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Original Research Article

Role of zinc supplementation in acute respiratory tract infections in children aged 2 to 60 months

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ABSTRACT

Background: Zinc has a major role in improving immune function and decreasing morbidity in various infectious diseases like acute respiratory tract infections, diarrhoeal diseases etc. The objective of the study was to study the effect of zinc supplementation on clinical manifestations, progress of illness and duration of acute respiratory infections.
Methods: A randomized double blind controlled study was conducted in the Paediatric ward of a tertiary care hospital in New Delhi in 50 children aged 2 to 60 months. Children with previous episodes of wheezing, severe malnutrition, congenital heart diseases, pneumonia, history of taking multiple micronutrient formulations or zinc for any intercurrent illnesses like diarrhoea in the previous month prior to admission and history of any known immuno-deficiency disease or on any immunosuppressive medications(steroids) or anti malignancy treatment were excluded. Both placebo (syrup base) and zinc syrup (20 mg/5 mL elemental zinc as zinc sulfate) were given orally for a period of 14 days to the respective groups. Statistical analysis used: Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Chi-square test was done for qualitative variables and t-test was used for quantitative variables. $P<0.05$ was considered as statistically significant.
Results: The mean age of zinc group was 22.77 months (SD - 5.74) and that of placebo group was 22.86 months (SD - 5.88) with a p value of 0.98 which was not statistically significant. There were no significant differences in the clinical features in the two groups before starting therapy or after treatment at 24, 48 and 72 hours ($P>0.05$).
Conclusions: Zinc supplementation during episode of ARI did not show any substantial benefit in reducing duration or morbidity in children aged 2-60 months.

Keywords: Acute lower respiratory tract infections, Children, Cyanosis, Tachypnea, Zinc syrup

INTRODUCTION

Acute respiratory tract infections (ARI) are the most common illnesses in childhood. ARI comprises of as much as 50% of all illnesses in children less than 5 years old. It also comprises of 30% of all illnesses in children aged 5-12 years. There are many factors like infecting agents, environmental factors and host factors which determine the type of respiratory tract illnesses and their frequency.

Amongst the host factors, improvement in nutrition has been considered to be the most important factor contributing to decrease in mortality and morbidity due to ARIs in children of developing countries.[1] Recently, amongst all the nutrients, zinc deficiency has gained a lot of attention. Zinc deficiency is associated with impaired

immune function and has been incriminated in ARIs in children.[2] Deficiency of zinc also leads to increase in morbidity due to cognitive dysfunction, hypogonadism, growth retardation and infections of gastro intestinal and respiratory systems.[3]

Thirty percent of the world's population has zinc deficiency.[4] In developing countries, most children less than 5 years of age are malnourished and found to have zinc deficiency.[5] This dietary zinc deficiency is further aggravated by infections both acute and chronic.[6] Studies have shown that when even apparently well-nourished children were given zinc supplementation, morbidity and mortality of intercurrent illnesses were significantly reduced.[7] Zinc supplementation also reduced the time take to recover from common infectious diseases like ARI.

The objective of the study was to study effect of zinc supplementation in acute respiratory tract infections in children in developing countries in relation to clinical manifestations, progress of disease, complications associated with them and duration of illness.

METHODS

This was a randomised double–blind, parallel-arm placebo-controlled study on 50 children aged 2 to 60 months admitted in the Paediatric ward of a tertiary care hospital in New Delhi from January 2016 to December 2016.The study was conducted on all patients admitted with respiratory symptoms.

Inclusion criteria was children aged 2 months to 60 months with respiratory symptoms. Children who had cough or cold with or without fever, difficult breathing, rapid breathing or chest in drawing as informed by the parents or noticed by the medical professional were included in the study.[8] Exclusion criteria were children with previous episodes of wheezing, features of severe malnutrition, congenital heart diseases, pneumonia, history of taking multiple micronutrient formulations or zinc for any intercurrent illnesses like diarrhoea in the previous month prior to admission and history of any known immuno-deficiency disease or on any immunosuppressive medications (steroids) or anti malignancy treatment.

Patients were divided randomly into two groups. Simple randomization using computer generated random numbers were used for allocating to case (drug) group or to control (placebo) group. The bottles were labelled with serial numbers after randomization without the knowledge of the nursing staff administering the medicine or the parents of the children. The Paediatric residents monitoring the cases were also blinded to the treatment allocation till the end of discharge or follow up period. The mothers received the bottles with labelled serial numbers and names. The case group took oral zinc (20mg of elemental zinc /5ml) for 14 days during the acute episode of ARI. Children up to 6 months were given 10mg of elemental zinc once daily and those more than 6months were given 20 mg once daily. The control group received placebo of same volume. Both the bottles of drug and placebo were similar in size and shape.

The study purpose was explained to the parents of all the children enrolled and a written consent was obtained from them. Data was collected by a proforma after enrolling the patient to the study. Clinical signs considered were increased tachypnea / respiratory rate of >50 per minute up to the age of 12 months and >40 up to the age of 60 months. Other signs considered were fever (axillary temperature above 99°F/37.2°C), cyanosis, wheezing and increased work of breathing (retraction of subcostal and intercostal muscles and alae nasal flaring).[9] All these clinical signs were recorded by paediatric resident on duty at time of admission and also 24, 48 and 72 hours after start of treatment. Discharge criteria of both the case and control groups were absence of fever, cyanosis, tachypnoea, wheezing and no evidence of increased work of breathing.

Medications were carried out for a total of 14 days even after discharge. Patients were reviewed even after to ensure compliance discharge on Day 7 and Day 14 of start of medications. Data for any possible side effects with the drug was also collected from the parents during the review visits. Socioeconomic status was assessed using the Modified Kuppuswamy Scale (based on education and occupation of family head and total family income) modified for Consumer Price Index for industrial workers of India for 2011.[10] Z-scores for length and weight were calculated using WHO reference tables for length and weight.[11,12]

Ethical clearance was obtained from the Institutional Ethics Committee. Statistical analysis was done using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Chi-square test was done for qualitative variables and t-test was used for quantitative variables. $P<0.05$ was considered as statistically significant.

RESULTS

The case / zinc group consisted of 13 males and 12 females while the control/placebo group consisted of 12 males and 13 females with a $p = 0.96$ which was not statistically significant (Table 1). The mean age of zinc group was 22.77 months (SD - 5.74) and that of placebo group was 22.86 months (SD - 5.88) with a p value of 0.98 which was not statistically significant. In the zinc group, 9 out of 25 children were exclusively breast fed in the first 6 months while 16 children had mixed feeding. In the placebo group, 10 out of 25 children were exclusively breast fed in the first 6 months while 15 children had mixed feeding. There was no statistical significance between the 2 groups in relation to ARI. There were no significant associations with mean age and

nutritional status of case and control groups. Clinical findings before treating and 24, 48, 72 hours after treating is shown in Table 2. There was improvement in clinical signs like wheezing, intercostal and subcostal retractions, cyanosis and tachypnoea in both the groups after 24, 48 and 72 hours. However, there were no significant differences in these clinical features in the two groups before starting therapy or after treatment at 24, 48 and 72 hours (P>0.05) as shown in Table 2.

Table 1: Basic profile of participants of both case and control groups.

Basic profile	Case / zinc group (n=25)	Control / placebo (n=25)	P value
Male/female gender; n (%)	13 / 12 (52 / 48%)	12 /13 (48 / 52%)	0.96
Mean age(months)*	22.77 (5.74)	22.86 (5.88)	0.98
Exclusive breast feeding/mixed feeding	9/16	10/15	0.82
Socioeconomic status			
Upper and upper middle	18 (72 %)	19 (76 %)	
Lower middle and lower	7 (28 %)	6 (24 %)	
Weight-for-age *	-1.48 (1.17)	-1.46 (1.23)	
Wasted; n (%)	8 (32%)	10 (40%)	
Length/ ht for age *	-1.74(1.54)	-1.68 (1.36)	
Stunted; n (%)	9 (36%)	10(40%)	

*Mean (SD)

Analysis of pre- versus post-values for each parameter resulted in non-significant change compared to baseline in selected parameters between the Zn supplemented and placebo supplemented group (Table 2). This was more likely due to the small number of patients and the large standard deviation within each group. There were no cases of drop outs due to side effects in either group.

Table 2: Comparison of clinical manifestations between the two groups at admission and after starting therapy.

	At Admission			24 hours after admission			48 hours after admission			72 hours after admission		
Clinical Sign	**Case**	**Control**	**p**	**Case**	**Control**	**p**	**Case**	**Control**	**p**	**Case**	**Control**	**p**
Fever	17	18	0.9	9	10	0.9	2	2	1	0	0	1
Coryza	22	18	0.2	18	12	0.1	7	4	0.4	1	2	0.5
Cyanosis	2	3	0.7	1	2	0.5	1	0	0.4	1	0	0.4
Dyspnoea	22	19	0.5	8	9	0.8	3	4	0.6	1	2	0.6
Tachypnoea	24	22	0.5	13	18	0.3	7	6	0.8	1	2	0.6
Intercostal retractions	14	10	0.5	2	6	0.3	0	1	0.5	0	1	0.5
Subcostal retractions	16	18	0.8	7	8	0.8	1	3	0.6	1	2	0.5
Nasal flare	10	11	0.9	5	7	0.8	2	3	0.6	1	2	0.5
Wheeze	20	24	0.01	14	16	0.5	7	8	0.9	2	2	1

DISCUSSION

Deficiency of zinc has been associated with anorexia, learning disabilities, skin disorders, impaired immunity and stunting of growth.[13] Zinc deficient children are at increased risk of restricted growth and developing diarrhoeal diseases, as well as respiratory tract infections such as acute lower respiratory tract infections.[14] Diarrhoeal disorders and acute lower respiratory tract infections, especially pneumonia are the two most common causes of infant and child death in low-income countries.[15] Some research studies have suggested that zinc supplementation may reduce the number of episodes and severity of bronchiolitis and pneumonia cases in children.[16,17]

There are a few studies which have found no correlation between pulmonary or nutritional status and zinc levels.[18,19] In a developing country like India with resource-limited settings, it is difficult to determine zinc deficiency. Therefore, the present study was done to see if supplementing zinc during an episode of ARI would decrease the morbidity or mortality associated with an episode of ARI.[20]

Prior zinc supplementation has a lot of benefit in preventing morbidity and mortality in many infections or illnesses of children when observed prospectively. In a prospective study, preventive zinc supplementations to all age groups (infants, pre-schoolers and older prepubertal children) showed a 6% non-significant reduction in mortality due to all causes.[21] Prospective studies specifically on risk of incidence of ARIs in young children in developing countries have shown that routine zinc supplementation reduced them.[22,23] These studies were done to assess the association between respiratory morbidity and zinc in children.

Many mechanisms have been implicated in role of zinc deficiency in causing increased susceptibility to ARIs. Zinc plays an important role in the protection of the integrity of respiratory epithelial cells, and also regulates the secretion of pro-inflammatory cytokine.[24] It also affects T lymphocyte function and lymphocyte proliferation. A study conducted in Ecuador showed that when children with malnourishment were supplemented with zinc for 60 days, they had a lesser incidence of respiratory infections with fever and cough.[25] Other large trials from India and Bangladesh also have confirmed a lesser incidence of ARI in children supplemented with zinc.[26] The association of Zn supplementation with the reduction in the average days of oral antibiotic usage required to treat ARIs was also studied in children with cystic fibrosis.[27] They concluded that slightly higher doses of Zn may be needed to change pulmonary functions statistically.

Zinc supplementation also decreased the severity of acute respiratory exacerbations in children with cystic fibrosis. The present study included all cases which had respiratory symptoms. This may have led to inclusion of bacterial pneumonia, viral bronchiolitis, chronic infections like tuberculosis and also non-infectious respiratory conditions like asthma and respiratory complications of sickle cell disease.[28] The varied clinical spectrum of respiratory illnesses suggest that nutritional interventions like zinc supplementation may cause different response on the immune functions that protect against these different respiratory conditions.

Our results did not show any positive correlation improvement in clinical signs in the zinc supplemented group as compared to the placebo. This may be because we included all acute lower respiratory tract infections (ALRIs) like both pneumonia and bronchiolitis, sepsis and other systemic infections associated with respiratory manifestations (e.g. metabolic acidosis leading to tachypnoea). The respiratory manifestations in all these conditions may not have been due to zinc deficiency or these acute conditions would themselves not have responded to zinc supplementation. Moreover, many of these conditions may have been a cause for high morbidity and mortality otherwise also. Larger studies are required to prove the correlation of zinc supplementation with the acute clinical signs mentioned.

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REFERENCES

1. Roth DE, Caulfield LE, Ezzati M, Black RE. Acute lower respiratory infections in childhood: opportunities for reducing the global burden through nutritional interventions. Bull World Health Organ. 2008;86:356-64.
2. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr. 1998;68:447S-63S.
3. Prasad AS. Discovery of human zinc deficiency and studies in an experimental human model. Am J Clin Nutr. 1991;53(2):403-12.
4. Caulfield L, Black RE. Zinc deficiency. In Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, CJL; 2004.
5. Gibson RS, Ferguson EL. Assessment of dietary zinc in a population. Am J Clin Nutr. 1998;68(2 Suppl):430S-4S.
6. Chakravarty I, Sinha RK. Prevalence of micronutrient deficiency based on results obtained from the national pilot program on control of micronutrient malnutrition. Nutr Rev. 2002;60(5.2):S53-8.
7. Bhutta Z, Black R, Brown K. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. J Pediatr. 1999;135:689-97.
8. Rahman MM, Vermund SH, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomized double blind controlled trial. BMJ. 2001;323:314-8.
9. Nield LS, Kamat D. Fever. In: Kliegman RM, editor. Nelson's textbook of Pediatrics, 20th ed. Philadelphia, PA: Chapter177:Elsevier; 2016;1:1277.
10. Kuppuswamy B. Manual of Socioeconomic Status (Urban), Manasayan, Delhi; 1981.
11. World Health Organization. Child growth standards. Weight-for-age. Available from: www.who.int/childgrowth/standards/weight_for_age/en/index.html.

12. World Health Organization. Child growth standards. Height-for-age. Available at: http://www.who.int/childgrowth/standards/height_for_age/en/index.htm.
13. Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lönnerdal B, et al. International Zinc Nutrition Consultative Group (IZiNCG) Technical Document no. 1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutri Bull. 2004;25:S94-S203.
14. Roth DE, Caulfield LE, Ezzati M, Black RE. Acute lower respiratory infections in childhood: opportunities for reducing the global health burden through nutritional interventions. Bulletin of the World Health Organization. 2008;86:356-64.
15. Doherty CP, Sarkar MA, Shakur MS, Ling SC, Elton RA, Cutting WA. Zinc and rehabilitation from severe protein-energy malnutrition: Higher dose regimens are associated with increased mortality. Am J Clinical Nutri. 1998;68:742-8.
16. Gibson RS, Bailey KB, Parnell WR, Wilson N, Ferguson EL. Higher risk of zinc deficiency in New Zealand Pacific school children compared with their Māori and European counterparts: A New Zealand national survey. B J Nutri. 2011;105(3):436-46.
17. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS. How many child deaths can we prevent this year? Lancet. 2003;362:65-71.
18. Bhutta ZA, Ahmed T, Black RE, Cousens S, Dewey K, Giugliani E, et al. What works? Interventions for maternal and child undernutrition and survival. Lancet. 2008;371:417-40.
19. Lassi ZS, Haider BA, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. Cochrane Database System Rev. 2010;(12):CD005978.
20. Roth DE, Richard SA, Black RE. Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials. Internat J Epidemiol. 2010;39(3):795-808.
21. Bao S, Knoell DL. Zinc modulates airway epithelium susceptibility to death receptor-mediated apoptosis. Am J Physiol Lung Cell Mol Physiol. 2006;290:L433–41.
22. Castillo-Duran C, Heresi G, Fisberg M, Uauy R. Controlled trial of zinc supplementation during recovery from malnutrition: effects on growth and immune function. Am J Clin Nutr. 1987;45:602-8.
23. Raqib R, Roy SK, Rahman MJ. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. Am J Clin Nutr. 2004;79:444-50.
24. Baqui AH, Zaman K, Persson LA. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. J Nutr. 2003;133:4150-7.
25. Bhandari N, Bahl R, Taneja S. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomized controlled trial in an urban slum. Br Med J. 2002;324:1358-62.
26. Shann F, Barker J, Poore P. Clinical signs that predict death in children with severe pneumonia. Pediatr Infect Dis J. 1989;8:852-5.
27. Demers AM, Morency P, Mberyo-Yaah F. Risk factors for mortality among children hospitalized because of acute respiratory infections in Bangui, Central African Republic. Pediatr Infect Dis J. 2000;19:424-32.
28. Howie S, Zaman SM, Omoruyi O, Adegbola R, Prentice A. Severe pneumonia research and the problem of case definition: the example of zinc trials. Am J Clin Nutr. 2007;85:242-3.

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