

Original research article

A case-control study to investigate the relation between zinc deficiency and acute lower respiratory tract infections in children**Dr. Krishna Keshav¹, Dr. Girijanand jha², Dr. Sushil Kumar Pathak³, Dr. Binod Kumar Singh⁴****¹Senior Resident, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.****²Senior Resident, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.****³Assistant Professor, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.****⁴Professor and HOD, Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India.****Corresponding Author: Dr. Girijanand Jha****Abstract**

Aim: This study was performed to estimation the relation between zinc deficiency and acute lower respiratory tract infections in children.

Material and Methods: This Case-Control study was done the Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India for 1 years. Total of 220 cases and 110 controls were included in the study. The details of blood investigations and imaging for confirmation of clinical diagnosis were also noted during the stay of the patient in the hospital. The serum zinc estimation was done by using colorimetric test.

Results: The mean age of cases was 1.59 ± 1.38 yrs and that of controls was 1.86 ± 1.77 yrs. The Sex wise distribution of the cases and controls consisted of 68(61.82%) of cases being male and 42(38.18%) being female as compared to 65(59.10%) of controls being male and 45(40.90%) being female. The Mean serum zinc levels in the cases and controls, after comparison, were found to be significantly different ($p=0.0001$), with mean value for the cases being 61.58 ± 10.92 ug/dl as compared to 86.89 ± 14.73 ug/dl for the controls. A total of 29 cases and controls (26.36%) were found to have deficiency of zinc, of which majority (88.18%) were cases (normal range of 60 to 150 ug/dl). Severe Pneumonia group (Mean= 40.19 ± 5.69 ug/dl) having significantly lower value than that of Pneumonia group (Mean= 64.12 ± 6.88 ug/dl). This is also reflected when we see serum zinc levels according to oxygen requirements, with cases managed on room air having mean of 63.65 ± 6.87 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of 59.36 ± 9.77 ug/dl and cases requiring mechanical ventilation having mean of 38.25 ± 6.13 ug/dl (Table 3). The serum zinc analysis of patients according to outcome shows significantly lower zinc values (p value= 0.0001) in cases who eventually died due to the ALRTI and its complications ($n=15$) as compared to those who got discharged after treatment ($n=95$).

Conclusion: we concluded that the zinc deficiency occurs in the majority of recurrent respiratory infection in children and therefore a decreased serum zinc level is considered an additional risk factor for recurrent respiratory infection.

Keywords: Zinc Level, Children, Lower Respiratory Tract Infection.

Introduction

Acute lower respiratory tract infection predominantly pneumonia is a substantial cause of morbidity and mortality.¹ It is the leading cause of mortality and a common cause of morbidity in children below five years of age. In developing countries an estimated 146–159 million new episodes of pneumonia are observed per year.² Zinc is an essential antioxidant mineral that is involved in numerous aspects of cellular metabolism. A potent antioxidant can act against inflammation and prevent the resulting tissue injury.³ Zinc deficient children are at increased risk of restricted growth, developing diarrheal diseases and respiratory tract infections. It is thought to decrease susceptibility to ALRTI by regulating various immune functions including protecting the health and integrity of respiratory cells during lung inflammation and injury. Supplementation of zinc could reduce the risk of pneumonia and the risk and duration of diarrhea, dysentery and malaria deaths among all infectious diseases, and they accounted for 3.9 million deaths worldwide.⁴ Zinc deficiency decreases the ability of the body to respond to infection and also adversely affects both cell-mediated and humeral immune responses. It has a fundamental role in cellular metabolism, with profound effects on the immune system and the intestinal mucosa.^{5,6} The zinc concentration in plasma, hair and urine can be assessed in detecting zinc deficient states but measuring the serum zinc level has been recommended as an appropriate biomarker.^{7,8} The serum concentration is affected by factors such as age, dietary intake and infections.⁸ Children with pneumonia have been found to have lower blood zinc levels as compared to uninfected children.^{9,10} Even in well nourished children with ALRI, serum zinc levels have been found to be lower compared with the uninfected.¹⁰ Trials of zinc supplements also constitute a reliable method of assessing the health consequences of zinc deficiency.⁷ Zinc is an essential antioxidant mineral that is involved in numerous aspects of cellular metabolism. A potent antioxidant can act against inflammation and prevent the resulting tissue injury. In 2009, a systematic review of studies evaluating preventive effects of zinc supplementation on the morbidity burden of ALRI noted an overall reduction of 15-21% in the incidence of ALRI among zinc-supplemented preschool children.¹¹ ALRTI are the leading cause of mortality and a common cause of morbidity in children below five years of age. Most of these deaths are caused by pneumonia and bronchiolitis. Pneumonia kills more children each year than AIDS, malaria or measles combined with more than 2 million deaths per year.¹² The need for the study was to establish that zinc deficiency may lead to LRTI. This study was performed to estimate the relation between zinc deficiency and acute lower respiratory tract infections in children.

Material and methods

This Case-Control study was done the Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India for 1 years. after taking the approval of the protocol review committee and institutional ethics committee. 110 Children between the age of 2 months to 5 years and children with Acute Lower Respiratory Tract infection were include in this study. Children suffering from Acute Gastroenteritis or diarrheal illness, reactive airway disease/asthma or with underlying chronic illnesses and congenital heart disease were exclude from this study.

Total 220 children were included in this study. Thus a total of 110 cases and 110 controls were included in the study. The detailed demographic information, history, clinical findings, laboratory findings and details of clinical course of cases and controls included in the study were entered in predesigned and validated proforma. Socio-economic status was assessed according to the Modified Kuppaswamy scale updated in 2017.¹³ Detailed General examination was carried out in the patients along with Respiratory system and other systemic examination and a clinical diagnosis was made and entered into the proforma. The details of blood investigations and imaging for confirmation of clinical diagnosis were also noted

during the stay of the patient in the hospital. The serum zinc estimation was done by using colorimetric test. The kit used for this study was manufactured by Centromic GMBH, Germany. The Sample used was serum obtained by centrifugation of 2 ml of blood sample collected at 3000 rpm for 3 to 5 minutes. The blood sample was obtained at Day 1 of admission of cases and controls. In two different ependoff tubes, 1000 ul of reagent in both along with 50 ul of serum in one tube and standard solution in other were mixed and incubated at 37⁰ for 5 minutes. Absorption of the standard A (Standard) and the sample A (Sample) was measured against the reagent blank A (Blank) via the spectrophotometer at 560nm wavelength, which was directly proportional to the concentration of total zinc in the sample.¹⁴ Apart from measuring the serum zinc levels, the details of clinical course of the cases were also documented in terms of the duration of stay, oxygen requirements, severity of disease according to WHO IMNCI grading 2014 and outcome of the cases.

Results

The mean age of cases was 1.59±1.38 yrs and that of controls was 1.86±1.77 yrs. The Sex wise distribution of the cases and controls consisted of 68(61.82%)of cases being male and 42(38.18%) being female as compared to 65(59.10%) of controls being male and 45(40.90%) being female. On comparison, the distribution of cases and controls in this study according to age, sex, nutritional status and socioeconomic status was statistically not significant.(table.1)

Table 1: Demographic profile of children

Parameter	Cases	Controls
Age(mean)	1.59±1.38 yrs	1.86±1.77 yrs
Sex		
Male	68(61.82%)	65(59.10%)
Female	42(38.18%)	45(40.90%)

The Mean serum zinc levels in the cases and controls, after comparison, were found to be significantly different [p=0.0001], with mean value for the cases being 61.58 ± 10.92 ug/dl as compared to 86.89 ± 14.73 ug/dl for the controls (Table 1).A total of 29 cases and controls (26.36%) were found to have deficiency of zinc, of which majority (88.18%) were cases (normal range of 60 to 150 ug/dl) .(Table 2)

Table 2: Comparison of Zinc level in cases and controls

Group	N	Mean(ug/ dl)	Std. Deviation(ug/ dl)	Std. Error Mean	t-value
Cases	110	61.58	10.92	1.41	11.12,
Controls	110	86.89	14.73	2.19	p=0.0001,S

Table 3 shows comparison of serum zinc levels according to the clinical characteristics of cases. Here, the difference in mean serum zinc levels of cases according to WHO IMNCI grading was statistically significant (p value=0.0001) with cases belonging to Severe Pneumonia group (Mean=40.19 ± 5.69 ug/dl) having significantly lower value than that of Pneumonia group (Mean=64.12 ±6.88 ug/dl).This is also reflected when we see serum zinc levels according to oxygen requirements, with cases managed on room air having mean of 63.65 ± 6.87 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of 59.36 ±9.77 ug/dl and cases requiring mechanical ventilation having mean of 38.25 ±6.13 ug/dl(Table 3). The serum zinc analysis of patients according to outcome shows significantly lower zinc values (p value=0.0001) in cases who eventually died due to the ALRTI and its complications (n = 15) as compared to those who got discharged after treatment (n=95)(Table 3)

Table 3: Zinc level according to clinical characteristics in cases

IMNCI Grading	No of cases	Mean(ug/dl)	SD	t-value
Pneumonia	75(68.18%)	64.12	6.88	9.87 p=0.0001,S
Severe Pneumonia	35(31.82%)	40.19	5.69	
Total	110(100%)	57.22	11.27	
O2 Requirement				
Room Air	42(38.18%)	63.65	6.87	33.22 p=0.0001,S
Supplemental Oxygen	38(34.55%)	59.36	9.77	
Mechanical Ventilation	30(27.27%)	38.25	6.13	
Outcome				
Discharge	95(86.36%)	58.45	10.74	36.45 p=0.0001,S
Death	15(13.64%)	39.77	5.87	

The mean serum zinc level was found to have a negative correlation ($r' = -0.049$) with the duration of stay of cases, however, this correlation was statistically not significant (p value = 0.644)

Discussion

Pursuant to data published by World Health Organization, 10.5 million children under the age of 2 across the world lose their lives due to preventable and curable 5 diseases every year. Respiratory tract infections are responsible for 28% of all these deaths. The mean serum zinc levels were comparable to that found in the study by Hussain et al.¹⁵ A study in Bangladesh by Shakur et al. and a study in Egypt by Rady et al. showed mean serum zinc levels in cases to be higher than this study.^{16,17} On the other hand, a study done by Ibraheem et al. in Nigeria showed mean serum zinc levels of cases to be lower than this study.¹⁸ This variation of mean zinc values can be ascribed to the dietary habits of the country and nutritional status of the subjects of the study as a whole.¹⁶⁻¹⁸ The difference in serum zinc levels of the cases and controls in this study, as well as in the above mentioned studies is statistically significant (p value=0.0001). Study by Kumar et al. in India and Arica et al in Greece also showed similar results.^{19,20} These finding could be explained by the fact that serum zinc level is decreased by interleukins and tumour necrosis factor alfa as a part of a cute phase reaction in response to inflammatory stimulus.¹⁹ The difference in mean serum zinc levels of cases according to WHO IMNCI grading was statistically significant (p value = 0.0001) with cases belonging to Severe Pneumonia group (Mean=40.19 \pm 5.69 ug/dl) having significantly lower value than that of Pneumonia group (Mean=64.12 \pm 6.88 ug/dl) and similar findings were seen in study by Rady et al., Hussain et al. and Brooks et.al.^{15,17,21} This may be due to the fact that in zinc deficiency, there is loss of immunomodulatory effect of zinc causing unregulated immune response in the respiratory tract, leading to increased airway injury.²¹ However, evidence to the contrary was found in studies by Bose et al. and Valentiner - Branth et al.^{22,23} Argument has been put by the above studies that as zinc is required to mount a better immune response by the host against infection, there will be increased damage to the respiratory epithelium due to the increased immune response and thus leading to worsening of symptoms.²³ Regarding the duration of stay of cases, Basnet et al. also found lower duration of stay in zinc supplemented group as compared to placebo, but similar to our study, the difference was statistically not significant. However, Brooks et al., Singh et al. and Malik et al. found significant reduction in duration of stay of patients of ALRTI after supplementation of Zinc.^{21,24,25} Meanwhile, Bose et al., Valentiner-Branth et al. and Yuan et al found the supplementation of zinc either had no benefit or increased the duration of stay of patients of ALRTI.^{22,23,26} A similar trend is also seen while evaluating the patients in terms of oxygen requirement during treatment. In this study with cases managed on room air having mean of 63.65 \pm 6.87 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of

59.36 \pm 9.77 ug/dl and cases requiring mechanical ventilation having mean of 38.25 \pm 6.13 ug/dl. While studies by Rady et al. and Brooks et al. concur with the findings of our study, studies by Bose et al. and Valentiner-Branth et al. have found no significant reduction of oxygen requirement.^{17,21-23} When comparing the outcome of cases according to serum zinc levels, the findings of our study were in concordance with Rady et al., Brooks et al. and Basnet et al.^{17,21}. Also, a large systematic review of zinc supplementation by Mayo- Wilson et al. found that giving children zinc supplements might reduce their risk of death in general, and their risk of death due to lower respiratory tract infection.²⁸

Conclusion

We concluded that the zinc deficiency occurs in the majority of recurrent respiratory infection in children and therefore a decreased serum zinc level is considered an additional risk factor for recurrent respiratory infection.

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