Role of Zinc in Pediatric diseases: Evidence based Guidelines

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Abstract

Role of zinc in human health including growth, development, immune status and acute diarrhea is indisputable. Zinc deficiency is well known because of poor dietary habits, increased secretion and poor absorption of zinc during diarrhea. Present review will demonstrate role of zinc in various pediatric disorders and newer update. We have tried to include recent review on role of zinc in childhood diseases as per evidences available on electronic databases.

Introduction

Zinc deficiency in humans is now known to be an important malnutrition problem world-wide. It is a required for proper functioning of most human body systems. Respiratory, GIT, Immune, CNS, Skeletal and Reproductive systems are most affected in deficiency. In this review we will provide a brief discussion on evidence based role of Zinc in various childhood diseases.

Role of Zn in paediatric Diarrhea

Acute diarrhea is leading cause of under five mortality in most of developing countries including India despite the use of Oral rehydration solution. Worldwide it accounts for 1.5 billion episode and 1.5-2.5 million deaths estimated annually in children below 5 years of age. In developing countries like India scenario is worse due to triad of Malnutrition, Infections and Poverty. Of India’s more than 2.3 million annual deaths among children, about 334 000 are attributable to diarrhoeal disease. It means around 1000 babies are dying every day due to diarrhea. First recommendation for Zinc use came years back in 1992 when Centre for disease control has recommended its use for Acute diarrhea. As per Joint statement of World health Organization (WHO), United Nations International children’s Emergency Fund (UNICEF) & United States agency for International Development (USAID) has recommended Use of Zinc in children. It has been recommended that Low Osmolar Oral Rehydration Solution (Low Osmo ORS) with low glucose and salt along with Zinc reduces severity and Duration of diarrhea. It also reduces recurrence in next 2-3 months. But according to recent cocharane Review which consist of 9128 children and 24 clinical trials in acute diarrhoea, there is currently not enough evidence from well conducted randomized controlled trials to be able to say whether zinc supplementation during acute diarrhoea reduces death or hospitalization (very low quality evidence).

Review also indicated that In children above than 6 months zinc supplementation can decrease the duration of diarrhea (low quality evidence) Conversely, In children aged less than six months, the available evidence
suggests zinc supplementation may have no effect on mean diarrhoea duration (low quality evidence), and may even increase the proportion of children whose diarrhoea persists until day seven. Zinc supplementation during acute diarrhoea causes vomiting in both age groups (high quality evidence). In children with persistent diarrhoea, zinc supplementation probably shortens the duration of diarrhoea by around 16 hours (moderate quality evidence).

Mechanism of action: 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. As this study was not performed in Zn-deficient animals, it provides evidence that Zn is probably effective in the absence of Zn deficiency. 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.

Role of Zinc in Respiratory disorder

In India, around 1.7 million children died before reaching the age of 5 years in 2010, and more than half of them (52%) died in the first month of life. The major causes of deaths were pneumonia (24%) with Diarrhea (13%) and Pneumonia (13%)12.

Zinc supplementation in young children demonstrated inconsistent results. One study in developing countries demonstrated that zinc supplementation reduces risk of Pneumonia13. Another clinical trial from Bangladesh suggested that it reduces duration of hospital stay, Hypoxia, Tachypnia and rapid recovery is possible14. However some double blind trials from developing countries suggested no beneficial effect of zinc supplementation in severe pneumonia either in duration of hospital stay or duration of pneumonia recovery15. Another meta analysis has demonstrated No significant difference between the two groups for common parameters (duration of resolution of hypoxia, chest indrawing or tachypnoea, change of antibiotics and treatment failure rates)16. As per evidences available Zinc supplementation is not indicated for severe pneumonia17-20.

Role of Zinc in asthma

Acute severe asthma is associated with low level of Zinc but recovery from asthma is not associated with zinc level. Routine supplementation of zinc is not advised in asthma21.

URI

Zinc administered within 24 hours of onset of symptoms reduces the duration of common cold symptoms in healthy people but some caution is needed due to the heterogeneity of the data. As the zinc lozenges formulation has been widely studied and there is a significant reduction in the duration of cold at a dose of ≥ 75 mg/day, for those considering using zinc it would be best to use it at this dose throughout the cold. Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data. When using zinc lozenges (not as syrup or tablets) the likely benefit has to be balanced against side effects, notably a bad taste and nausea22.

In another clinical trials Zinc bis-glycinate given in a dose of 15 mg once a day for 3 months failed to reduce the incidence of the common cold in 8 to 13-year-old school children, but decreased the number of days on which children suffered from cough, rhinorrhoea and the likelihood of having two or more symptoms of the common cold23.

Zinc in Neonatal Health

Twice daily administration of oral zinc in a dose of 10 mg/day does not reduce the incidence of hyperbilirubinemia in at-risk term and late-preterm neonates during first wk of age24. Another study demonstrated Zinc status was poor in many infants at birth irrespective of BW. Zinc status worsened significantly during early infancy, with infants with BW <2,000 g having the lowest zinc levels25. Supplementation with multivitamin drops doesn’t affect zinc level. One study does not report decrease in mortality rates, duration of
hospital stay and requirement of higher lines of antibiotic therapy following zinc supplementation in neonatal sepsis\textsuperscript{26}.

Another study by Christian P et al demonstrated that antenatal micronutrient supplements including Zinc were not associated with improved symptoms of neonatal morbidity in the first 10 days of life or at 6 weeks of age\textsuperscript{27}. In a review\textsuperscript{28} of Nutritional need of surgical Neonate it was stated that Zinc supplementation must begin at initiation of Parental Nutrition of surgical neonate (PN). All other trace elements can be added to PN 2 to 4 weeks after initiation. Although it is not clear that nutritional supplementation is associated with rapid recovery & less morbidity or not.

**Zinc in Sepsis**

Zinc supplementation is associated with immune modulation in infection related diseases like Sickle cell anemia, Human immunodeficiency virus infection, Down’s Syndrome. Zinc supplementation has shown to restore lymphocyte production, NK cell function, wound healing and resistance to infection\textsuperscript{29}. One animal study on mice has shown significant better survival with prophylactic zinc supplementation\textsuperscript{30}. Although at present evidences are not available for routine supplementation of zinc in sepsis.

**Zinc in Dengue**

One study\textsuperscript{31} demonstrated that lower zinc level during illness was associated with higher grade of Dengue severity and more liver cell injury demonstrated by higher liver enzyme level (SGPT & SGOT). Although at present evidences are not available for routine supplementation of zinc in Dengue.

**Zinc in ADHD**

Attention Deficit hyperactivity disorder is common behaviour problem in children with multifactorial etiology. One double blind randomized trial demonstrated beneficial effect of Zinc supplementation when given with Methylphenidate\textsuperscript{32}. More evidence based studies needed to confirm role of zinc in ADHD. Some study\textsuperscript{33} stated significantly low level of zinc when compare with normal child. Another study also suggested improvement in symptoms with zinc supplementation in ADHD patients\textsuperscript{34}. Less conclusive evidence exists for the effectiveness of zinc alone or in general community samples. Recommendations for further research in this area are provided\textsuperscript{15}.

**Zinc in Autism**

Autism spectrum disorders (ASDs) are a group of behavioural disorder that can cause significant social & communication challenges. Few studies demonstrated low zinc level in children suffering from autism\textsuperscript{36}. Result of other studies are not conclusive\textsuperscript{37,38}.

**Zinc in oral Health**

According to one randomized trial zinc deficiency is associated with higher caries prevalence and poor gingival health compared to zinc sufficient patient\textsuperscript{39}.

**Zinc in Wilsons Disease**

Zinc is approved by US Food and Drug Administration (USFDA) in 1997 for treatment of Wilsons Disease for life long treatment. Recent review also supports this recommendation. Although higher serum zinc level and urinary excretion was observed but only with few gastrointestinal side effects\textsuperscript{40}.

**Zinc in Malignancy**

According to one Double blind controlled trial it has become evident that supplementary zinc exerts a positive effect on nutritional status as positive weight gain. Moreover, the number of infection episodes was significantly reduced; possibly because of the immune stimuli in patients with acute leukemia on chemotherapy. To conclude zinc supplementation can prevent some of the chemotherapy adverse effects in children with leukemia, improving their quality of life\textsuperscript{41}.
Conclusion

Zinc deficiency is common in developing counties because of their dietary habits and poor quality of food. Role of zinc is crucial in severe diarrhea. It reduces duration of recovery and malnutrition in diarrheal episode. Although Cochrane review does not support zinc supplementation in diarrhea. As per evidences available zinc supplementation is not indicated for severe pneumonia. In Wilson’s disease in role of zinc supplementation is well established. In other pediatric problem like Asthma, URI, Neonatal disorder, ADHD, Autism & Sepsis enough evidences are not available to support routine zinc supplementation.

References


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