Zinc Prophylaxis to Reduce Mortality and Morbidity in Under-5 Children: Clinical and Global Health Points of View

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Dear Editor

We read with interest the recently published randomized controlled trial (RCT) on the effect of zinc supplementation among healthy children in the 6-months to 5-year age group.[1] It is commendable that the authors identified the positive impact of zinc supplementation on diarrhea morbidity, not reported previously among Egyptian children.

Multiple RCTs conducted over the past 3 decades have demonstrated variable effects of zinc in decreasing morbidity and mortality in children due to gastrointestinal as well as respiratory infections.[2,3] In the study, the authors reported that about 70% of children (n = 140) had low baseline serum zinc levels (<60 µg/dL). Apart from the effects on diarrheal episodes, it would be interesting to follow up on the study recruits regarding the growth parameters and respiratory morbidity.

As per WHO, zinc supplementation at 10 to 20 mg/day for up to 2 weeks in children with acute diarrhea can lower the incidence of diarrhea in the following 2 to 3 months after the episode of diarrhea. In the RCT, the authors have used zinc supplementation at 3 mg/day for <10 kg and 7 mg/day for >10 kg (low dose) for 4 months in healthy children. As cited by the authors, zinc supplements in the same doses for 9 months failed to reduce the incidence of diarrhea or respiratory infections in a large-scale intervention in Laos. Recently, 10 mg/day or more zinc supplementation for a maximum of 11 months has been suggested as a preferable prophylaxis regime.[4] However, a meta-analysis in 2011 indicated that neither the dose nor the duration of zinc prophylaxis influenced the observed benefit of supplementation.[2]

Regarding the zinc preparation, the authors have used zinc sulfate. The meta-analysis by Patel et al showed that trials using zinc gluconate showed the most significant reduction in diarrheal incidence when compared to zinc sulfate and zinc acetate. Therefore, there are important unanswered questions on the type of zinc formulation, time of initiation, and duration of zinc prophylaxis to get optimal clinical outcomes.

Also, zinc formulations, dosage, and duration would directly influence the cost of treatment and therefore cost-effectiveness of the prophylaxis regime. Zinc supplementation was estimated to cost approximately $11 per child in a recent study.[5] Based on decision-analytic modeling, the authors reported that prophylactic zinc for 18 months did not appear to be cost-effective for the prevention of diarrhea in their setting. It is prudent that future studies address the above critical questions that determine the cost-effectiveness of 4, 9, or 11 months of zinc supplementation. Forthcoming cost-effectiveness studies must also consider contentions on underestimation of the total sum of benefits of such nutritional interventions.[6]

There are some additional expositions to be deliberated from the global public health perspective:

About 17.3% of the global population is at risk of inadequate intake and therefore, zinc deficiency is a public health concern, especially in low- and middle-income countries.[7] Although undernourished populations tend to have a higher prevalence of zinc deficiency (>25%), studies conducted in developed countries in Europe have demonstrated a beneficial effect of zinc in acute diarrhea.[8] Mild zinc deficiency is largely considered subclinical and is likely to be common worldwide and not exclusive to the developing world.

The present study brings into focus the burden of subclinical zinc deficiency and acute diarrhea within the Eastern Mediterranean region (EMR) wherein Egypt reportedly has one of the highest diarrhea-attributed

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mortality among under-5 children.[9] Within the EMR, the effect of zinc supplementation has particularly not been studied in the Gulf Cooperation Council (GCC) countries. Justifications to conduct interventional trials in this region exist. For instance, the International Zinc Nutrition Consultative Group has published the country-specific prevalence of inadequate zinc intake based on the estimated absorbable zinc content of the national food supply.[7] As per the report, 21.2% of the population in Oman, a GCC country, is estimated to have inadequate zinc intake and hence included in the medium risk category. The role of subclinical zinc deficiency in such non-high-risk groups was reflected as a global phenomenon in the recent COVID19 pandemic.

To conclude, currently, there are no evidence-based recommendations on zinc supplementation to prevent childhood diarrhea regardless of nutritional or socioeconomic status. Zinc is not a universally included micronutrient in many countries where postharvest food fortification standards exist. Even people who regularly take supplements may have insufficient zinc levels as many multivitamin preparations lack zinc because of the unpleasant flavor of its salts. Subclinical zinc deficiency remains a major public health concern even as the search for a universally accepted "gold standard" biomarker to assess zinc status is on. The present RCT adds to the existing pool of evidence favoring the use of zinc prophylaxis yet there are more questions than answers on this intervention, both from the clinical and global pediatric health points of view.

Author Contributions

Gowda Parameshwara Prashanth: contributed to conception and design; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. Deeparaj G. Hegde: contributed to interpretation; gave final approval.

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