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Review

Zinc supplementation in young children: A review of the literature focusing on diarrhoea prevention and treatment

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SUMMARY

Background & aims: It is estimated that zinc deficiency is responsible for 4.4% of childhood deaths in Africa, Asia, and Latin America. This review examines the impact of zinc supplementation, administered prophylactically or therapeutically, on diarrhoea.
Methods: Relevant published articles were identified through systematic searches of electronic databases. Bibliographies of retrieved articles were examined.
Results: A total of 38 studies were included in this review, 29 studies examined the effect of prophylactic zinc and nine studies examined the effects of therapeutic use of zinc for treatment of diarrhoea in children under five years.
Conclusion: Prophylactic zinc has been shown to be effective in decreasing both prevalence and incidence of diarrhoea, reducing respiratory infections and improving growth in children with impaired nutritional status. There is less conclusive evidence of reduction in diarrhoea duration or diarrhoea severity. While prophylactic zinc decreases mortality due to diarrhoea and pneumonia, it has not been shown to affect overall mortality.
Therapeutic use of zinc for the treatment of diarrhoea in children has been shown to reduce diarrhoea incidence, stool frequency and diarrhoea duration as well as respiratory infections in zinc deficient children. However, stool output is only reduced in children with cholera. Less conclusive evidence exists for therapeutic zinc reducing mortality due to diarrhoea and respiratory infections. Specific definitions of diarrhoea severity, respiratory infection in further studies as well as examination of prophylactic zinc effectiveness in diarrhoea duration and severity effectiveness of therapeutic zinc in reducing mortality due to diarrhoea and respiratory infections are warranted.
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1. Introduction

In humans, zinc is a vital micronutrient essential for protein synthesis, cell growth, and differentiation. Zinc is also a pro-antioxidant and anti-inflammatory agent [1]. Dietary deficiency of zinc is common in several parts of the world, particularly low income countries and low income populations in the United States. It is estimated that inadequate zinc intake affects up to a third of some populations in Southeast Asia and sub-Saharan Africa, with children and pregnant women being most severely affected [2,3]. It is estimated that zinc deficiency is responsible for over 400,000 child deaths in Africa, Asia, and Latin America every year [4].

In May 2004, the World Health Organization (WHO) and the United Nations Children's Emergency Fund (UNICEF), released a joint statement advocating oral zinc to decrease diarrhoea deaths in the world's most vulnerable children based on the evidence that oral zinc treatment reduced diarrhoea duration and severity in children with diarrhoea aged six months to five years. While over 45 countries included zinc in diarrhoea management policies, few countries have implemented effective programs and very few children are currently being appropriately treated [5].

Zinc, administered either prophylactically or in the treatment of diarrhoea has been extensively examined in the last five years. However, meta-analysis and systematic reviews of studies examining the role of zinc in the prevention and treatment of diarrhoea

Abbreviations: WHO, World Health Organization; UNICEF, United Nations Children's Emergency Fund; LBW, low birth weight; RDA, recommended dietary allowance.

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[6] had limited information on impact of dose and form of zinc and no discussion on potential mechanisms of action. While the effects of zinc supplementation in respiratory infections and mortality were discussed, the effects on growth were not included. There are no guidelines for implementation and cost-effectiveness of intervention strategies for reducing zinc deficiency that could be used by governments or other implementing agencies.

This review will summarize the data from human intervention studies that have administered zinc either prophylactically or therapeutically to treat diarrhoea and examined outcomes on respiratory infections, otitis media, anthropometric measurements and mortality in children under five years of age. Potential mechanisms of action, impact of dose for the prevention and treatment of diarrhoea and criteria to identify zinc deficiency will be highlighted. Findings from relevant reviews examining this topic will also be summarized.

2. Methods

2.1. Search strategy

We searched the following electronic databases: MEDLINE, Science Direct and EBSCO. All databases were searched from the earliest available date up until May 2012. A combination of key words addressing "zinc supplement*" or "oral zinc" and "infants" or "children" were used. Reference lists of short-listed articles for other relevant studies were further examined.

2.2. Inclusion criteria

Studies were included if:

- There was a control group not receiving zinc supplementation
- Included children from birth to 5 years old
- Participants received zinc supplementation either for treatment of diarrhoea or for prevention of diarrhoea
- Outcomes of interest were reported: diarrhoea outcomes (prevalence, incidence, stool output), respiratory infections, otitis media, anthropometric measurements and mortality

2.3. Data extraction

Data extracted from each eligible study included the following variables: study context, study design, intervention specifics and outcome effects.

3. Results

A total of 38 studies were included in this review. The effect of prophylactic zinc was examined in 29 studies; 14, 7, 1 and 18 examined diarrhoea outcomes, respiratory diseases and pneumonia outcomes, otitis-media outcomes and anthropometric measurements, respectively.

Nine studies examined the effects of therapeutic use of zinc for treatment of diarrhoea; 9, 3 and 1 examined diarrhoea outcomes, respiratory infections outcomes and mortality.

3.1. Prophylactic effects of zinc

3.1.1. Diarrhoea

In 2008, it was estimated that over 1.3 million of the 8.8 million child deaths worldwide were caused by diarrhoeal diseases [7]. The primary cause of diarrhoea among infants worldwide is viral gastroenteritis caused by rotavirus. Other causes include bacterial pathogens such as *Vibrio cholerae*, *Shigella*, and *Salmonella* and *protozoa* such as *Cryptosporidium parvum* and *Giardia lamblia* [8].

There are 28 studies included in this review examining the effect of prophylactic zinc; 9 of the 14 which examined prevalence and incidence of diarrhoea showed positive effects of prophylactic zinc, although one showed positive effects only in stunted children [9], one only in children older than 11 months [10], and one only in boys [11] (Appendix 1 online). One study conducted in South Africa did not show any benefit of prophylactic zinc in diarrhoea in children. Prevalence of stunting and wasting in study populations may explain the disparate findings. Trials in regions with high prevalence of stunting and/or wasting such as Bangladesh [12–14] and India [15–17] are more likely to show benefits of zinc supplementation to entire study populations. On the other hand, trials in regions with lower prevalence of stunting and wasting such as South Africa did not report any differences [18] in the prevalence or incidence of diarrhoea in children receiving prophylactic zinc or reported benefits only to malnourished subgroups [9,19].

Difference between male and female responses to zinc supplementation, often in opposite directions for diarrhoeal diseases has been suggested by other authors but had never been systematically analysed [11]. When prophylactic zinc was administrated to urban children of low socioeconomic status aged six to 35 months in India, incidence and prevalence of diarrhoea was 26% and 35% lower in boys compared to girls (17% and 19%), respectively [10].

Diarrhoea results from an imbalance of absorption and secretion of ions and solute across the gut epithelium, followed by the movement of water in an attempt to restore the appropriate ion concentrations. Often, this imbalance is caused by the presence of bacteria that secrete toxins that disturb the organization of the epithelium. Although a number of factors, including genetic mutations, hormonal alterations, radiation injury and mal-absorption, can cause diarrhoea, the most common cause is infection by bacterial pathogens and the subsequent release of bacterial toxins. Such toxins typically trigger signalling molecules such as cyclic AMP or intracellular Ca^{2+}, which, in turn, activate cellular Cl^- channels leading to an increase in secretion of Cl^- and consequently water. Cl^- absorption can also be affected. Increased secretion and decreased absorption of Cl^- have the same net effects on luminal Cl^- concentrations. Attenuation of Na^+ absorption can also cause diarrhoea. In addition, a single layer of contiguous cells executes the vectorial transport of ions and solutes across the apical and basolateral surfaces of the intestinal epithelium. Gross alterations in homeostatic functioning of the intestinal epithelium, such as loss of the epithelial monolayer by mechanisms including apoptosis and delayed wound repair, are likely to result in unregulated fluid loss and consequent diarrhoea. Finally, the innate immune response has a significant role in the development of diarrhoea: First, the innate immune response is important for the maintenance of intestinal homoeostasis and controlling the commensal flora. Second, innate immune responses interfere with colonization by pathogenic organisms. Third, several pathogens stimulate the recruitment and transmigration of neutrophils into the intestinal lumen. Neutrophils attached to the apical side of epithelial cells release 5′-AMP, which is converted to adenosine in the lumen [20].

Cytokines are the hormonal messengers responsible for most of the biological effects in the immune system, such as cell mediated immunity and allergic type responses. T lymphocytes are a major source of cytokines. These cells bear antigen specific receptors on their cell surface to allow recognition of foreign pathogens. There are two main subsets of T lymphocytes, distinguished by the presence of cell surface molecules known as CD4 and CD8. T lymphocytes expressing CD4 are also known as helper T cells, and these are regarded as being the most prolific cytokine producers. This subset can be further subdivided into Th1 and Th2 and the optimal scenario seem to be that humans should produce a well-balanced

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