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Oral zinc and common childhood infections—An update

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ABSTRACT

Zinc is an essential micronutrient important for growth and for normal function of the immune system. Many children in developing countries have inadequate zinc nutrition. Routine zinc supplementation reduces the risk of respiratory infections and diarrhea, the two leading causes of morbidity and mortality in young children worldwide. In childhood diarrhea oral zinc also reduces illness duration and risk of persistent episodes. Oral zinc is therefore recommended for the treatment of acute diarrhea in young children. The results from the studies that have measured the therapeutic effect of zinc on acute respiratory infections, however, are conflicting. Moreover, the results of therapeutic zinc for childhood malaria also are so far not promising.This paper gives a brief outline of the current evidence from clinical trials on therapeutic effect of oral zinc on childhood respiratory infections, pneumonia and malaria and also of new evidence of the effect on serious bacterial illness in young infants.

Introduction

Since its discovery as an important element for human health in the 1960s, zinc has been widely studied but many questions regarding its mechanism of action and utility still remain unanswered [1]. It is the second most abundant essential trace element in the human body [2] and is required for cellular division, differentiation and growth which makes the demand for this essential trace element high in individuals with a rapid growth rate such as children. A regular intake of zinc is required as there are no large stores in the body from which it can be easily mobilized. Recommended daily allowances for zinc are 2 mg/day for infants below 6 months, 3 mg daily for young children up to 3 years and 5 mg for older children till the age of 8 years [3]. Organs that are dependent on continuous cell division for proper function, such as the immune system and the gut, are particularly sensitive to zinc deficiency. Zinc deficiency reduces nonspecific immunity, including neutrophil and natural killer cell function and complement activity; reduces numbers of T and B lymphocytes; and suppresses delayed hypersensitivity, cytotoxic activity, and antibody production [4].

Status of zinc in the human body is dependent on the quantity and bioavailability of this element in the food [5]. Although meat and fish are the most readily bioavailable sources of zinc, cereals and pulses continue to be the main sources of zinc in the diet globally [5]. Bioavailability of zinc is influenced by plant ligands such as phytate, dietary fibers and lignin as well as calcium in foods. Phytates make insoluble complexes with zinc in the gut and presence of calcium enhances this effect. High phytate/zinc molar ratios (>15) in ingested foods impair zinc absorption and contribute to zinc deficiency [6]. In developing countries, access to meat and fish is limited and the vegetarian diet consumed confers higher risk of zinc deficiency and its consequences on health.

The International Zinc Nutrition Consultative Group has proposed a method to calculate and classify risk of zinc deficiency in a population as high, medium or low based on the prevalence of stunting in the population and availability of zinc in the diet at the country level. Countries at high risk of zinc deficiency are those with more than 20% stunted under-five children and an estimated prevalence of inadequate zinc intake of more than 25%. A country with less than 10% stunting and 15% inadequate zinc intake is at low risk. According to these estimates the national risk of zinc deficiency is high in South Asia, most of sub-Saharan Africa and parts of Central and South America [7]. Countries in these regions are also those with higher child mortality rates.

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Recent estimates suggest that the highest rates of child mortality are still in Sub-Saharan Africa – where 1 in 8 children (121 per 1000 live births) dies before age 5; more than 18 times the average for developed regions (6.8 per 1000). South Asia with 65.5 deaths per 1000 live births has the second highest rate, where one in every 15 children dies before their fifth birthday [8]. Of 7.6 million childhood deaths occurring in the first 5 years of life, 64% (4.879 million) are due to infectious causes. Pneumonia and diarrhea remain the leading causes of post neonatal deaths worldwide with 72% deaths from diarrhea and 81% deaths from pneumonia occurring in children younger than 2 years [9].

Respiratory tract infections

Respiratory tract infections (RTI) encompass upper and lower respiratory infections. Common cold is a leading cause of doctor visits and absenteeism from school and work worldwide. Complications include otitis media (middle ear infection), sinusitis and exacerbations of reactive airway diseases. There is no proven effective treatment for the common cold. Pre-school children may have 6–10 episodes of cold per year (and up to 12 cold episodes per year for school children) [10]. In the US, the estimated yearly cost is 40 billion US$ [11]. Over the last 30 years, about 20 trials have looked at the efficacy of zinc, given as doses of 30–60 mg per day, in reducing duration of the common cold. Most of these have been done in adults and none have been undertaken in developing countries. two recent meta-analyses [12,13] concluded that oral zinc given within 3 days of the onset of illness, significantly reduced its duration. Both reviews included only randomized, placebo controlled trials but revealed a substantial heterogeneity between the studies. The effect was seen in adults only but there were only 3 studies that had included children < 5 years of age.

Acute respiratory infection (ARI) is one of the leading causes of illness and death in children. Estimates for 2010, suggest there were 120 million episodes of pneumonia (14 million of which progressed to severe episodes) in children younger than 5 years and 1.3 million of these episodes led to death [9]. The estimated incidence of pneumonia in children < 5 years of age in low- and middle-income countries is 0.22 (interquartile range (IQR) 0.11–0.51) episodes per child-year. The regions with the highest incidence are South-East Asia and sub-Saharan Africa. In contrast, the incidence in industrialized/high-income countries is 0.015 (IQR 0.012–0.020) episodes per child-year [14]. The incidence in the community vary with the prevalence of several risk factors; malnutrition, low birth weight, non-exclusive breastfeeding, lack of measles immunization the first year of life, indoor air pollution, and crowding have been shown to be definite risk factors for pneumonia in developing countries [15,16].

Studies on zinc in common childhood infections

Role of prophylactic zinc supplementation

Despite a declining trend, <age 5 mortality remains high in low- and middle-income countries. Zinc supplementation has been identified as one of the interventions that can be used to further reduce childhood deaths [17]. In a review of 18 studies done in developing countries, zinc supplementation resulted in a reduction of all – cause mortality by 9%, diarrhea and pneumonia deaths by 18% and 15%, respectively. Similarly administration of zinc resulted in reductions in the incidence of pneumonia by 19% (RR 0.81 95% CI 0.73, 0.90) and 13% (RR 0.87 95% CI 0.81, 0.94) for diarrhea. The median dose of zinc was 10 mg/day and median duration of supplementation was 6 months [18].

In a trial, in 42,546 children over a period of three and a half years, in Zanzibar with zinc supplementation compared to placebo, a 10% reduction in malaria specific mortality was observed (RR = 0.90; 95% CI: 0.77, 1.06) with 272 deaths in the zinc supplementation and 302 deaths in the control arm [19]. In Tanzania, neither zinc nor other multi-nutrients influenced malarial rates in a 2×2 factorial trial in 612 children, under five years of age (adjusted HR, 95% CI: 1.04, 0.93–1.18 and 1.10, 0.97–1.24, respectively) in a study undertaken over a 6 month period [20].

Role of therapeutic zinc

In 2004, the World Health Organization (WHO) included oral zinc in their recommendations for treatment of acute diarrhea and many countries have adapted this recommendation. Several reviews and meta-analyses support the utility of this inexpensive intervention [21–23]. It has also been estimated that oral, therapeutic zinc given for acute diarrhea reduces all – cause mortality by 46% and hospital admission rates by 23% [24]. However, it is difficult to disentangle the effect of oral rehydration solution (ORS) from the effect of zinc in the two studies that measured the effectiveness of therapeutic zinc on morbidity and mortality as ORS was included in the intervention [25,26].

The therapeutic effect of zinc given during pneumonia is still not clear. Till date, 14 clinical trials on the efficacy of zinc as adjunct therapy, i.e. in addition to standard treatment, given during childhood pneumonia have been published [27–40]. While all these trials were done in hospitalized children with pneumonia with illness severe enough to warrant admission, the definition of the illness varies across studies. Most studies have used modified versions of the WHO criteria for severe pneumonia which includes a history of cough and/or difficult breathing with either of the following, i.e. a general danger sign, cyanosis or documented hypoxia with pulse oximetry and severe respiratory distress [41]. Table 1

Table 1
Effect of zinc on recovery from severe pneumonia – findings from clinical trials in hospitalized children.

Study site	Age of participants (months)	Sample size	Median time to recovery in hours (IQR)		Hazard ratios (95% CI)
			Zinc group	Placebo group	
Bangladesh (25)	2–23	270	72 (72, 96)[a]	96 (72, 96)[a]	1.43 (1.02, 1.96)
India (26)	2–23	299	111 (89,138)[a]	97 (78, 113)[a]	0.86 (0.62, 1.18)
India (27)	2–24	106	60 (24, 78)	54 (30, 72)	*Not reported*
Nepal (28)	2–35	149	*Not reported*	*Not reported*	1.10 (0.77, 1.5)
Iran (30)	3–60	128	42	47	*Not reported*
Nepal (32)	2–35	610	49 (33, 77)	49 (29, 91)	1.10 (0.94, 1.30)
Uganda (33)	6–59	352	24 (21, 27)[a]	18 (11, 25)[a]	1.04 (0.74, 1.46)
India (34)	2–24	550	79 (59,122)	77 (58, 117)	0.98 (0.82, 1.17)
Tanzania (37)	6–36	94	49 (25, 74)	47 (27, 69)	0.75 (0.49, 1.14)[b]

Ratio of >1 indicates beneficial effect of zinc.
[a] Figures in parentheses are 95% confidence intervals for median time.
[b] Incidence rate ratio with 95% CI.