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Research

*Corresponding author
Aakash Pandita, MD
Department of Paediatrics
Government Medical College
Jammu, India
E-mail: aakash.pandita@gmail.com

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Estimation of Zinc Levels in Children With Lower Respiratory Tract Infections: A Prospective Observational Study from India

Ansar Murtuza Hussain, MD[1]; Prakash RM Saldanha, MD[1]; Deepak Sharma, MD, DNB[2]; Aakash Pandita, MD, DNB[3*]; Monika Yachha, MD, DM[4]; Mir Tariq, DNB[5]

[1]Department of Paediatrics, Yenepoya Medical College, Mangalore, India
[2]Department of Paediatrics, Pt. B.D. Sharma Medical College, Rohtak, Haryana, India
[3]Department of Paediatrics, Government Medical College, Jammu, India
[4]SGPGI, Lucknow, India
[5]KDA Hospital, Mumbai, India

ABSTRACT

Aims: To assess the serum zinc levels in children aged 2 months to 5 years admitted with Lower Respiratory Tract Infections and to study the association between low zinc levels and other known risk factors LRTI.
Material and Method: This prospective, observational study enrolled 200 children in age group of 2 months to 5 years admitted with acute LRTI. Serum Zinc level were measured and its association was seen with other risk factors of LRTI.
Results: Mean serum zinc level of study population was 57.9±29.2 microgram/dL. There was significant difference in zinc level depending on severity of pneumonia, nutritional status, anemia, clinical vitamin A deficiency, breast feed infants and birth weight ($p<0.05$).
Conclusion: Low serum level of zinc were 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: Serum zinc; Lower respiratory tract infections; Severity of pneumonia; Nutritional status; Anemia; Clinical vitamin A deficiency; Breast feed infants; Birth weight.

ABBREVIATIONS: ALRTI: Acute Lower Respiratory Tract Infection; WHO: World Health Organization; IAP: Indian Academy of Pediatrics; ANOVA: Analysis of variance; WBC: White Blood Cell; IL-6: Interleukin 6; AT: Ataxia-telangiectasia; ZD: Zinc Deficiency; VAD: Vitamin A Deficiency; LBW: Low Birth Weight.

INTRODUCTION

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[1,2] and it plays a role in immune function,[3,4] protein synthesis,[4] wound healing,[5] DNA synthesis,[2,4] and cell division.[4] 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.[5] According WHO estimates respiratory infection cause about 987,000 deaths in India of which 969,000 are LRTI.[6] ALRTI are the leading cause of mortality and a common cause of morbidity in children below

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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.[7] The need for the study was to establish that zinc deficiency may lead to LRTI. The study was planned to assess the serum zinc levels in children aged 2 months to 5 years admitted with lower respiratory tract infections and to study the association between low zinc levels and other known risk factors for lower respiratory tract infections.

METHOD AND MATERIAL

This was a hospital based prospective, observational study done in Department of Pediatrics, Yenepoya Medical College, Mangalore, India between January 2012 to December 2012. The ethical committee approved the study protocol and the informed consent form. Prior to enrolment in the study informed consent of child's care taker was obtained. Two hundred cases of ALRTI were enrolled in study.

Inclusion Criteria:

- Children admitted with ALRTI from 2 months to 5 years.

Exclusion Criteria:

- Children less than 2 months and more than 5 years are excluded.
- Children with clinical diagnosis of Reactive airway disease/ asthma.
- Children associated with underlying chronic illnesses.
- Children with Inborn Errors of Metabolism
- Children on zinc supplementation

Children in age group of 2 months to 5 years admitted with acute lower respiratory tract infection during study period were enrolled as cases. All the cases are clinically diagnosed as acute lower respiratory tract infection as per World Health Organization (WHO), 1990 criteria. All cases are investigated and treated as per the protocol for treatment of LRTI.

WHO, 1990 criteria for acute lower respiratory tract infections (ALRTI) and Pneumonia.

Pneumonia:

- Symptoms : Cough or difficult breathing and
- Signs :
  - Infants aged 2 months to <1 year: Breathing >50/minute
  - Child aged 1 to 5 years: Breathing >40/minute and no chest in-drawing, stridor or danger signs

Severe Pneumonia:

- Symptoms: cough or difficult breathing and any danger sign or chest in drawing, stridor in a calm child.
- Danger signs: For children aged 2 months to 5 years: Unable to drink or breast feed, vomiting, convulsions, lethargic or unconscious

All cases were investigated and treated as per the protocol for treatment of LRTI.

All patients' general information, clinical profile, socio-economic status, immunization status, perinatal history, nutritional status, history of receiving any additional nutritional supplements is noted in predesigned proforma. Associated risk factors for LRTI were identified and noted as per following criteria.

Socio-Demographic Conditions

- Socioeconomic status: Was classified according to modified Kuppuswamy classification.[8]
- Immunization status: Complete immunization was taken as age appropriate immunization according to Indian Academy of Pediatrics (IAP) schedule.[9] Partial immunization was defined as incompletion of IAP schedule. Non-immunized child was defined as not received any vaccination
- 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.
- Family history of LRTI – h/o respiratory tract infection in family members in preceding 2 weeks.

NUTRITIONAL CONDITIONS

- Nutritional status: Detailed anthropometry was done and malnutrition was graded according to IAP classification of malnutrition.[9]
- Feeding history/weaning history: Detailed account of breast feeding or formula feeding were recorded. Weaning was divided as early weaning (<4 months), proper (4-6 months) and late (>6 months.)
- Vitamin A deficiency: Was diagnosed clinically with features of delayed dark adaptation, night blindness, conjunctival xerosis, bitot spots, corneal xerosis, corneal ulceration, corneal scarring.
- Vitamin D deficiency: Was diagnosed clinically with features of frontal bossing, rachitic rosary, Harrison sulcus, widening

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of wrists, genu valgus/varus deformities.

- Supplementation of nutrition: Whether child had received vitamin A supplementation as mega doses according to Vitamin A prophylaxis schedule. Also whether child had any recent iron supplementation.
- Anemia: If Hb was less than 12gm/dl it was considered as anemia.
- Birth weight: Child weighting less than 2.5 kgs was considered low birth weight and above 2.5-3.5 kgs appropriate for gestational age.

Environmental Factors

- Ventilation: Adequate ventilation was considered if 2 windows were present in one room facing different directions.
- Housing condition: Kachcha house was defined as walls/roof made of un-burnt bricks, bamboos, mud, grass, reeds, thatch, loosely packed stones. Pacca house has roof and walls made of Burnt bricks, stones (packed with lime or cement), cement concrete, timber. Semi pacca house has fixed walls but roof is made of kachcha material.
- Smoke exposure: Was taken in consideration with any h/o family member smoking and use of firewood for cooking

Principle of measuring serum zinc was by PHOTO-SPECTROMETRY-Nitro-PAPS2- [5-NITRO-2-PYRIDXY-LAZO]-5[N- n PRO PYL- {3 SULFO PRO PYL}] AMINO PHENOL DISODIUM SALT)[10] reacts with zinc in alkaline solution to form a purple colored complex, the absorption of which was measured at 575 nm. Interference from copper and iron were eliminated by pH and chelating agents. Taking aseptic precaution, 2ml of blood from venepuncture using 22 gauge sterile needles, was collected within 24 hours of contact of patient. The sample was then centrifuged for 3-4 minutes at 3000-4000rpm; serum thus obtained was collected and preserved at 2-8 °C in sterile deionised plain vials. Estimation of Zinc was carried out within 7 days of collection. Normal range of serum zinc was taken as 70-110 mg/dl.

All statistical procedures were performed using SPSS v 17.0. All results were expressed as number (percentage) or Mean±Standard Deviation (SD)/median (range) as appropriate. One way Analysis of variance (ANOVA) was used to compare the difference in mean values of zinc and assess the correlation with risk factors. The result were measured in terms of significance of association at 95% confidence level *i.e.* "p" value less than 0.05.

RESULTS

Two hundred cases aged between 2 months to 5 years admitted with clinical diagnosis of LRTI were enrolled in study. The demographic distribution showed fever was the most common presentation (Table 1).

Characteristic	Number	Percentage (%)
Distribution of sex of patients		
Male	116	58
Distribution of socio economic status of patients		
Upper middle	36	18.0
Middle	60	30.0
Upper lower	92	46.0
Lower	12	6.0
Clinical profile of children of LRTI		
Fever	176	88
Breathlessness	132	66
wheeze	120	60
Refusal to feed	12	6
Immunization status		
Complete	132	66.0
Partial	56	28.0
Non Immunized	12	6.0
Distribution of family history of LRTI of patients		
Yes	112	56.0
Distribution of overcrowding status of patients at home		
Present	152	76.0
Ventilation in house of patients		
Inadequate	33	66.0
Distribution of house condition of patients		
Pacca	32	16.0
Semipacca	56	28.0
Kachcha	112	56.0
Distribution of smoke exposure of patients		
Yes	76	38.0
Distribution of nutrition status of patients		
Normal	60	30.0
Grade I	52	26.0
Grade II	40	20.0
Grade III	28	14.0
Grade IV	20	10.0
Distribution of vitamin A deficiency of patients with clinical features		
Present	8	4.0
Distribution of vitamin D deficiency of patients with clinical features		
Present	56	28.0
Distribution of birth weight of patients		
Low birth weight (<2.5kgs)	76	38.0
Distribution of feeding history of patients		
Breast Feeding	104	52.0
Distribution of anemia of patients		
Present	144	72.0

Table 1: Table showing various demographic distribution of the population.

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The mean age of the study population was 24.9±16.3 months (4.0-60 months). The mean duration of illness was 9.6±2.3 days (5.0-16.0 days) whereas mean White blood cell (WBC) counts was 15.7±2.9*10^9/L (10.0-22.9*10^9/L).

The majority of the patient had bronchopneumonia as clinical diagnosis and pulmonary infiltrates were most common X-ray findings (Table 2).

The mean serum zinc level of all patients of LRTI was 57.9±29.2 microgram/dL (13.0-121.7 microgram/dL). The normal level being 70-110 microgram/dl.

There was no significant difference on the level of zinc depending on age, sex, socio-economic status, immunization and family history of LRTI. (Table 3)

No significant difference was noted in the serum zinc level depending on housing condition, ventilation of house, smoking exposure.

Significant difference in serum Zinc level was seen depending upon the severity of pneumonia, nutritional status, Vitamin A deficiency and anemia ($p<0.05$). (Table 4)

Characteristics	Frequency	Percentage (%)
Severity of pneumonia		
Pneumonia	168	84.0
Severe Pneumonia	32	16.0
Clinical diagnosis		
Bronchopneumonia	80	40.0
Bronchiolitis	32	16.0
Bronchiectasis	8	4.0
Lobar pneumonia	28	14.0
Interstitial pneumonia	16	8.0
Wheeze associated lower respiratory infection	36	18.0
Radiological distribution of LRTI		
Pulmonary infiltrates	92	46.0
Consolidation	48	24.0
Normal	32	16.0
Hyperinflation	16	8.0
Atelectasis	8	4.0
Pleural effusion	4	2.0

Table 2: Table showing the respiratory morbidities and clinical diagnosis of the study population.

Characteristics	Mean± Std. Deviation	Range	P value
Zinc level distribution age wise (months)			
≤ 5	43.8±20.3	17.3-64.0	0.846
6 - 15	60.0±26.7	13.7-113.0	
16 - 25	53.1±22.2	16.6-90.0	
26 - 35	63.8±37.7	26.6-109.0	
36 - 45	52.6±32.0	15.4-118.0	
≥ 46	63.6±30.1	34.0-121.7	
Zinc levels distribution sex wise			
Female	57.8±27.8	18.0-113.0	0.987
Male	57.9±30.7	13.0-121.7	
Distribution of serum zinc level as per socio economic status of patients			

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Characteristics	Mean± Std. Deviation	Range	P value
Lower	55.7±30.3	37.7-67.0	0.285
Upper Lower	58.2±30.9	13.0-121.7	
Middle	59.0±35.4	16.6-118.8	
Upper Middle	60.4±25.8	28.0-113.0	
Serum zinc level and immunization status of patients			
Complete	54.5±26.9	13.0-118.0	0.388
Partial	64.3±30.5	26.6-121.7	
Non Immunized	43.8±15.6	30.4-61.0	
Serum zinc level and family history of LRTI			
Yes	60.0±28.8	13.0-121.7	0.333
No	52.3±25.8	15.4-113.0	

Table 3: Table showing zinc association with socio-demographic conditions.

Characteristics	Mean±Std. Deviation		
Serum zinc levels as per severity of pneumonia			
Pneumonia	57.6±31.2	13.0-121.7	0.031
Severe Pneumonia	32.6±11.7	17.7-47.0	
Serum zinc level and nutrition status of patients			
Normal	78.1±24.7	54.0-113.0	0.045
Grade I	58.8±29.1	17.7-121.7	
Grade II	65.7±30.5	30.9-118.8	
Grade III	51.3±16.5	23.0-73.0	
Grade IV	48.2±32.5	13.0-108.9	
Serum zinc levels and anemia			
Yes	50.7±27.0	13.0-113	0.004
No	76.4±27.2	37.0-121.7	
Serum zinc level and clinical vitamin A deficiency of patients			
Yes	44.3±23.5	27.7-61.00	0.025
No	57.1±27.8	13.0-121.7	
Serum zinc level and clinical vitamin D deficiency of patients			
Yes	49.0±19.2	13.0-78.0	0.226
No	59.6±29.9	15.4-121.7	
Serum zinc level and birth weight of patients			
Low birth weight (<2.5 kgs)	32.6±12.0	13.0-58.0	0.000
Normal birth weight (2.5-3.5 kgs)	73.4±25.5	17.0-121.7	
Serum zinc level and feeding history of patients			
Breast feed	70.0±26.1	46.6-121.7	0.005
Formula feed	51.5±29.6	13.0-113.0	

Table 4: Table showing association of serum zinc level with severity of pneumonia and nutritional status.

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There was also significant difference based on birth weight and feeding as significant high zinc level was seen in breast feed infants and infants who were not low birth weight. (Table 4)

DISCUSSION

In our study the mean serum zinc levels of 57.9±29.2 mg/dl were found in patients, which is lower than normal range of (70-110 mg/dl).

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.[11,12] Further Meeks-Gardner J et al have shown a positive Zinc supplementation in these patients.[13]

There was statistical significance between serum zinc and severity of pneumonia. We observed that mean serum zinc of patients with pneumonia 57.6±31.2 microgram/dL was statistically higher than patients with severe pneumonia 32.6±11.7 microgram/dL (p value 0.031). This was in conformity with the earlier reports. The study by Pushpa et al14 on the association of serum zinc level with severe pneumonia in children that the mean serum zinc level of group of patient's severe pneumonia was lower than those with less severe pneumonia. The study by Arica et al[15] on serum zinc levels in children of 0-24 months diagnosed with pneumonia reported that Zn values as determined in the control group enrolled in the study were significantly higher compared to the pneumonia patient group (p<0.01).

About 70 % of the study patients were in different stages of malnutrition (grade I(26%), grade II(20%), grade III(14%) and grade IV(10%) respectively. We observed a statistical difference in the mean serum zinc level of the patients divided as per grades of malnutrition (p value 0.045). It was observed in present study that low serum zinc levels were present even in well-nourished children suffering from severe respiratory tract infection.

Singla PN et al[16] studied the Serum zinc levels in children with protein energy malnutrition. The levels of serum zinc and copper were found to be significantly low in children with severe malnutrition (grades III and IV PEM). There was a significant positive correlation between serum zinc and height-for-age (p<0.001).

Anemia is a widespread problem among infants and children in many parts of the world, and it is often associated with some trace elements (iron, zinc, copper) and heavy metals (cadmium and lead). In our study 72% of the studied patients had anemia and we observed a statistical difference between serum zinc level of patients with and without anemia, where the mean of zinc with anemia was 50.7±27.0 microgram/dL and without anemia was 76.4±27.2 microgram/dL (p value is 0.004). It is similar to other reports. Turgut S, et al[17] studied the Interaction between anemia and blood levels of iron, zinc, copper, cadmium and lead in children and reported that levels of copper, cadmium and lead in serum were significantly higher in children with IDA than those of controls.

De la Cruz-Gongora V et al[18] reported the results from the 2006 National Health and Nutrition Survey in Mexican children under 5 years, found that anemia was not associated with low serum zinc levels.

In our study there is significance of vitamin A deficiency and serum zinc levels (p=0.025).

A community-based study by Hettiarachchi M et al[19] on the coexisting micronutrient deficiencies among Sri Lankan pre-school children reported that 38.3% were deficient in both vitamin A and zinc.

Another study by da Silva R et al[20] on the relationship between nutritional status, vitamin A and zinc levels and oxidative stress in patients with ataxia-telangiectasia. Authors reported that ataxia-telangiectasia patients showed high rates of malnutrition with reduced lean body mass when compared to the control group. However, serum zinc in Ataxia-telangiectasia (AT) patients was similar to those of the control group. The AT patients assessed showed no change in nutritional status for vitamin A and zinc.

There are variable reports on the association of the serum zinc levels with the vitamin A deficiencies. The effects of prenatal Zinc Deficiency (ZD) and Vitamin A Deficiency (VAD) on birth weight are controversial and their interaction has not been investigated. Enquselassie F et al[21] studied the effects of prenatal Zinc and Vitamin A Deficiencies on birth weight showed that the occurrence of the deficiencies either in the second or third trimester were associated to Low Birth Weight (LBW). The deficiencies did not show synergetic interaction in causing

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LBW. LBW is of public health significance in the locality. The study did not witness any independent or interaction effect of prenatal Zinc Deficiency (ZD) and Vitamin A Deficiency (VAD) on birth weight.

We observed that 38% of study patients had deficiency of vitamin D but we did not observed any statistical difference in the mean serum zinc level of the patients with and without vitamin D deficiency (p value is 0.226).

In our study there is statistical correlation between breast feeding and serum zinc levels. (p=0.005), 52% were breast fed and 48% had addition of formula feeding. Van Biervliet S et al[22] studied the role of serum zinc in healthy Belgian children. The median Zn value is lower in infants than in older children (respectively 11.6 micromole/L *vs.* 12.8 micromole/L). Authors reported that the type of infant feeding does not influence the serum Zn concentrations (breast-feeding, adapted, hypoallergenic, soy, or thickened).

In our study low birth weight (38%) had lower serum zinc levels of 32.6+/-12 microgram/dL compared to normal birth weight (62%) mean zinc levels of 73.4+/-25.5 microgram/dL and there is highly significant correlation. *p*=0.000.

Sharda B et al[23] studied the zinc and copper in preterm neonates to assess copper and zinc levels in neonate's serum, mother's serum, neonate's hair and urine and to ascertain association between them. Neonates between 26-30 wks. Gestational age and <2.5 kg birth weight had significantly low serum zinc and copper. Breast milk zinc was low in mothers delivering preterm and <2.5 kg neonates. Urinary copper and zinc levels were high in preterm appropriate for gestational age (Pre AGA) than term neonates. The effect of mother's serum, breast milk, and neonate's serum copper and zinc collectively was significant for and hair zinc. Preterm and low birth weight infants during subsequent growth and development should be supplemented with zinc and copper when on breast feeding.

STRENGTH OF THE STUDY

1. Large sample size with range of patients from 2 month age to 5 years.
2. Evaluation of multiple socio-economic conditions on the zinc level.
3. Evaluation of nutritional conditions and severity of pneumonia on the zinc level of the patients.

LIMITATION OF THE STUDY

1. Absence of follow up prevents us to access the long term impact of altered serum zinc level patients with LRTI.
2. Absence of control is responsible for non-availability of base line serum zinc level of the study population.
3. Association between clinical profile and serum zinc was not done due to variation in subjective evaluation
4. Exclusion of patients of upper respiratory tract infection limits the clinical interpretation of result.
5. We did not include the assessment of dietary composition and intake of the child, which is an important confounding factor.

CONCLUSION

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. It is advised that zinc supplementation is required in LRTI patients especially those with the above mentioned risk factors. Although the present findings are promising and few recent studies have shown reduction of incidence of ALRTI with zinc supplemenataion,[24] but there is currently no standard guidelines to use Zinc in all malnourished children to prevent respiratory tract infection and additional studies are needed to further investigate whether Zinc should be given to all malnourished children as standard of care and any other micronutrients also along with zinc to boost immunity.[25,26]

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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DISCLOSURE

"There are no prior publications or submissions with any overlapping information, including studies and patients."

"The manuscript has not been and will not be submitted to any other journal while it is under consideration by Clinical Pediatrics."

CONTRIBUTIONSHIP STATEMENT

Dr. Ansar wrote the first draft of the manuscript.

Dr. Deepak, Dr Tariq, Dr. Aakash and Dr. Monika helped in writing manuscript and did primary corrections in the manuscript.

Dr. Prakash made final corrections of manuscript before submission

There was no honorarium, grant, or other form of payment given to anyone to produce the manuscript.

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manuscript and takes full responsibility for the manuscript.

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