RDA /day of elemental zinc during 14 days neither improved diarrhea recovery nor morbidity, despite significant increments in plasma zinc concentrations.

Specific recommendations regarding the use of zinc supplementation in acute diarrhea should await additional population based studies assessing the role of zinc supplementation in the treatment of children with acute diarrhea.
References