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Serum zinc levels in children hospitalized with pneumonia: A cross sectional study

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Abstract

Background: Pneumonia is the leading cause of morbidity and mortality in children aged below 5 years. Pneumonia is responsible for about 19% of all deaths in this age group. As per the data published by World Health Organization, 10.5 million children under the age of 2 years across the world lose their lives due to 5 preventable and curable diseases every year. Respiratory tract infections are responsible for 28% of all these deaths. Of the total 156 million new episodes each year worldwide, approximately 43(24%) million cases take place in India. Approximately 95% of pneumonia related deaths occur in developing countries and the youngest age group has the highest risk of death.

Zinc is known to protect children from respiratory tract infections by its role in regulation of immunomodulators, immuno regulators, protection of the epithelium of the respiratory tract from infections and improvement of T-lymphocytes.

Zinc is also an important antioxidant and a cytoprotective agent which acts against toxins and inflammatory mediators which damage the respiratory epithelium. Even a mild and moderate deficiency of Zinc impairs the function of the immune system, thus resistance against the infections is reduced and T-lymphocytes could not exhibit sufficient effectiveness. Recent works have provided conflicting evidence on the role of zinc against pneumonia. While some studies, report that there are no significant difference in blood zinc levels in pediatric pneumonia, some other studies have shown significant reduction in the blood zinc levels in pediatric pneumonia when compared to controls.

Hence the present study was conducted with an intent to estimate serum zinc levels in pediatric Pneumonia.

Objectives:

1. To study Serum zinc levels in children hospitalised with pneumonia
2. To assess the correlation between serum zinc levels and severity of pneumonia and its complications.

Methodology of Study: This cross sectional study included 100 subjects aged between 6 months and 5 years. A detailed history, clinical examination, chest X-ray findings, arterial oxygen saturation(SpO₂), haemoglobin (g/dl), WBC count and serum zinc levels(micg/dl) was noted.

Results: Mean serum zinc levels in cases was significantly low compared to age and sex matched controls (p value-0.001). Low serum zinc levels was associated with increasing severity of pneumonia (Pneumonia-120.4/dl, severe pneumonia-64.7/dl, very severe pneumonia-40.7 /dl). Mean serum zinc levels in complicated pneumonia and death cases was very low compared to those with no complications and who were discharged. Low serum zinc levels were associated with prolonged hospital stay. Indoor smoking emerged as a significant risk factor for pneumonia.

Conclusion: Serum zinc levels is low in children with pneumonia and Low serum zinc levels is associated with increased severity of pneumonia. Children who died had low serum zinc levels, hypoxia, features suggestive of shock and radiological features of bilateral interstitial infiltrate. Serum zinc levels measured at the time of admission is a better predictor of mortality. When used in conjugation with other risk factors like young age, hypoxia, shock, serum zinc levels play a role in identifying sick child with pneumonia going for complication.

Keywords: Serum zinc, pneumonia, mortality

Introduction

Globally, pneumonia represents 18% of mortality in children under 5 years of age and the main infectious purpose of early life mortality. Acute Respiratory infections (ARI) may cause inflammation of the respiratory tract anywhere from nose to alveoli. The upper respiratory tract infections include common cold, pharyngitis, otitis media. The lower respiratory tract infections include epiglottitis, Laryngitis, laryngotracheitis, bronchitis, bronchiolitis and pneumonia^[1]. Pneumonia is a severe form of acute lower respiratory

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Globally, pneumonia represents 18% of mortality in children under 5 years of age and the main infectious purpose of early life mortality. Acute Respiratory infections (ARI) may cause inflammation of the respiratory tract anywhere from nose to alveoli. The upper respiratory tract infections include common cold, pharyngitis, otitis media. The lower respiratory tract infections include epiglottitis, Laryngitis, laryngotracheitis, bronchitis, bronchiolitis and pneumonia [1]. Pneumonia is a severe form of acute lower respiratory infection that specifically affects lungs [2]. Pneumonia has been recognised as a common and potentially lethal condition for nearly two centuries and over 80 per cent of the cases have been found to be due to streptococcus pneumoniae. Physical findings include fever in 80 per cent of patients; most have a respiratory rate exceeding 20 breaths per minute; crackles are heard on auscultation in 80 per cent; and up to 30 percent have signs of consolidation. Mortality varies depending on the etiologic organism and host defense status; for outpatients, the mortality is low at about 5% with even higher rates for patients requiring intensive care unit (ICU) stay. Radiographic changes usually cannot be used to distinguish between bacterial and non-bacterial pneumonia, but they are often important for evaluating the severity of the illness and in determining the need for diagnostic studies.

Most of the ARI result in mild illnesses such as common cold, but in vulnerable children, infections that begin with mild symptoms may sometimes lead to more severe illnesses such as pneumonia [2].

The annual global incidence of pneumonia is 158 million new cases per year out of which 154 million are occurring in developing countries. Pneumonia is estimated to cause 3 million deaths or an estimated 29% of all deaths among children younger than 5 year of age worldwide. Incidence of pneumonia is more than 10 fold higher and number of deaths due to pneumonia is 2000 fold higher in developing than in developed countries.

Zinc is an essential trace element, which plays an important role in many important biological functions. These include mucosal barrier function, innate and adaptive immunity, oxidative stress responses and a cofactor for various enzymes. Trace elements, especially zinc is a cornerstone of the antioxidant defence in acute systemic inflammatory response syndrome (SIRS). SIRS is known to be associated with redistribution of zinc to the tissues involved in protein synthesis and immune cell proliferation and this leads to decrease in its serum level. Acquired critical illness stress-induced immune suppression (CRISIS) plays an important role in the development of nosocomial infection and sepsis. CRISIS has been shown to be associated with deficiencies in zinc, selenium, amino acids and hypoprolactinemia. Zinc deficiency has been responsible for up to 4.4% of deaths attributable to infection in developing countries. Various studies from India demonstrated that prevalence of zinc deficiency in apparently healthy children and adolescents ranged from 44% to 72% [7, 8].

Prophylactic zinc supplementation for 2 weeks may reduce the morbidity attributable to acute lower respiratory infections but the not overall rate of acute respiratory infections in infants aged 6-11 months in similar populations [9]. There is a higher pneumonia risk in a population with zinc deficiency. The aim of our study is to compare the level of serum zinc in children with pneumonia with age, sex, and nutritional matched healthy controls.

Objectives

1. To determine the serum levels of zinc in children (2 months to 5 years of age) hospitalised with pneumonia as compared to children hospitalised without pneumonia.
2. To study the correlation between the levels of serum zinc and severity of pneumonia and its complications.

Methodology

This Study was a cross sectional study conducted at SIMS, Hyderabad. All children between 2 months and 5 years of age admitted to Pediatric wards of SIMS Hospital, with pneumonia, severe pneumonia and very severe pneumonia graded according to WHO criteria were taken as cases. Children aged between 2 months and 5 years of age admitted to pediatric wards of SIMS Hospital for other than pneumonia were taken as controls. This is a Cross sectional study.

Inclusion criteria

Children between 2 months and 5 year of age admitted to NICU with a diagnosis of pneumonia (of any severity) according to WHO criteria.

Exclusion criteria

Children diagnosed as Protein energy malnutrition according to Indian academy of Pediatrics classification or as severe acute malnutrition according to WHO criteria. Children with associated diarrhoea. Children who are on Zinc supplements or who have received Zinc supplements in the past 6 months.

Method of study

Sample size was 100. A total of 50 children between 2 months and 5 years of age admitted to Hospital during the study period fulfilling the inclusion criteria were included in the study and 50 normal, age, sex matched children were taken as controls. A written informed consent was taken from the parents/guardian of all children after fully explaining the study procedure. A detailed history, demographic data, clinical examination, severity of pneumonia according to WHO criteria, chest X-ray findings consistent with pneumonia, arterial oxygen saturation measured by pulse oximetry (SpO₂), haemoglobin (g/dl), total WBC count, serum zinc levels (g/dl) were noted.

Results

The present study was conducted from January 2019-january 2021 A total of 100 cases of pediatric pneumonia cases fulfilling the inclusion criteria were selected. Sixty age and sex matched healthy subjects were selected as controls. The study was conducted at SIMS, Hyderabad. Study included 100 cases with pneumonia. Among them, 60 were males (60%) and 40 were females (40%). There was no statistically significant difference in sex distribution between cases and controls. Hence, cases and controls were similar in terms of sex distribution. Most of the cases i.e., 70 (70%) was seen in the age group of 7 months to 18 months. There was no statistically significant difference between cases and controls. Out of 100 cases, 83 (83%) children were exclusively breastfed till 6 months of age. 8 (8%) were started on complementary feeding even before completion of 6 months of age. Similar observation was also seen among controls. Sixty eight (68%) children out of 100 cases

were continued with breastfeeding along with complementary feeding till 2 years of age. While in control group only 32 (32%) were continued with breastfeeding till 2 year. However, there was no statistically significant difference among cases and controls in terms of continued breastfeeding till 2 years of age. Eighteen (18.0%) out of 100 cases had overcrowding at home compared to 8 (8%) among control group. There is no statistical significant difference between cases and controls in terms of overcrowding.

Overcrowding is considered to exist if two persons over 9 years of age, not husband and wife, of opposite sexes are obliged to sleep in the same room. Best expressed as number of persons per room. One room – 2 person, 2 room – 3 person, 3 room – 5 person, 4 room – 7 person, 5 room – 10 person. Children under 12 months not counted, children between 1-10 yrs. as half unit. The former definition was used in the present study.

Out of 100 cases, 25 (25%) were exposed to indoor smoking compared to only 10 (10%) among control group. There is a statistically significant difference among cases and controls in terms of exposure to indoor smoking. Hence, exposure to indoor smoking can be taken as a risk factor for developing pneumonia.

Indoor smoking-Was taken in consideration if there is a family history of passive smoking or second hand smoking. Ventilation was poor in 24 (24.0%) cases out of 100 compared to 15 (15%) among controls. There was no statistically significant difference among cases and controls in terms of ventilation.

Adequate ventilation was considered if 2 windows were present in one room facing different direction. Mean serum zinc levels in pneumonia cases was 103.6 g/dl and in controls mean serum zinc levels was 168.82 g/dl. The difference in mean serum zinc between controls and cases was 62.22 g/dl which was statistically significant (p value 0.001).

Table 1: Comparison of mean serum zinc levels among cases and controls

	Controls [?]	Cases
Mean serum zinc (g/dl)	166.82	103.6

P value 0.001

Present study showed more number of cases in the age group of 7 months to 18 months (70 out of 100 approximately 70%). Hence mean serum zinc values and standard deviation was calculated for the above group due to significant scattering of cases. The mean serum zinc was found to be 132.15 g/dl in cases between 7 months and 12 months and 82.5 g/dl in cases between 13-18 months. There is no statistically significant difference among cases with respect to different age group.

Table 2: Age-wise distribution of mean serum zinc levels among cases

Age group (months)	Number	Mean serum zinc (g/dl)
<6	5	70.1
7-12 [?]	25	132.15
13-18	12	82.5
19-24	8	79.8
>24	10	98.1

P value 0.409

Out of 100 cases, 60 (60%) were males and 40 (40%) were females. The mean serum zinc levels among males and females were 108.15 g/dl and 69.9 g/dl respectively.

There is no statistically significant difference among cases in terms of gender.

Table 3: Gender-wise distribution of mean serum zinc levels among cases

Gender	Number	Mean serum zinc (g/dl)
Males	60	108.15
Females	40	69.9

P value 0.616

Mean serum zinc values among pneumonia cases was 120.4 g/dl. It was 64.7 g/dl and 40.7 g/dl among cases with severe pneumonia and very severe pneumonia respectively. Thus there was inverse relationship between serum zinc levels and severity of pneumonia. Though mean serum zinc levels is decreasing with the severity of pneumonia, p value fell short of <0.05. Hence statistically significant difference was not seen.

Table 4: Mean serum zinc levels and severity of pneumonia among cases

Grading of pneumonia	Number	Mean serum zinc (g/dl)
Pneumonia	62	120.4
Severe pneumonia	31	64.7
Very severe pneumonia	7	40.7

P value 0.058

Out of 100 cases, 32 were hypoxic at the time of admission. Serum zinc levels among hypoxic children was found to be very low (50.27 g/dl). There is statistically significant difference between serum zinc levels and SpO2 (oxygen saturation) at the time of admission among pneumonia cases

Table 5: Comparison of mean serum zinc levels and SpO2 (oxygen saturation) among cases

SpO2	Number	Mean serum zinc (g/dl)
≤94%	32	50.27
>94%	68	113.7

P value 0.033

Ten cases out of 100 cases with features suggestive of shock had very low serum zinc concentration (42.21 g/dl). Serum zinc levels among those without shock was 110.65 g/dl. There is no statistically significant difference between serum zinc levels and shock at the time of admission among pneumonia cases.

Most of the cases with pneumonia had leucocytosis which is probably due to bacterial infection and mean serum zinc in them was found to be 104.2 g/dl. While mean serum zinc in those cases with normal leucocyte count was 101.2 g/dl. There is no statistically significant difference between serum zinc levels and total leucocyte count among study group.

Forty-two out of 100 cases were found to be anemic. The mean serum zinc in this group was 82.01 g/dl. Mean serum zinc in non-anemic group was 112.3 g/dl. There is no statistically significant difference between serum zinc levels and haemoglobin values among pneumonia cases.

Thirty-nine cases out of 100 had features of bilateral interstitial infiltrate on chest X-ray. Mean Serum zinc in this group was 70.5 g/dl. 18 cases had features of peribronchial

cuffing and 3 cases had consolidation on chest X-ray. There is statistically significant difference between serum zinc levels and X-ray finding among cases. Cases with bilateral interstitial infiltrate had low serum zinc levels which is statistically significant. Out of 100 cases, 7 cases developed empyema as complication. The mean serum zinc in them was found to be 62.0 g/dl. Mean serum zinc in those without empyema was 98.2 g/dl. There is no statistically significant difference between mean serum zinc levels and complications among cases.

Out of 100 cases, 8 cases with pneumonia expired. The mean serum zinc in death cases was found to be very low (30.6 g/dl). 92 cases were discharged. Though the mean serum zinc levels was very much low in death cases, statistically significant difference was not seen between mean serum zinc levels and outcome among cases.

Inverse relation was seen between duration of hospital stay and mean serum zinc levels. Those with prolonged duration of stay in hospital had very low zinc values.

Discussion

Pneumonia is one of the most important causes of under five deaths in India. More than 1.1 million under five years of age children die from pneumonia every year accounting for almost 17% under five deaths worldwide.

Most of the deaths can be prevented by appropriate treatment. Zinc is a trace element and an essential mineral which is present in all tissues, fluids and secretions in the body. It plays an important role in the cellular metabolism, physical growth, immuno competence, reproductive functions, integrity of intestinal mucosa and neuro behavioural development.

It has been hypothesized that zinc functions as intercellular hormone contributing to regulation of cellular growth and also impacts on nucleic acid metabolism and protein synthesis. Zinc deficiency is associated with decreased immuno competence, high rates of serious infections such as skin infection, diarrhoea, respiratory infection, malaria¹³ and delayed wound healing. Thus zinc supplementation help in faster recovery and reduces the mortality due to pneumonia. Most of the cases in the present study were in the age group 7 months' to 18 months (70%). The fact that infants and toddlers constituted the majority of the cases is in accordance with other studies. Increased susceptibility of this group may be due to decreased immunity making them more prone for infections. Present observation of stepwise decrease in age specific disease burden with increasing age is in accordance with other studies.

Another important demographic observation in the present study was an overall male preponderance which is consistent with other studies.

In the present study, the following environmental risk factors for pneumonia was analysed-overcrowding, poor ventilation, indoor smoking, bio mass fuel usage.

Overcrowding-Overcrowding is considered to exist if two persons over 9 years of age, not husband and wife, of opposite sexes are obliged to sleep in the same room. Best expressed as number of persons per room. One room – 2 person, 2 room – 3 person, 3 room – 5 person, 4 room – 7 person, 5 room – 10 person.

Children under 12 months not counted, children between 1-10 yrs. as half unit. V Ventilation-Adequate ventilation was considered if 2 windows were present in one room facing different directions.

Indoor smoking-Was taken in consideration if there is a family history of passive smoking or second hand smoking. Second hand smoke is smoke from burning tobacco products such as cigarettes, cigar or pipes or smoke that is exhaled or breathed out by person smoking.

Significant association was seen between indoor smoking and incidence of pneumonia (p value-0.031). Children who are exposed to indoor smoking are at increased risk of developing pneumonia. Environmental tobacco smoke (ETS) contains over 4000 chemicals in the form of particles or gases. ETS is a combination of side stream smoke emitted from the burning end of a cigarette and the remainder of main stream smoke exhaled by a smoker. Side stream smoke constitutes about 80% of smoke present in the room where active smoker smoke and contains many potential lytoxic components. The particulate phase consists of tar, nicotine, benzopyrene and hundreds of other noxious compounds. Gases in tobacco smoke are carbonmonoxide, benzene, ammonia, dimethylnitrosamine, formaldehyde, hydrogen cyanide and acrolein. Passive smoking increases the risk of lower respiratory tract infections like bronchitis, pneumonia and bronchiolitis. Tobacco smoking reduces the local defence mechanisms and predisposes the children to respiratory tract infections.

Studies have shown that parental smoking is an important cause of lower respiratorytract infection.

Study done by Hussain MA *et al.*^[10] on 'Estimation of Zinc Levels in Children With Lower Respiratory Tract Infections: A Prospective Observational Study from India' studied overcrowding, ventilation, smoke exposure, housing standards as a risk factors for pneumonia and found no significant difference between incidence of pneumonia and these risk factors. Another study done by Kumar S Aswathi *et al.*^[11] on 'Blood zinc levels in children hospitalised with severe pneumonia: A case control study' found that use of bio mass fuels (Coal, wood, dung and kerosene) was significantly associated with severe pneumonia. But in our study though use of biomass fuel was more among cases (16.7% cases and 10% controls) it did not emerge as a statistically significant risk factor for pneumonia (p value-0.484). Biomass fuel like firewood are burnt within complete combustion generating lot of toxic products that adversely affects specific and non-specific local defence mechanisms of respiratory tract.

Duration of breast feeding did not had any association with the occurrence of pneumonia in our study. Most of the cases (93.3%) and controls (96.7%) were exclusively breastfed till 6 months of age. Similar observation was seen in a study done by Kumar N *et al.* 'Low serum zinc levels – a possible marker of severe pneumonia'^[12].

Breast milk is known to fight against infections by virtue of its immunological properties. Breast milk contains various antibodies against Respiratory syncytial virus and also high concentration of C3, IgA antibodies and lactoferrin which protects against gram negative organisms.

In the current study, mean serum zinc levels in cases with pneumonia was significantly low compared to healthy age and sex matched controls (p value- 0.001).The finding of lower zinc levels in children with pneumonia compared with controls is consistent with earlier studies by Kumar S Aswathi *et al.*,^[11] Ram B Devraajani^[13], and Kumar N *et al.*^[12] However the magnitude of relative differences in serum zinc levels between children with pneumonia and controls in the earlier reports is less than that of current

study (65.22 g/dl). The low magnitude of difference in serum zinc levels between controls and cases in earlier reports may be due to better nutritional status of study subjects in those reports.

The high prevalence of low serum zinc levels in current study may be due to local food habits rich in phytates and fibre contents which potentially inhibit the absorption and utilization of zinc. It may also be due to pre-existing zinc deficiency state due to inadequate intake of food containing zinc or decreased absorption which is commonly seen in developing countries.

Zinc is known to protect children from respiratory tract infection by its role in immunomodulation, protection of epithelium of respiratory tract from infections and improvement of T lymphocytes function. 24 Even a mild to moderate zinc deficiency impairs the function of immune system. 26 The benefit of zinc supplementation to prevent and decrease severity of pneumonia is mainly due to correction of zinc deficiency. The finding of low zinc levels in pneumonia favour this.

There was a statistically significant difference between serum zinc levels and severity of pneumonia. We observed serum zinc levels in pneumonia was 120.4 g /dl and in severe pneumonia and very severe pneumonia 64.7 g /dl and 40.7 g /dl respectively. This is in accordance with earlier studies. Study by Hussain AM *et al.* on 'Estimation of zinc levels in children with LRTI' reported low serum zinc levels in cases with severe pneumonia than with pneumonia cases. Zinc deficiency leads to increased apoptosis of pre-B and pre-T cells resulting in lymphopenia and decreased B cell production. In zinc deficient individuals, there is a decrease in Th1 function leading to decreased IL-2 and IFN-g. This results in impairment in the function of natural killer cells and cytolytic activity of T cells. IL-10 is increased in zinc deficiency which results in increased production of IL-1B, IL-8 and TNF- α . Therefore overall the programming of the immune system is impaired, decreasing the NK cell activity in zinc deficiency [16].

Zinc is also known to inhibit free NFkB translocation to the nucleus, thus preventing pro inflammatory cytokines gene expression. 22 The NF-kB pathway is activated rapidly in humans in response to sepsis. Activation of NF-kB pathway though important in triggering innate immune response, prolonged activation is associated with increased lung injury, compromised tissue oxygenation and subsequent dysfunction of other vital organs [14].

Thus Zinc deficiency enhances the activity of NF-kB pathway thereby causing more severe extensive inflammation and injury in lungs and more severe pneumonia.

Many earlier studies have reported lower serum zinc levels in cases with pneumonia. But a very few studies have studied the association between serum zinc levels and various clinical parameters like SpO₂, shock, anemia, total count, X-ray findings, complications, duration of stay and outcome of cases. One study from Mangalore by Hussain AM *et al.* has studied the association between severity of pneumonia and X-ray finding and anemia and reported that there is no statistically significant difference between anemia and severity of pneumonia. Pulmonary infiltrate on X-ray was the common finding with pneumonia cases [36]. similar observation is seen in our study. In the present study, 65% cases had features of bilateral interstitial infiltrate on X-ray, 30% had peribronchial cuffing and 5% had

consolidation on X-ray. Accordingly serum zinc levels was 78.5 g/dl, 120.9 g/dl and 265.8 g/dl in each group. Thus bilateral interstitial infiltrate was associated with low serum zinc levels and very severe pneumonia.

Study by Kumar N *et al.* [12] reported that there is no significant difference between duration of hospital stay and mean serum zinc levels. Though statistically not significant, inverse relation was seen between duration of hospital stay and mean serum zinc levels in the present study. Those with prolonged duration of stay in hospital had very low zinc values.

Zinc has an antioxidant and anti-inflammatory properties. Zinc is also known to lower reactive oxygen species (ROS) accumulation during infection. ROS are said to induce cell death (apoptosis) through activation of Fas apoptotic receptor in the lung epithelial cells by down regulation of apoptosis inhibitory proteins. This effect is reversed by antioxidant scavenging enzymes glutathione peroxidase and SOD for which zinc acts as cofactor. Zinc also acts as growth factor for regeneration of damaged epithelial cells, a process needed for restoration of damaged lungs following severe pneumonia. 22 Thus zinc deficiency impairs faster restoration of damaged lung tissue to normal and thereby causing prolonged hospital stay [15].

Current study has found statistically significant difference between serum zinc levels and SpO₂ at the time of admission (p value – 0.033). Those with SpO₂ \leq 94% had serum zinc of 53.27 g/dl and those with SpO₂ $>$ 94% had 113.7 g/dl. Cases of pneumonia with shock had very low serum zinc levels than those without shock though the difference was not statistically significant. Various studies have shown that pneumonia, severe and very severe pneumonia cases were associated with significantly low blood oxygen saturation (SpO₂). But earlier studies have not reported relation between serum zinc levels and SpO₂ at time of admission and shock.

Conclusion

Serum zinc levels is low in children with pneumonia and Low serum zinc levels is associated with increased severity of pneumonia. Children who died had low serum zinc levels, hypoxia, features suggestive of shock and radiological features of bilateral interstitial infiltrate. Serum zinc levels measured at the time of admission is a better predictor of mortality. When used in conjugation with other risk factors like young age, hypoxia, shock, serum zinc levels play a role in identifying sick child with pneumonia going for complication.

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Conflict of Interest

None

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