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Original Article

Therapeutic Effects of Oral Zinc Supplementation on Acute Watery Diarrhea with Moderate Dehydration: A Double-Blind Randomized Clinical Trial

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This article has Continuous Medical Education (CME) credit for Iranian physicians and paramedics. They may earn CME credit by reading this article and answering the questions on page 137.

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Abstract

Background: To assess the therapeutic effects of oral zinc supplementation on acute watery diarrhea of children with moderate dehydration.

Methods: All 9-month to 5-year-old children who were admitted with acute watery diarrhea and moderate dehydration to the Children Ward of Motahari Hospital, Urmia, Iran in 2008 were recruited. After the application of the inclusion and exclusion criteria, the patients were randomly allocated to two groups: one group to receive zinc plus oral rehydration solution (ORS) and the other one to receive ORS plus placebo. All the patients were rehydrated using ORS and then receiving ORS for ongoing loss (10 ml/kg after every defecation). Additionally, the patients in the intervention group received zinc syrup (1 mg/kg/day) divided into two doses. A detailed questionnaire was filled daily for each patient by trained pediatrics residents; it contained required demographic characteristics, nutrition and hydration status, and disease progression. The primary outcome (frequency and consistency of diarrhea) and the secondary outcomes (duration of hospitalization and change in patients' weight) were compared between the two groups.

Results: The mean diarrhea frequency (4.5±2.3 vs. 5.3±2.1; P=0.004) was lower in the group receiving zinc +ORS; however, the average weight was relatively similar between the two groups (10.5±3.1 vs. 10.1±2.3; P=0.14). The qualitative assessment of stool consistency also confirmed earlier improvement in the treatment group in the first three days of hospitalization (P <0.05). The mean duration of hospitalization was significantly lower in the patients receiving zinc supplements (2.5±0.7 vs. 3.3±0.8 days; P=0.001).

Conclusion: Our results imply the beneficial effects of therapeutic zinc supplementation on disease duration and severity in patients with acute diarrhea and moderate dehydration in Iran.

Trial Registration Number: IRCT201201241580N2

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Keywords ● Zinc ● Diarrhea ● Dehydration ● Children ● Acute gastroenteritis

Introduction

Diarrhea is still deemed a leading cause of pediatric mortality and morbidity, especially in children below 5 years of age in developing countries. Although its mortality rate has been substantially reduced, diarrhea still accounts for a considerable proportion of deaths in this age group.[1,2] Oral or intravenous rehydration is considered as the first-line therapy. However, as much as this basic approach is substantially effective in most of mild to moderate cases, it is unable to reduce frequency, volume, and duration of diarrhea, hence the need to develop new modalities to sufficiently address this issue.

In 1992, the Center for Disease Control (CDC) reported the first national guideline, emphasizing the emergency of the treatment of childhood diarrhea and the importance of zinc supplementation.[3] Since then, a variety of trials have been established, especially in developing countries, to assess the effect of zinc supplementation on the duration and severity of diarrhea.[4-13] The beneficial effects of zinc supplementation on childhood diarrhea have been discussed in several studies,[8,9,14,15] yet the exact underlying mechanisms leading to these favorable effects are still unclear. Zinc is an essential trace element for humans.[16,17] Some plausible mechanisms might be 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, conferring early clearance of diarrheal pathogens from the intestine.[18,19]

Given these findings, zinc supplementation is currently recommended as a universal treatment for all children with acute gastroenteritis.[13,15] Be that as it may, some other scientists, particularly in developed countries, believe that there is not enough evidence to support its routine use.[20] Despite the reported encouraging benefits of zinc supplementation in childhood (up to 18% decline in children with acute diarrhea frequency),[12] the cost effectiveness of such treatment is still arguable.[21-23]

Although there are numerous studies evaluating the safety and efficacy of zinc supplementations in the treatment of acute gastroenteritis [7-11,14,24] and its proven effects on persistent diarrhea,[25] there have been only a few studies about the potential beneficial effects of zinc supplementation on selected categories of acute diarrhea. The lack of a well-designed randomized trial assessing the effects of zinc supplements on the severity and duration of diarrhea in Iran, as a developing country, renders new research necessary. This study was, therefore, designed to compare the severity and duration of diarrhea between patients with acute diarrhea who received zinc plus oral rehydration solution (ORS) and those who received only routine ORS.

Materials and Methods

Study Design, Inclusion and Exclusion Criteria

This double-blind randomized clinical trial (RCT) recruited all 9-month to 5-year-old children who were admitted with acute watery diarrhea and moderate dehydration to the Children Ward of Motahari Hospital, Urmia, Iran in 2008. The exclusion criteria were comprised of diagnosed chronic diseases (cystic fibrosis, inflammatory bowel diseases, and malabsorption), severe malnutrition (weight curve was under 3% for age), dysentery and bloody diarrhea confirmed with the existence of red blood cells (RBC) or white blood cells (WBC) in stool examination (S/E), recent consumption of antibiotics, severe dehydration or persistent vomiting, recent consumption of zinc supplements (last month), and drug intolerance. An informed consent was obtained from the patients' parents prior to their participation. Those without informed consent were excluded. Sample size using Web-based sample size calculation software, with power of 90%, significance level of 0.05, and ability to detect differences 10% or more was determined at 132 people. Nevertheless, sampling reduction due to attrition was prevented by recruitment of 200 patients.

Randomization and Study Protocol

Each patient was given a specific code prior to enrollment. After the application of the inclusion and exclusion criteria, the patients were simple randomly allocated to two groups: one group to receive zinc plus ORS and the other one to receive ORS alone, using computerized software. Paraclinic evaluations, including complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), blood culture, S/E, stool culture (S/C), urine analysis and culture, sodium, potassium, blood urea nitrogen (BUN), and creatinine, were initially performed for all the participants. In cases of infectious diarrhea in S/E, positive blood culture, leukocytosis, or positive CRP or ESR (without other reasons), intravenous antibiotic (Ceftriaxone) was commenced and the patient was excluded. After initial rehydration with ORS solution (50-100 ml/kg over 4-6 hr until presenting dehydration symptoms disappeared), all the patients were given ORS for ongoing loss (10 ml/kg after every defecation). Additionally,

the patients in the intervention group received zinc syrup (1 ml/kg/day), which contained 1 mg zinc sulfate/1ml divided into two doses. A placebo with similar taste, color, and smell and with a similar option (1 ml/kg/day) was given to the control group. The drug and placebo were coded by a trained nurse before the study began, and neither the patients nor physicians were aware of the used material and the patients' groups. A detailed questionnaire, containing required demographic characteristics, growth criteria, nutrition and hydration status, paraclinic data, stool consistency, frequency of diarrhea, patient's weight, and disease progression, was filled daily for each patient by trained pediatrics residents. Figure 1 summarizes the study flow diagram.

Primary and Secondary Outcomes

The primary outcome was frequency and consistency of diarrhea, and the secondary outcomes were duration of hospitalization and change in the patients' weight. Acute diarrhea was defined as acute onset of change in stool frequency and consistency lasting for fewer than 14 days and without blood in stool examination. Complete recovery was defined as diarrhea discontinuation and return to the past defecation status. Relative recovery was defined as decreased frequency to 1-2 times per day and change stool consistency from watery to soft or firm. Non-recovery was considered when no improvement in stool frequency or consistency was found over a 5-day period, requiring further treatment intervention. The patient's weight was checked and recorded by the same person using the same scales each day. Stool consistency (watery, soft, or firm) and its frequency (in 24 h) were checked by the patients' mothers and reevaluated and recorded by trained pediatrics residents. The study protocol was approved by the Ethics Committee of Urmia University of Medical Sciences.

Statistical Analysis

The results are reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Student *t* test for the continuous variables and the chi-square test (or the Fisher exact test, if required) for the

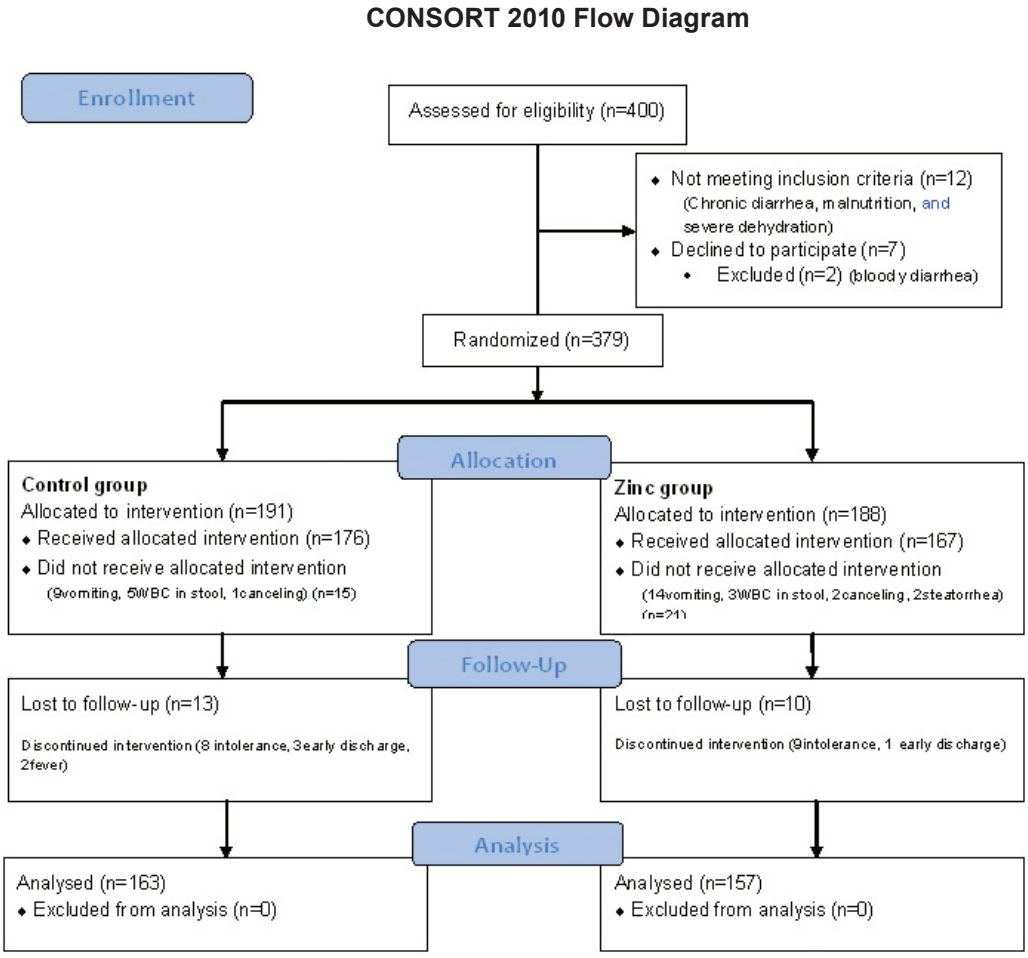

Figure 1: Study flow diagram.

categorical variables. Statistical significance was based on two-sided design-based tests, evaluated at 0.05 level of significance. All the statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

A total number of 379 patients (188 in the intervention group and 191 in the control group) were assessed after the application of the inclusion and exclusion criteria. Twenty-one persons in the treatment group (14 due to vomiting, 3 due to report of WBC/RBC in stool, 2 due to later cancellation of participation, and 2 due to report of significant steatorrhea in stool examination) and 15 in the control group (9 due to vomiting, 5 due to report of WBC/RBC in stool, and 1 due to later cancellation of participation) were excluded after the random allocation of the study population to the two groups. Ten patients in the intervention group (9 due to intolerance and 1 due to early discharge because of personal consent) and 13 in the control group (8 due to intolerance, 3 due to early discharge [personal consent], and 2 due to late onset fever) were lost to follow-up. Finally, 157 patients (59.2% boys, mean age=18.7±9.7 months) were classified in the treatment group; in addition, a control group of 163 patients (52.1% boys, mean age=17.0±8.0 months) was recruited. Table 1 summarizes the patients' baseline and demographic characteristics in each group. There were no significant differences in terms of the initial profiles between the two groups.

As is shown in table 2, the patients treated with zinc supplements had shorter hospital stays (2.5±0.7 days) than those receiving routine care in the placebo group (3.3±0.8 days) (P=0.001). In the intervention group, the mean diarrhea frequency was lower than that of the control group (4.5±2.3 vs. 5.2±2.1; P=0.004). Stool consistency exhibited better improvement in the intervention group than in the placebo group (P=0.017, P=0.001, and P=0.06 for post-treatment days one, two, and three, respectively), and the mean patients' weight at discharge time was non-significantly greater in the intervention group than in the placebo group (10.5±3.1 vs. 10.1±2.3 kg; P=0.135).

Discussion

The considerable prevalence of diarrhea in children under 5 years of age, its mortality and morbidity

Table 1: Patients' demographic characteristics at enrollment

Variables	Intervention (n=150)	Placebo (n=156)	P value
Mean age (months)	18.7±9.7	17.0±8.0	0.087
Boys (%)	59.2	52.1	0.201
Breastfeeding (%)	33.1	41.1	0.139
Mean diarrhea frequency	8.4±1.84	7.94±2.04	0.26
Mean diarrhea period	2.7±1.69	3.03±0.23	0.16

Table 2: Primary and secondary outcomes

Groups Variables	Intervention	Placebo	P value
Mean weight (Kg)	10.5±3.1	10.1±2.3	0.135
Mean diarrhea frequency	4.5±2.3	5.2±2.1	0.004
Stool consistency			
Day 1	N=157	N=163	
Watery	126 (80.3)	147 (90.2)	
Soft	31 (19.7)	16 (9.8)	0.017
Firm	0 (0.0)	0	
Day 2	N=152	N=163	
Watery	59 (38.8)	111 (68.1)	
Soft	92 (60.5)	52 (31.9)	<0.001
Firm	1 (0.7)	0	
Day 3	N=115	N=152	
Watery	19 (16.5)	44 (28.9)	
Soft	95 (82.6)	107 (70.4)	0.06
Firm	1 (0.9)	1 (0.7)	
Hospitalization duration	2.5±0.7	3.3±0.8	<0.001

rates, and its heavy direct and indirect burden on society and family have created a serious challenge to public health policy-makers in developing countries. The addition of micronutrient supplements to the routine rehydration therapy is a new treatment modality, which has been proven to be effective in various assessments.[7-9,15]

We assessed the therapeutic effects of zinc supplements as an adjuvant therapy to the routine oral rehydration. Our results confirmed that the addition of zinc supplements to routine ORS is associated with more favorable clinical and economic outcomes. The mean diarrhea frequency (4.5±2.3 vs. 5.3±2.1; P=0.004) was lower in those receiving zinc besides ORS; however, the average weight was relatively similar between the two groups (10.5±3.1 vs. 10.1±2.3 kg; P=0.135). The qualitative assessment of stool consistency also confirmed earlier improvement in the treatment group in the first three days of hospitalization. One of the superiority of our assessment compared to previous works was that all probable infectious diarrhea cases were excluded and only those with watery diarrhea and moderate dehydration underwent evaluation.

Zinc supplements have been used for both preventive and therapeutic goals in patients with various disease severity and countries with different prevalence of zinc deficiency. Despite the fact that the preventive benefits of zinc supplements in diarrhea incidence rate have been previously proven,[4,26] zinc supplements may be associated with some transient side effects.[27,28] Regarding the therapeutic effects of zinc, the WHO and UNESCO have recommended that zinc be used for children with acute and persistent diarrhea all over the world. Not all scientists, however, subscribe to this view.[11,29] A considerable number of randomized clinical trials and meta-analyses have already confirmed the beneficial effects of zinc supplements not only in terms of shortening the duration and frequency of diarrhea but also with respect to reducing treatment failure and mortality rates.[7,15] Most of these studies were conducted in developing countries, where zinc deficiency is rife. Recent studies in regions with well-nourished children and low prevalence of zinc deficiency were not able to detect considerable clinical differences between those treated with and without zinc supplements.[11,29,30] In our study, the serum levels of zinc were not measured at baseline, but our country being high risk for zinc deficiency, it could be presumed that our patients might have had zinc deficiency: this might explain the considerable response to zinc supplements among our patients.

Another significant aspect to consider is whether or not the effectiveness of zinc supplements is pathogen-specific. We excluded patients with probable infectious etiologies, and more likely the majority of our study population had viral infections. Diagnostic microbiology study has been performed in only a few randomized clinical trials so far,[31-34] and various reported responses to zinc might be due to the difference response rates of various pathogens. Patient populations, disease severity (mild, moderate, or severe), therapeutic approaches, and treatment options (syrup, tablets, and dosage) differ between various studies, which might affect the observed outcomes of zinc supplements.

The economic implication is another important factor that should be simultaneously weighted toward the clinical outcome. In the present study, the mean duration of hospitalization was significantly lower in the patients who received zinc supplements (2.5±0.7 vs. 3.3±0.8 days; P=0.001). The cost-effectiveness of zinc supplements in patients with acute diarrhea has been widely discussed. Gregario GV et al.[23] in a trial on subjects between 2 and 59 months old with acute diarrhea of durations shorter than 7 days receiving zinc plus ORS (60 patients) or ORS alone (57 patients) confirmed that disease duration was lower in the group receiving zinc plus ORS. Our findings showed the clinical (quantitative and qualitative) benefits of therapeutic zinc supplements in patients with moderate noninfectious diarrhea in terms of shorter hospital stays; these findings, however, cannot be generalized to other countries.

The severity of disease at enrollment seems to be an important predictive factor for diarrhea duration.[7,35] It is wiser to classify patients with similar severity in order to diminish probable bias. All of our participants had moderate dehydration; however, we did not consider diarrhea frequency for the initial classification. And nor did we measure the serum zinc levels in our subjects at baseline, which is the salient limitation of the current study. Indeed, Iran is high-risk for zinc deficiency,[36] and our patients were all hospitalized; consequently, our patients might have suffered from zinc deficiency and this might give reasons for the study population's considerable response to zinc supplements.

Conclusion

Our study results imply the beneficial effects of therapeutic zinc supplementation in patients with acute diarrhea and moderate dehydration in Iran. Further studies balancing the clinical significance of zinc supplements against economic implications in acute diarrhea are required.

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Conflict of Interest: None declared.

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