Original research article

A case-control study to assess the outcome of administering zinc sulphate on improving the clinical symptoms of the children diagnosed with pneumonia

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Abstract

Aim: This study was investigating the effect of prescribing zinc sulphate on improving the clinical symptoms of pneumonia in children below 60 months of age.

Material and Methods: This Case-Control study was done the Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India for 12 months. Among 300 patients divided into two equal groups. 150 Children between the age of 2 months to 59 months and children with Acute Lower Respiratory Tract infection were included in case group and 150 children for control group. 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 1.63±1.44 yrs and that of controls was 1.77±1.85 yrs. The Sex wise distribution of the cases and controls consisted of 91(60.67%) of cases being male and 59(39.33%) being female as compared to 87(58%) of controls being male and 63(42%) 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 58.98 ± 10.22 ug/dl as compared to 85.12 ± 12.12 ug/dl for the controls. A total of 42 cases and controls (28%) were found to have deficiency of zinc, of which majority (89.29%) were cases. Severe Pneumonia group (Mean=39.95±5.98ug/dl) having significantly lower value than that of Pneumonia group (Mean=63.78 ±6.76 ug/dl). According to oxygen requirements, with cases managed on room air having mean of 66.11±7.22 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of 63.23±10.29 ug/dl and cases requiring mechanical ventilation having mean of 41.17±7.88 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=17) as compared to those who got discharged after treatment (n=133).

Conclusion: we concluded that the low serum level of zinc was seen in severe pneumonia cases. Serum zinc levels were found to be lower in risk factors of LRTI like poor nutritional status, anemia, vitamin A deficiency, low birth weight and formula fed patients. Zinc supplementation is required in LRTI patients especially those with the above mentioned risk factors.

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

Introduction

According to WHO, annually 4.1 million deaths occur worldwide due to acute respiratory infections (ARIs), with 90% being due to acute pneumonia. Specifically, 1.9 million of them are children younger than five years old[1], mostly related to developing countries because of malnutrition.[2] Meanwhile, lower respiratory tract infections and especially pneumonia constitute around 20% of the causes of pediatric mortality; per every 1000 live children born in developing countries, 12-20 children die before the age of five because of pneumonia.[1,3,4] By definition, lung inflammation is called pneumonitis, and if the cause of this inflammation is a microbial agent, it is called pneumonia. Microbial agents can include bacterial, viral, or parasitic. According to WHO, clinically, pneumonia involves acute cough attacks with or without fever associated with respiratory problems or tachypnea.[5] According to this definition, fever and tachypnea have high sensitivity and low specificity, while auscultating pulmonary crackles or pleural pain have high specificity and low sensitivity in diagnosing pneumonia.[6] Zinc is an essential mineral that is involved in numerous aspects of cellular metabolism. It is required for the catalytic activity of approximately 100 enzymes[7,8] and it plays a role in immune function,[9,10] protein synthesis,[10] wound healing,[11] DNA synthesis,[8,10] and cell division.[10] It is required for maintaining intestinal cells, bone growth and immune function. It is second to iron as the most abundant trace element in the body. Zinc deficient children are at increased risk of restricted growth and developing diarrheal diseases and respiratory tract infections. Zinc is thought to decrease susceptibility to Acute Lower Respiratory Tract Infection (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.[11] According WHO estimates respiratory infection cause about 987,000 deaths in India of which 969,000 are LRTI.[12] 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.[13] The need for the study was to establish that zinc deficiency may lead to LRTI. The study was investigating the effect of prescribing zinc sulphate on improving the clinical symptoms of pneumonia in 2 to 59 months of children's.

Material and methods

This Case-Control study was done the Department of Paediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India for 12 months. Among 300 patients divided into two equal groups (150 cases and 150 controls) were included in the study. 150 Children between the age of 2 months to 59 months and children with Acute Lower Respiratory Tract infection were include in case group. Children suffering from Acute Gastroenteritis or diarrheal illness, reactive airway disease/asthma or with underlying chronic illnesses and congenital heart disease were excluded from this 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 Kuppuswamy scale updated in 2017.[14] 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 37^0 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 560 nm wavelength, which was directly proportional to the concentration of total zinc in the sample.[15] 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 1.63±1.44 yrs and that of controls was 1.77±1.85 yrs. The Sex wise distribution of the cases and controls consisted of 91(60.67%)of cases being male and 59(39.33%) being female as compared to 87(58%) of controls being male and 63(42%) 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)	1.63±1.44yrs	1.77±1.85 yrs
Sex		
Male	91(60.67%)	87(58%)
Female	59(39.33%)	63(42%)

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 58.98 ± 10.22 ug/dl as compared to 85.12 ± 12.12 ug/dl for the controls (Table 1). A total of 42 cases and controls (28%) were found to have deficiency of zinc, of which majority (89.29%) 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	150	58.98	10.22	1.68	10.66, p=0.0001,S
Controls	150	85.12	12.12	2.55	

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=39.95 ± 5.98 ug/dl) having significantly lower value than that of Pneumonia group (Mean=63.78 ±6.76 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 66.11 ± 7.22 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of 63.23 ±10.29 ug/dl and cases requiring mechanical ventilation having mean of 41.17 ±7.88 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 = 17) as compared to those who got discharged after treatment (n=133)(Table 3)

Table 3: Zinc level according to clinical characteristics in cases

IMNCI Grading	No of cases	Mean(ug/dl)	SD	t-value
Pneumonia	102(68%)	63.78	6.76	9.21 p=0.0001,S
Severe Pneumonia	48(32%)	39.95	5.98	
Total	150(100%)	56.71	10.88	
O2 Requirement				
Room Air	63(42%)	66.11	7.22	35.09 p=0.0001,S
Supplemental Oxygen	48(32%)	63.23	10.29	
Mechanical Ventilation	39(26%)	41.17	7.88	
Outcome				
Discharge	133(88.67%)	61.66	12.20	39.12 p=0.0001,S
Death	17(11.33%)	40.98.	6.09	

The mean serum zinc level was found to have a negative correlation ('r' = -0.045) with the duration of stay of cases, however, this correlation was statistically not significant (p value = 0.712)

Discussion

One explanation for lower zinc level in severe respiratory tract infection can be pre-existing deficiency making these children susceptible to respiratory tract infection due to impaired immunity. In addition, LRTI are also known to result in lower zinc levels in response of cytokines Interleukin 6 (IL-6) which causes shifting of zinc from plasma to liver. The other hypothesis could be explained by the effect of zinc on the extent of inflammation and its resolution rate surrounding infection. Zinc supplementation may be protective to lung parenchyma against the inflammatory mediators and conditions, therefore its deficiency may increase airway damage, inflammation and cellular damage. It has also been seen that in the presence of zinc, there is decreased inflammation of other organ systems of the body with increased bacterial inhibition and cellular regeneration. Thus, zinc may have important role in reduction of inflammation and decrease lower airway obstruction, in supplemented children and thus leading to faster inflammation resolution time. This leads to shorter duration of chest in-drawing, tachypnea and hypoxia. This finding was also observed in previous studies in which serum zinc level was significantly higher at the discharge than at baseline which shows cessation of acute phase response. De Raeve HR et al have reported a decreased Zn-SOD activity airway and Zinc serum in children with lower respiratory tract infection.[16,17] Further Meeks-Gardner J et al have shown a positive Zinc supplementation in these patients.[18] The mean serum zinc levels were comparable to that found in the study by Hussain et al.[19] 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.[20,21] 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[22] 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.[20-22] 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.[23,24] 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.[23] 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=39.95 ± 5.98 ug/dl) having significantly lower value than that of Pneumonia group (Mean=63.78 ±6.76 ug/dl) and similar findings were seen in study by Rady et al., Hussain et al. and Brooks et.al.[19,21,25] 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.[25] However, evidence to the contrary was found in studies by Bose et al. and Valentiner - Branth et al.[26,27] 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.[27] 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.[25,28,29] 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.[26,27,30] 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 66.11 ± 7.22 ug/dl, cases requiring supplemental oxygen by nasal prongs having mean of 63.23 ±10.29 ug/dl and cases requiring mechanical ventilation having mean of 41.17 ±7.88 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.[21,25-27] 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.[21,25,31]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.[32]

Conclusion

We concluded that the Conclusion: low serum level of zinc was seen in severe pneumonia cases. Serum zinc levels were found to be lower in risk factors of LRTI like poor nutritional status, anemia, vitamin A deficiency, low birth weight and formula fed patients. Zinc supplementation is required in LRTI patients especially those with the above mentioned risk factors.

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