Selected Summaries

Does zinc supplementation prevent acute lower respiratory tract infections in children?

Roth DE, Richard SA, Black RE. (Department of International Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.) Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: Meta-analysis and meta-regression of randomized trials. *Int J Epidemiol* 2010;**39:**795–808.

SUMMARY

This meta-analysis was done to assess the effect of zinc on the prevention of acute lower respiratory infections (ALRI). Trials conducted in developing countries, with randomization and double blinding, were included. Trials with routine zinc supplementation for >3 months, in children <5 years of age, with a proper surveillance system to record respiratory morbid conditions were included. The literature search was made with appropriate search strings in Pubmed, Medline (1950–January 2008), EMBASE (1988–2008), Cochrane Central Database of Controlled Trials and Global Health without any language restrictions. Reference articles were searched and experts were consulted. Full-text manuscripts were reviewed independently by 2 authors. Discrepancies were resolved by the third author. The exposure variable was supplementation with zinc/placebo; the moderator variables considered were definition used for ALRI incidence, study location, mean age at enrolment, baseline nutritional status, mean serum zinc concentration and weekly cumulative zinc dose. The outcome variable ascertained was incidence rate ratio (IRR) between the incidence rate of ALRI in the zinc and the control arms. Four of 10 eligible studies included in the meta-analysis reported analyses using 2 ALRI case definitions. Hence, data for 14 zinc–control comparisons were available. Using the most specific definition of ALRI (which is most severe and specific to ALRI diagnosed by increased respiratory rate, and at least one additional sign of ALRI, and abnormal sounds on pulmonary auscultation suggestive of pneumonia) showed an IRR of 0.65 (95% CI 0.52–0.82) and a 35% reduction of ALRI in the zinc arm. When the less specific case definition was used to ascertain the outcome (category corresponds to less severe and specific cases diagnosed without auscultatory findings), the IRR was 0.94 (95% CI 0.88–1.01). The random effect model was used appropriately according to heterogeneity statistics to find out the pooled effect size.

Meta-regression analysis showed that the differential effect of zinc across various studies was contributed by different definitions of ALRI use for ascertaining outcomes. Other factors such as study location, baseline nutritional status, etc. were not responsible for heterogeneity between the trial results. The authors concluded that routine zinc supplementation was associated with a lower incidence of ALRI when a highly specific definition was used; this association did not exist when definitions of lower specificity were used.

COMMENT

This meta-analysis included 10 trials involving 49 450 children <5 years of age. The authors have classified their outcome of ALRI incidence into 4 types: score 1 was least severe and specific, while score 4 was the most severe and specific to ALRI. The definition of severe ALRI compares with the one used in studies from India.[1,2] The authors have appropriately selected studies from developing countries, since 98% of respiratory mortality is reported from developing countries.[3] Quality assessment of individual studies could have been better explained to the readers. Though the Begg and Egger tests did not suggest any publication bias, the asymmetry of the forest plots did indicate low representation of small studies with negative results. The sensitivity analyses did not alter the inferences. This is especially important as 86.6% of participants were from a single study in Nepal. The authors have adjusted for design effect due to the occurrence of repeated infections in the same child by an appropriate statistical model, viz. generalized estimating equations. In meta-regression, the actual duration of zinc supplementation was not taken into account, which could have been an important variable to decide the magnitude of the effect of zinc, which is proven from prior trials. However, the authors did include the weekly cumulative dose of zinc as a possible moderator variable.

Despite the reported limitations, this study does provide some thought for the conduct of future trials. It answers puzzling questions such as why some of the recent zinc supplementation trials did not report protection against ALRI. It emphasizes the need for defining ALRI *a priori* with high specificity in future ARLI prevention trials. Sample size should be calculated according to the number of episodes of specific ALRI, and not according to the number of episodes of general acute respiratory infections (ARIs). The authors have explained why zinc is protective only in severe ALRI, and not in less severe episodes. Sometimes cough, because of bronchial asthma, indoor air pollution and other hyperactive airway diseases, may be misclassified as ALRI. These misclassification errors most likely happen with less specific/less severe ALRI definitions, and not with highly specific/highly severe ALRI definitions. This is more evident from the comparison of various ALRI definitions in some of the included studies as well.[4–6] This meta-analysis provides sound evidence of the protective effect of zinc in preventing ALRI when the diagnosis of ALRI is based on clinical criteria other than increased respiratory rate.

ARIs are a major cause of morbidity and mortality among children under 5 years worldwide.[7] It causes 150 million episodes of illness per annum, leading to a heavy burden on the family and the health system. In India, under-5 children constitute 13% of the total population[8] and contribute 25% to the mortality. Mortality statistics in India have shown that ARIs including neonatal pneumonia cause 20%–35% of the mortality among under-5 children.[9]

In India, various community-based studies have reported that the incidence of upper respiratory tract infection among under-5 children is 3–5 episodes/child/year, resulting in 41 million episodes of ARI episodes/year. The incidence of lower respiratory tract infection is 0.25–0.5 episodes/child/year.[10,11] Various studies have shown that among the ARI events in children, 87%–90% are due to upper respiratory infections, and 10%–13% by ALRI.[12–14] Further, 96.5% of mortality due to respiratory events is contributed by lower respiratory tract infections. Studies have shown that 33% each of paediatric outpatients and admissions are due to acute respiratory events. Among the paediatric respiratory care admissions, >90% are due to lower respiratory tract infections.[14,15] The estimates of the

Child Health Epidemiology Reference Group of WHO also confirms this epidemiological pattern. The estimates report that annually, 2 million under-5 children die worldwide because of ARI. India contributes to 25% (400 000–500 000 under-5 deaths) of these.[16] The WHO has recommended various measures to decrease respiratory mortality in resource-poor settings. Case-finding and management, vaccine strategy, decrease of indoor air pollution and improvement in nutrition are some of these. Biological models have shown that increased susceptibility to infections among malnourished children was due to impairment of cell-mediated immunity via zinc.[17] Even though there is a paucity of community-based data on zinc deficiency, analysis from surrogate markers and baseline zinc status of all randomized zinc supplementation trials have shown that >35% of under-5 children in India were zinc-deficient.[18,19] Considering the huge burden of mortality due to ARI, in 1983, WHO started the ARI control programme, worldwide. India started its ARI control programme in 1989. Respiratory mortality has been reported to have decreased after the introduction of the Integrated Management of Neonatal and Childhood Illness approach; however, there is a long way to go. Along with the current meta-analysis, evidence is accumulating on the beneficial effects of zinc in ALRI. This particular study explains the reason why some studies have not been able to demonstrate the protective effect of zinc. This study also gives recommendations for improving future trials on ARI prevention. Researchers need to consider the definition of ALRI when they are planning such studies, or interpreting results from the published scientific literature. Future trials need to include well-defined criteria, from the least specific to highly specific definitions; the difference in effect of zinc between the various ALRI definitions is evident from the studies themselves.

Even though studies have explained the protective effect of zinc in ALRI beyond doubt, variation in the magnitude of its effect in subgroups was not identified. With this limited evidence on subgroups, it may not be possible to identify specific target groups in low-resource settings such as India. However, if one considers the burden of ALRI, vulnerability of Indian children to zinc deficiency (inadequate breastfeeding, improper weaning foods, cereal-based diet, frequent diarrhoeal illness), people's health-seeking behaviour, various issues in the case management strategy with scientific evidence for the protective effect of zinc, low cost, easy administration, and immune impairment and onset of illness even at a subclinical level of zinc deficiency, as well as the non-toxicity of zinc up to 2 times the recommended dietary intake,[20] zinc supplementation may revolutionize the steps taken to achieve a reduction in mortality due to ARI.

The global action plan for the prevention and control of pneumonia (GAPP)[20] also recommends zinc supplementation for pneumonia control. This study adds evidence. WHO[21] recommends that in resource-poor countries, individual methods alone cannot control ALRI effectively. If case management strategies, vaccine strategies and improved nutrition such as exclusive breastfeeding and zinc supplementation are used, mortality reduction in pneumonia will be faster and more effective.

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