Oral Zinc for the Treatment of Acute Gastroenteritis in Polish Children: A Randomized, Double-Blind, Placebo-Controlled Trial

Bernadeta Patro, MD, Henryk Szymański, MD, and Hania Szajewska, MD

Objective To evaluate the efficacy and safety of zinc in the treatment of acute gastroenteritis (AGE) in children in Poland.

Study design Children aged 3 to 48 months with AGE were enrolled in a randomized, double-blind, placebo-controlled trial in which they received zinc sulfate (10 or 20 mg/day depending on age) or placebo for 10 days. A total of 141 of 160 children recruited were available for intention-to-treat analysis. The primary outcome was the duration of diarrhea.

Results In the experimental group (n = 69) compared with the control group (n = 72), there was no significant difference in the duration of diarrhea ($P > .05$). Similarly, there was no significant difference in the groups in secondary outcome measures such as stool frequency on days 1, 2, and 3, vomiting frequency, intravenous fluid intake, and the number of children with diarrhea lasting >7 days.

Conclusion Children living in a country where zinc deficiency is rare do not appear to benefit from the use of zinc in the treatment of AGE. *(J Pediatr 2010;157:984-8)*.

The morbidity and mortality rates from acute diarrhea remain significant in children <5 years of age, especially those in developing countries.[1] In the developed world, although the mortality rate is low, gastroenteritis leads to a high number of physician visits, hospital admissions, and consequently, a significant economic burden. It is estimated that the incidence of diarrhea in European children up to 3 years of age ranges from 0.5 to 1.9 episodes per child per year.[2] Most cases of acute gastroenteritis (AGE) are usually mild and self-limited. Oral or intravenous re-hydration is used as the first-line therapy. Although this elementary approach is effective in substantially reducing morbidity and mortality rates, new treatment options are required to address the severity and duration of the symptoms. The administration of zinc appears to be such an option. The mechanisms underlying the beneficial anti-diarrheal effect of zinc are unclear. In brief, plausible mechanisms include improved absorption of water and electrolytes by the intestine, faster regeneration of gut epithelium, increased levels of enterocyte brush-border enzymes, and an enhanced immune response.[3] However, it is questionable whether administered zinc can exert its actions independent of zinc deficiency in the host.

A number of randomized controlled trials performed in developing countries have shown that zinc supplementation is effective in reducing the duration and severity of diarrhea. On the basis of these findings, the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) currently recommend zinc supplementation as a universal treatment for all children with AGE.[4] However, according to the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases (ESPGHAN/ESPID) recommendations, there is not enough evidence to support its routine use in children with AGE living in Europe, where zinc deficiency is rare.[2] Therefore, the aim of this study was to evaluate the efficacy and safety of zinc supplementation in the treatment of AGE in a different clinical population and setting (ie, in well-nourished, otherwise healthy children living in Poland).

Methods

This was a randomized, double-blind, placebo-controlled trial conducted at 2 pediatric hospitals in Poland. Candidates for inclusion in the study were children 3 to 48 months of age who were diagnosed with AGE lasting less than 5 days but with at least some degree of dehydration; they had either been admitted to the hospital or visited the hospital emergency ward as an outpatient. Children were excluded from the study when any of these criteria were present: diarrhea lasting <1 day or >5 days, recent history of diarrhea (last 2 weeks before enrollment day), chronic gastrointestinal disease with diarrheal manifestation

AGE	Acute gastroenteritis
ESPGHAN/ESPID	European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases
HDI	Human Development Index
RCT	Randomized controlled trial
UNICEF	United Nations Children's Fund
WHO	World Health Organization

From the Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland (B.P., H. Szajewska); and Department of Paediatrics, St Hedwig of Silesia Hospital, Trzebnica, Poland (H. Szymański)

Supported in part by the Nutricia Research Foundation. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2010.05.049

(eg, food allergy, celiac disease), weight-to-height ratio <5th percentile, severe dehydration, coexistence of serious systemic disease(s), administration of antibiotics (during current infection), exclusive or >50% breastfeeding, history of immunodeficiency, and administration of immunosuppressive therapy.

Parents provided informed consent for all study participants. The Ethical Committee at the Medical University of Warsaw approved the study. All children eligible for recruitment were assessed for the inclusion and exclusion criteria. The physician examined each child, and the hydration status was evaluated (as defined by the method of WHO).[5] Nude body weight and height were recorded, and the nutritional status was assessed with weight-for-age, height-for-age, and weight-height ratio percentiles. Stool samples were collected to investigate the etiology of the diarrhea. Tests performed included bacteriological culture to detect bacterial pathogens (*Salmonella spp*, *Shigella spp*, *Escherichia coli*) and chromatographic immunoassay (VIKIA Rota-Adeno; BioMerieux, Lyon, France) to detect rotaviruses and adenoviruses.

Dehydration was managed according to ESPGHAN/ESPID[2] and WHO guidelines.[5] After re-hydration, early re-feeding with the patient's usual diet was practiced. Patients were assigned randomly to receive either placebo or zinc sulfate at a dose of 10 mg (for patients <6 months of age) or 20 mg (for children >6 months) daily, in 2 doses, for 10 days. Zinc was supplied as a syrup containing 2 mg of zinc in 1 mL of sirupus simplex; sirupus simplex is a solution of 64 parts of saccharose in 36 parts of purified water. The placebo was identically supplied and formulated. There was no difference between zinc and the placebo in appearance; a minor metallic aftertaste of zinc was hardly detectable. The study products were provided by the pharmacy department in the hospital in Warsaw for both centers. The syrup was offered between meals to prevent the negative influence of some dietary factors on absorption.[6] Each parent of an included child received a diary to record the number and consistency of stools and to specify the time of the day (1-hour period) when the stool was passed. They were also asked to record any vomiting episodes and any other symptoms that they considered to be important or to represent an adverse event. Children were examined by the physician every day until they were discharged from the hospital. Discharged children and outpatients were followed up with hospital visits or with daily telephone calls, depending on the patient's condition and the parents' decision. Treatment compliance was assessed with direct interview of the parents and review of the diary cards.

Randomization

Two different randomization lists for each center were computer-generated by an investigator at the Medical University of Warsaw. Block randomization of block size 6 was done. The glass bottles containing the products were labeled with the patient's number corresponding to the randomization list by an independent individual who was not involved in patient enrollment. Randomization codes were secured until the completion of data collection and initial analysis. All investigators, participants, outcome assessors, and data analysts were blinded to the assigned treatment for the duration of the study.

Primary and Secondary Outcome Measures

The primary outcome measure was the duration of diarrhea. Diarrhea was defined as the passage of ≥3 loose stools in a 24-hour period. The duration of diarrhea was defined as the time from administration of zinc/placebo to the cessation of diarrhea (the passage of 2 formed stools or no stool for 12 hours on the last day meeting the criteria for diarrhea). Secondary outcome measures were stool frequency on days 1, 2, and 3, vomiting frequency on days 1, 2, and 3, total intravenous fluid intake, the number of children with diarrhea lasting >7 days, and adverse events.

Sample Size

The sample size was calculated on the basis of the assumption that a 1-day reduction in the primary outcome measure (diarrhea duration) would be a clinically important difference in the study groups. We estimated that with a power of 80%, an α level of 0.05, and a 20% dropout rate, 160 children would be required.

Statistical Methods

The statistical analyses were conducted with StatsDirect software version 2.7.7 (StatsDirect Ltd., Altrincham, United Kingdom). The Mann-Whitney *U* test was used to compare the means of continuous variables because of their non-normal distribution. The Shapiro-Wilk *W* test was used to investigate a sample for evidence of "non-normality." Proportions were compared with the Fisher exact test. The difference in study groups was considered significant when the *P* value was <.05. All statistical tests were 2-tailed and performed at the 5% level of significance. We analyzed the results of this study on the basis of intention to treat.

Results

We enrolled 160 children from a group of 249 eligible patients between February 2008 and December 2009. The main reason for exclusion at this stage of the study was lack of parental consent. The **Figure** (available at www.jpeds.com) shows the flow of participants through each stage of the study. Eighty-one children were assigned to the zinc group, and 79 children were assigned to the placebo group. Four patients in the experimental group and 3 patients in the control group did not receive the allocated intervention because of their parents' decision and refusal to drink, respectively. Nine patients in the zinc group and 8 patients in the placebo group discontinued the intervention because of refusal to drink and parents' decision. Most of these parents decided not to continue administration of the syrup because the symptoms of diarrhea had ceased. Nineteen patients