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Indian J Pharmacol. 2011 May-Jun; 43(3): 232–235. PMCID: PMC3113371
doi: 10.4103/0253-7613.81495

Role of zinc in pediatric diarrhea

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Received 2010 Mar 3; Revised 2010 Oct 2; Accepted 2011 Feb 23.

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Abstract

Zinc supplementation is a critical new intervention for treating diarrheal episodes in children. Recent studies suggest that administration of zinc along with new low osmolarity oral rehydration solutions / salts (ORS), can reduce the duration and severity of diarrheal episodes for up to three months. The World Health Organization (WHO) and UNICEF recommend daily 20 mg zinc supplements for 10 – 14 days for children with acute diarrhea, and 10 mg per day for infants under six months old, to curtail the severity of the episode and prevent further occurrences in the ensuing -two to three months, thereby decreasing the morbidity considerably. This article reviews the available evidence on the efficacy and safety of zinc supplementation in pediatric diarrhea and convincingly concludes that zinc supplementation has a beneficial impact on the disease outcome.

Keywords: Acute diarrhea, oral rehydration solutions/salts, zinc salts

Introduction

Acute diarrhea remains a leading cause of childhood deaths despite the undeniable success of oral rehydration therapy (ORT). Worldwide, diarrheal diseases are the leading cause of pediatric morbidity and mortality, with 1.5 billion episodes and 1.5 - 2.5 million deaths estimated annually among children below five years of age.[1,2] In developing countries, the scenario is worse due to infection, malnutrition, and illiteracy. One out of every five children who die of diarrhea worldwide is an Indian. Daily around 1,000 children die of diarrhea in India, which means 41 children lose their lives every hour.[3] Giving oral fluids using an oral rehydration solution (ORS) saves children's lives, but does not seem to have any effect on the length of time the children suffer with diarrhea.

Hence, new revised recommendations have been formulated by the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF), in collaboration with the United States Agency for International Development (USAID) and other experts. It recommends zinc salt along with low osmolarity ORS, with reduced levels of glucose and salt, during acute diarrhea, which reduces the duration and severity of the episode; and zinc supplementation given for 10-14 days lowers the incidence of diarrhea in the following two to three months.[4]

Despite the evidence of benefit, there has been little progress on the widespread introduction of low osmolarity ORS and zinc for the treatment of diarrhea. Many countries have changed diarrhea management policies to include low osmolarity ORS and zinc, but there is a gap between policy change and effective program implementation, with very few children currently being appropriately treated.[5] Although the Government of India has initiated the provision of zinc in addition to low osmolarity ORS through the public health system, under the National Rural Health Mission, a survey conducted by UNICEF in India documented less than 1% prescriptions for zinc. One of the main reasons for this is the lack of knowledge

and awareness among the care providers on how to implement the existing cost-effective interventions. The challenge is to achieve a greater coverage of these interventions in resource poor settings.[6]

Mechanism of Action of Zinc in Diarrhea

The physiological effect of zinc on intestinal ion transport has not yet been established thoroughly. Therefore, the fundamental information of the mechanism by which zinc may be effective in improving diarrhea is needed. A very recent publication has established that zinc inhibits cAMP-induced, chloride-dependent fluid secretion by inhibiting basolateral potassium (K) channels, in *in-vitro* studies with rat ileum. This study has also shown the specificity of Zn to cAMP-activated K channels, because zinc did not block the calcium (Ca)-mediated K channels. As this study was not performed in Zn-deficient animals, it provides evidence that Zn is probably effective in the absence of Zn deficiency.[7,8] Zinc also improves the absorption of water and electrolytes, improves regeneration of the intestinal epithelium, increases the levels of brush border enzymes, and enhances the immune response, allowing for a better clearance of the pathogens.[9] Another report has recently provided evidence that zinc inhibits toxin-induced cholera, but not Escherichia coli heat-stable, enterotoxin-induced, ion secretion in cultured Caco-2 cells.[10] Thus, Zinc plays an important role in modulating the host resistance to infectious agents and reduces the risk, severity, and duration of diarrheal diseases. It also plays a critical role in metallo-enzymes, polyribosomes, and the cell membrane and cellular function, giving credence to the belief that it plays a central role in cellular growth and in the function of the immune system.[11]

Pharmacokinetics of Zinc in Diarrhea[12]

Absorption

The molecular weight of elemental zinc is 65.37 and zinc sulfate is 287.5. Crude zinc sulfate is also known as white Vitriol. Each gram of zinc sulfate represents 3.5 millimoles of Zn. Its solubility is 1 in 0.6 ml of water and it is insoluble in alcohol. Zinc and its salts are poorly absorbed from the gastrointestinal tract (GIT) (only 20 to 30%), duodenum, and ileum. Endogenous zinc is reabsorbed in the ileum and colon, creating enterohepatic circulation.

Distribution

After absorption zinc is bound to protein metallothionein in the intestines. Zinc is widely distributed throughout the body. It is primarily stored in RBCs, WBCs, muscles, bones, Skin, Kidneys, Liver, Pancreas, retina, and prostate. The extent of binding is 60 - 70% to plasma albumin, 30 - 40% to alpha 2 macroglobulins or transferring, and 1% to amino acids like histidine and cysteine. Peak plasma concentration occurs in approximately two hours.

Elimination

Zinc is excreted mainly in the feces (90%) and only traces are found in the urine, as the kidney plays a small role in regulating the body Zn content.

Convincing evidence for the clinical importance of zinc has come from the randomized controlled trials (RCTs) evaluating the impact of zinc supplementation during acute and persistent diarrhea.

Zinc supplements reduce the severity and duration of diarrhea

A study tested the hypothesis that daily supplementation of zinc had an effect on the clinical course of acute diarrhea, that is, frequency of stool, stool amount, and duration of acute diarrhea, in 117 children, of age six to fifty-nine months. Reduction in stool frequency per day was found to be 62% in the zinc-supplemented group and 26% reduction was found in the placebo-supplemented group, with an obvious difference of 36% between the two groups from day 1 to day 3 and day 5, which was found to be statistically significant. Similarly, a significant difference was observed for reduction in amount of stool per day from day 1 to day 3 and day 5, with an obvious difference of 45% between the study groups.[13] A meta-analysis of 12 studies examined the impact of zinc supplements on the management of acute diarrhea, 11 of which showed a reduction in the duration of the diarrheal episode. In eight of these, the reduction was statistically significant. Five of these studies also collected data on stool volume and frequency, and found that zinc supplements reduced stool output and frequency. The data showed that zinc supplementation had

a significant and beneficial impact on the clinical course of acute diarrhea, reducing both its duration and severity.[4] Another meta-analysis of 18 trials with 6165 enrolled participants showed that in acute diarrhea, zinc resulted in a shorter diarrhea duration (MD -- 12.27 hours, 95% CI -23.02 to -1.52 hours; 2741 children, nine trials), and less diarrhea by day three (RR 0.69, 95% CI 0.59 to 0.81; 1073 children, two trials), day five (RR 0.55, 95% CI 0.32 to 0.95; 346 children, two trials), and day seven (RR 0.71, 95% CI 0.52 to 0.98; 4087 children, seven trials). Zinc also reduced the duration of persistent diarrhea (MD -15.84 hours, 95% CI -25.43 to - 6.24 hours; 529 children, five trials). Few trials reported the severity, but the results were inconsistent.[14]

The results of a recent systematic review suggest that zinc supplementation reduced the mean duration of acute diarrhea by approximately 20%, and persistent diarrhea by 15 – 30%, but had no significant effect on stool frequency or stool output. There was a high degree of statistically significant heterogeneity across the published studies for the effects of zinc supplementation on mean diarrheal duration and risk of vomiting following the administration of zinc.[15]

Zinc supplementation in prevention of acute and persistent diarrhea

Studies evaluating the effect of zinc supplementation on diarrheal diseases found a preventive and long-lasting impact. These showed that 10 mg to 20 mg of zinc per day, for 10 – 14 days, reduced the number of episodes of diarrhea in 2 – 3 months after the supplementation.[4,16] The WHO and UNICEF, therefore, recommend 20 mg zinc supplements daily, for 10 – 14 days, for children with acute diarrhea, and 10 mg per day for infants under six months of age, to curtail the severity of the episode and prevent further occurrences in the ensuing 2 -3 months.

Zinc supplementation in the treatment of persistent diarrhea

An RCT in 40 infants (6 - 18 months old) with persistent diarrhea (greater than two weeks′ duration) evaluated the effect of oral zinc supplementation. It concluded that in persistent diarrhea there was depletion of zinc with the progression of the disease and oral zinc administration improved the zinc status. [17]

A pooled analysis of four RCTs has been reported on the effects of supplementary oral zinc in children, under the age of five, with persistent diarrhea. The Cox survival regression analysis was used to evaluate the overall effect of zinc on the continuation of diarrhea and possible differential effects in the subgroups. Zinc-supplemented children with persistent diarrhea had a 24% lower probability of continuing diarrhea (95% CI: 9%, 37%) and a 42% lower rate of treatment failure or death (95% CI: 10%, 63%) than those in the control group.[18]

Zinc supplementation in the treatment and prevention of bloody diarrhea

Studies conducted during acute shigellosis showed that zinc therapy was associated with enhanced antigen-specific antibody responses. The bactericidal antibody titers against Shigella increased the proportions of B cells and plasma cells, as also higher lymphocyte proliferation responses in the peripheral circulation, during the early convalescent phase of shigellosis. For all these reasons, it is clear that zinc supplementation should be given as an adjunct to antimicrobial (AM) treatment in bloody diarrhea.[19]

Zinc supplementation and cost-effectiveness

A study analyzed the incremental costs, effects, and cost-effectiveness when zinc was used as an adjunct therapy to the standard treatment of acute childhood diarrhea, including dysentery, and reassessed the cost-effectiveness of standard case management with ORS. The probabilistic cost-effectiveness analysis was performed using a Monte-Carlo simulation technique and the potential impacts of uncertainty in single parameters were explored with one-way sensitivity analyses. In this study, the ORS was found to be less cost-effective than was previously thought. The use of zinc as an adjunct therapy, however, significantly improved the cost-effectiveness of the standard management of diarrhea for dysenteric as well as non-dysenteric illnesses.[20]

Zinc supplementation and irrational use of antimicrobials

Excessive use of antimicrobials (AMs) for diarrhea is a major contributing factor toward increasing rates of AM-resistance in developing countries. A study of AM use in a rural area of Bangladesh found that 26% of the purchased medicines were AMs, which were most frequently purchased for children aged 0 – 4 years to use for diarrhea. A community-based controlled trial was conducted in Bangladesh where there were 30 service areas (clusters), around the Matlab Treatment Center, each with about 200 children between the ages of 3 and 59 months, who were randomly allocated to intervention or comparison areas. All children between the ages of 3 and 59 months were included in the study. The significant reduction in AM use and related behavior in the intervention group demonstrated that the benefits of zinc supplementation extend well beyond reducing childhood morbidity and mortality. Zinc supplementation for diarrhea with education programs, in addition to ORT, can reduce inappropriate AM use that leads to resistant pathogens.[21]

Recommended dose of zinc in diarrhea[22]

Elemental zinc is used orally, as an adjunct to ORT in acute diarrhea, in infants (under six months): 10 mg daily for 10 – 14 days; and in children (six months - five years): 20 mg daily for 10 - 14 days.

How to administer zinc salt?[22]

Zinc sulfate, acetate, and gluconate are all acceptable zinc salt formulations, of which zinc sulfate is low-cost, efficacious, safe, and therefore, optimal for the national program. Zinc sulfate tablets may be dispersed in breast milk, in oral rehydration solutions, or in water on a small spoon; older children may chew the tablets or swallow them with water. Zinc sulfate dispersible tablet is also available in the market, containing 20 mg of elemental zinc. Pediatric zinc sulfate tablets are also available.

Drug Interaction[22–24]

If zinc is given concomitantly with the following, drug interaction may occur. Phytate, which is present in staple foods like cereals, corn, and rice, decreases zinc absorption from composite meals. Experiments *in vitro* have shown that zinc is precipitated by phosphate and phytate at pH values close to those of the intestinal lumen.Dairy products and brown bread decrease zinc absorption. Coffee also inhibits zinc absorption. Iron supplements inhibit absorption of Zn and therefore Zn supplements are administered two hours before iron supplements. Penicillamine and other chelators reduce absorption of Zn. Calcium salts reduce absorption of zinc. Oral tetracyclines reduce absorption of Zn, and hence, Zn supplements are administered two hours before tetracyclines. Amino acids, such as histidine and methionine, and other low-molecular-weight ions, such as EDTA and organic acids (e.g., citrate), enhance zinc absorption. Zn inhibits copper absorption from the intestine. Thiazide diuretics increase urinary excretion of Zn. Zinc reduces absorption of Ciprofloxacin, Levofloxacin, and Ofloxacin. Absorption of both zinc salts and ferrous salts will reduce if used concomitantly.

Side effects of zinc supplementation

To date there have been no reports of severe adverse reactions from any form of zinc supplementation used in the treatment of diarrhea. A zinc dose of 40 mg has been approved as being safe to use by the Food and Drug Administration (FDA), and a zinc dosage of more than this can pose certain risks. Too much zinc will probably interfere with the metabolism and absorption of other essential minerals in the body, especially iron, magnesium, and copper, reduce the body's immune function, and reduce the HDL level. Oral zinc sulfate supplements can also cause side effects such as stomach upset, heartburn, and nausea. Rare side effects include fever, sore throat, mouth sores, weakness, and fatigue. Trials have included more than 8,500 children who participated in efficacy trials in both the placebo and zinc study arms, with nearly 12,000 child-years of observation, from one large effectiveness trial. No differences in adverse reactions based on the different zinc salts (sulfate, acetate, and gluconate) were noted in the supplementation trials. One trial reported higher vomiting in the zinc versus the control group, when zinc was given with multiple micronutrients, but not when given alone. The copper status has been evaluated in four trials. Three of these have not found a difference in the serum copper status after supplementation. However, one trial did find a significant trend of decreased copper level when comparing zinc-supplemented children with non-zinc supplemented children. However, these children were malnourished with persistent diarrhea at baseline. Overall, there is no substantial evidence of short-term zinc supplementation for the treatment of diarrhea adversely affecting the copper status.[25]

Recommendations

The Indian Academy of Pediatrics, WHO, and UNICEF have already endorsed the use of zinc as a supplement to ORS in the management of diarrhea. A dosage of 20 mg of elemental zinc per day has been shown to be effective and safe in age group six months -to five years. Administration of zinc is recommended through a primary healthcare.

For maximum impact on diarrheal diseases, zinc and ORS should be made available at the community level. Community-based programs increase the use of zinc and the introduction of zinc increases the use of ORS in the same communities

The revitalization of community-health workers with a reach into the least fortunate communities will be critical to achieving the targeted coverage rates. In addition, incorporating the private sector, the medical and non-medical sectors, and the formal and informal sectors, may help reach additional segments of the population.

Conclusion

Oral zinc administration provides substantial benefit in the reduction of stool output, frequency, and duration, combined with safety, efficacy, and affordability in acute diarrhea. Thus, it can be concluded that oral zinc supplementation is a simple and effective therapeutic intervention in the management of acute diarrhea.

Footnotes

Source of Support: Nil.

Conflict of Interest: None declared.

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