Serum zinc levels and predictors of severity of acute lower respiratory tract infections in children under five years of age

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Abstract

Background: Zinc has a central role in immunity and body`s response to infection. The detrimental effects of zinc deficiency on the immune system can lead to a worse outcome in pneumonia and other infections. There has been renewed interest in zinc in the wake of the SARS Coronavirus 2 pandemic.

Objectives: To estimate the serum zinc levels in children with acute lower respiratory infection (ALRI) and determine its association with respiratory rate, heart rate and oxygen saturation in room air.

Method: This hospital based descriptive study included 40 children admitted with varying degrees of severity of ALRI.

Results: Nineteen (47.5%) cases presented as wheeze-associated lower respiratory infection (WALRI) and bronchiolitis, 12 (30%) presented as pneumonia, 7 (17.5%) as severe pneumonia and 2 (5%) as very severe pneumonia. The mean serum zinc level was statistically different among these groups of children (p=0.0001). The mean serum zinc level in children with WALRI / bronchiolitis was 63.0532 ± 5.6283µg/dl while in children with pneumonia, severe pneumonia and very severe pneumonia the mean serum zinc levels were 48.5817 ± 1.7937µg/dl, 38.1043 ± 3.8443µg/dl and 36.305 ± 2.86378µg/dl respectively. Children with tachypnoea, tachycardia and low oxygen saturation levels had lower mean serum zinc levels of 44.579µg/dl (p=0.0001), 44.1113µg/dl (p = 0.0001) and 54.3073µg/dl (p=0.009) respectively which were statistically significant.

Conclusions: The mean serum zinc level was significantly low in children with tachypnoea, tachycardia and low oxygen saturation levels which are predictors of severe illness. Significantly low mean serum zinc levels were observed in children with different grades of pneumonia when compared to children with WALRI / bronchiolitis and in children with severe pneumonia when compared to those with pneumonia.

(Key words: Preschool children, Pneumonia, Tachypnoea, Tachycardia, Zinc)

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Introduction

The current global pandemic of Covid-19 has rekindled interest in the protective and therapeutic roles of zinc, a micronutrient, in pneumonia. Though data is limited, zinc has been potentially used as supportive therapy in SARS CoV-2 pneumonia because of its direct antiviral effect, anti-inflammatory properties and modulation of antibacterial and antiviral immunity[1]. Zinc regulates intracellular signalling pathways in immune cells and has a key role in both innate as well as adaptive immune responses in the body. Deficiency of zinc causes impaired phagocyte function, reduction in lymphocytes and T4+/T8+ ratio and diminished immunoglobulin and interleukin-2 production which can lead to a potentially worse outcome in infections[2]. The incidence of pneumonia worldwide is over 1400 cases per 100,000 children, with the highest incidence in South Asia (2500 cases per 100,000 children) followed by West and Central Africa (1620 cases per 100,000 children)[3]. The results of a critical review of randomised control trials studying the effects of nutritional interventions and breastfeeding promotion on acute lower respiratory infection (ALRI) morbidity and mortality, undertaken by Roth DE, *et al*[4] showed that zinc supplementation in zinc deficient populations prevented around 25% of episodes of ALRI.

Objectives

To estimate the serum zinc levels in children with ALRI and determine its association with respiratory rate, heart rate and oxygen saturation in room air.

Method

This was a descriptive study performed on 40 children aged 1-5 years admitted with ALRI to the paediatric department of a tertiary care hospital over a period of one year and 7 months. Children were recruited into the study based on clinical symptoms and abnormal lower respiratory tract signs including abnormal chest auscultatory findings. Clinical diagnoses of bronchiolitis, wheeze-associated lower respiratory infection (WALRI) and pneumonia were made based on symptoms and physical examination findings by the primary investigator. Children having pneumonia were further categorised into pneumonia, severe pneumonia or very severe pneumonia based on clinical features according to the revised WHO classification of pneumonia in children[5]. Radiological analysis of the cases was not considered for the grading of severity. Children with chronic illnesses, inborn errors of metabolism, malnutrition (IAP classification of protein energy malnutrition: weight for age <80%) and those receiving zinc supplements were not included in the study.

Setting a confidence interval of 95%, a sample size of 40 was estimated using a standard deviation of 25.3[6] and a relative precision of 10% of the mean.

Data were collected from the patients regarding their nutritional status, vital functions on admission, including temperature, respiratory rate (RR), heart rate (HR), oxygen saturation (SaO2) in room air, clinical features and recorded on data collection forms.

Tachypnoea was defined as a respiratory rate ≥40/ minute for the children in the study group according to WHO guidelines[5]. The normal range of heart rate for children 1-3 years of age was taken as 70-110/minute and for children 3-5 years as 65-110/minute[7]. A heart rate >110/minute was taken as tachycardia. The normal range of SaO2 at sea level is 97-99%, with a lower limit of 94%. SaO2 <90% indicates hypoxaemia[8].

Two ml of blood was drawn by venepuncture after properly preparing the site with povidone-iodine and alcohol, within 24 hours of admission. Sample taken was sent for serum zinc level analysis by the Inductively Coupled Plasma Mass Spectrometry (ICPMS) method. The normal reference value of serum zinc concentration for males and females are 75-291µg/dl and 65-256µg/dl respectively. The cut off level of serum zinc concentration for defining zinc deficiency was taken as less than 65µg/dl for males and females in this age group[9].

***Ethical issues**:* Approval for the study was obtained from the Institutional Ethics Committee of Amala Institute of Medical Sciences, Thrissur (Registration number ECR/653/Inst/ KL/2014) prior to the beginning of the study. Written informed consent was obtained from the parents of all the children who participated in the study.

***Statistical analysis**:* The data obtained was coded and entered in Microsoft Excel Sheet and analysed using the statistical software Statistical Package for Social Sciences (SPSS) version 23. The results are expressed in percentage and proportions. The statistical technique independent t-test was used for analysis.

Results

Out of 40 cases included in study, 21 were males and 19 were females. Mean age of children in the study group was 2.650 ± 1.4901 years. Children with WALRI / bronchiolitis constituted 19 (47.5%) cases while 21 (52.5%) children had pneumonia. Children with pneumonia were categorised into pneumonia 12 (30%) cases, severe pneumonia 7 (17.5%) cases and very severe pneumonia 2 (5%) cases.

In our study group the mean respiratory rate was 30.53 ± 2.563/minute in children with WALRI / bronchiolitis, 45.83 ± 10.461/minute in those with pneumonia, 51.14 ± 7.647/minute in those with severe pneumonia and 50 ± 14.142/minute in those with very severe pneumonia. The mean respiratory rates were significantly different between the four groups of children in the study population (p=0.0001). The mean heart rates were also significantly different between the subsets of children in the study group (p=0.002). The mean heart rate in children with WALRI/bronchiolitis was 104.63 ± 11.927/minute, in pneumonia 114.17 ± 15.643/minute, in severe pneumonia 123.71 ± 16.790/minute and in very severe pneumonia 140 ± 0.2/minute respectively. Significantly different mean SaO2 levels (p=0.0001) also were found between the children with WALRI / bronchiolitis (mean SaO2 level 99.8 ± 0.501%), pneumonia (mean SaO2 level 98.33 ± 1.826%), severe pneumonia (mean SaO2 level 95.71 ± 3.773%) and very severe pneumonia (mean SaO2 level 96.00 ± 5.657%). None of the children in the study population had hypoxaemia with oxygen saturation < 90% on pulse oximeter, in room air.

Table 1 shows the respiratory rates of children in the study group and their mean serum zinc levels.

Table 1: ***Respiratory rates of children in the study group and their mean serum zinc levels***

Respiratory rate per minute	Number of children	Mean serum zinc level µg/dl	Standard deviation	p value (T test)
<40	19	63.0532	5.62830	0.0001
≥40	21	43.9200	6.10646	

It was seen that children who developed tachypnoea, with a respiratory rate >40/minute had lower mean serum zinc levels compared to those who did not have tachypnoea, which was statistically significant (p <0.0001).

Table 2 shows the heart rates of children in the study group and their mean serum zinc levels

Table 2: ***Heart rates of children in the study group and their mean serum zinc levels***

Heart rate per minute	No. of children	Mean serum zinc level µg/dl	Standard deviation	T test value	p value
<120	24	58.9396	9.90204	5.299	0.0001
120-150	16	44.1113	6.33299		

Similarly, children with higher heart rates in the study group had lower mean serum zinc levels when compared to children who had normal heart rates (p =0.0001).

Table 3 shows the oxygen saturation (SaO2) levels in room air of children in study group and their mean serum zinc levels.

Table 3: ***Oxygen saturation levels in room air of children in study group and their mean serum zinc levels***

SaO2 level in room air %	No. of children	Mean serum zinc level µg/dl	Standard deviation	T test value	p value
≤94	3	36.9867	3.31212	2.766	0.009
>94	37	54.3073	10.68897		

SaO2: Oxygen saturation

A comparison of the mean serum zinc levels between children with SaO2 ≤94% and those with SaO2 level >94% in room air showed statistically significant lower mean serum zinc level in the group with lower oxygen saturation levels (p = 0.009).

Among the children with severe (7 children) and very severe (2 children) pneumonia, convulsions were noted in 2 children, inability to drink in 2 children and stridor and altered sensorium in one of the two children with very severe pneumonia.

Mean serum zinc level in our study was 53.0083 ± 11.286µg/dl. Mean serum zinc level in children with WALRI / bronchiolitis was 63.0532 ± 5.6283µg/dl, in children with pneumonia 48.5817 ± 1.7937µg/dl, in severe pneumonia 38.1043 ± 3.8443µg/dl and in very severe pneumonia 36.305 ± 2.86378µg/dl as shown in Table 4. Statistically significant difference in mean serum zinc level (p=0.0001) was observed between the mean serum zinc levels in children with WALRI / bronchiolitis, pneumonia, severe pneumonia and very severe pneumonia.

Table 4: ***Mean zinc levels of children with lower respiratory tract infection***

Lower respiratory tract infection	Serum zinc level µg/dl		P value (ANOVA)
	Mean	Standard deviation	
WALRI/Bronchiolitis	63.0532	5.62830	0.0001
Pneumonia	48.5817	1.79377	
Severe pneumonia	38.1043	3.84434	
Very severe illness	36.3050	2.86378	

WALRI- wheeze associated lower respiratory infection

On further analysis (Tukey`s post-hoc test), given below in Table 5, the mean serum zinc levels were found to be statistically significant when comparing the levels of children with WALRI / bronchiolitis with those having pneumonia (p = 0.00) or severe pneumonia (p = 0.00). The mean serum zinc levels were also observed to be significantly low when comparing the levels in children with pneumonia with those of severe pneumonia (p = 0.00) but not significant when comparing children with severe and very severe pneumonia (p = 0.957).

Table 5: ***Comparison of mean serum zinc levels among the groups of children with ALRI***

(I) LRTI subgroups	(J) LRTI sub groups	Mean difference of serum zinc level (I-J)	Standard error	P value
WALRI/ Bronchiolitis	Pneumonia	14.47149*	1.62883	0.000
	Severe pneumonia	24.94887*	1.95309	0.000
	Very severe pneumonia	26.74816*	3.28383	0.000
Pneumonia	WALRI/ Bronchiolitis	-14.47149*	1.62883	0.000
	Severe Pneumonia	10.47738*	2.10087	0.000
	Very severe Pneumonia	12.27667*	3.37381	0.005
Severe pneumonia	WALRI/ Bronchiolitis	-24.94887*	1.95309	0.000
	Pneumonia	-10.47738*	2.10087	0.000
	Severe Pneumonia	1.79929	3.54176	0.957
Very severe pneumonia	WALRI/ Bronchiolitis	-26.74816*	3.28383	0.000
	Pneumonia	-12.27667*	3.37381	0.005
	Severe Pneumonia	-1.79929	3.54176	0.957

LRTI: Lower respiratory tract infection

Discussion

In this study, we found that out of 40 cases of ALRI studied, males (21 cases 52.5%) outnumbered females (19 cases 47.5%). An analysis of the mean serum zinc level of males and females in the present study showed no statistically significant difference between the mean serum zinc levels of males (53.13±11.96) and females (52.86±10.81) (p =0.941) which is similar to the findings obtained in studies by Paneerselam R, *et al*[10], Kumar DE, *et al*[11] and Hussain AM, *et al*[12]**.**

In the present study**,** 50% of children belonged to the age group 12-30 months, and 50% belonged to the age group 30 to 60 months. The mean age of the children in the study group was 31.075 months. The mean serum zinc level in children ≥ 30 months (51.92±11.10) was lower when compared to the level in children <30 months (54.09±11.64) but it was not statistically significant (p =0.551). This contrasts with the study by Hussain AM, *et al*[12] where lower mean serum zinc levels were noted in infants than in older children, but the difference was not statistically significant. Other studies by Kumar S, *et al*[13] and Kumar DE, *et al*[11] have shown that the mean serum zinc levels of children did not vary significantly with age.

In the present study, a comparison of the mean serum zinc levels between children with tachypnoea (RR >40/min) and respiratory distress, and children without tachypnoea showed a statistically significant lower mean zinc level (p <0.001) in children with respiratory distress. This is similar to the study by Rady HI, *et al*[6] where they found serum zinc levels were lower in children with higher grades of respiratory distress and those who required respiratory support compared to patients who were not in respiratory distress. Similarly, children with tachycardia also had significantly lower mean serum zinc levels compared to children without tachycardia (p<0.001). Mean serum zinc levels of children with SaO2 levels ≤94% were significantly less (p<0.001) as against the mean serum zinc level of children with higher SaO2 levels. Similar findings have been reported in the study by Shivalingaiah M, *et al*[14]. Children who developed increasing severity of illness with respect to tachypnoea, tachycardia and decreased SaO2 levels had lower mean serum zinc levels in our study.

The mean serum zinc level in children with WALRI / bronchiolitis was 63±5.6µg/dl, with pneumonia 48.58±1.793µg/dl, with severe pneumonia 38.10±3.844 µg/dl and in children with danger signs and very severe pneumonia 36.3±2.863µg/dl. The mean serum zinc level was significantly different among the above mentioned groups of children (p =0.0001). The mean serum Zinc levels were found to be statistically significant when the levels in children with WALRI / bronchiolitis were compared with those having pneumonia (p=0.00), severe pneumonia (p=0.00) or very severe pneumonia (p=0.00). The mean serum zinc level was also observed to be significantly low when the levels in children with severe pneumonia were compared with those of pneumonia (p=0.00) but not significant when compared with the level in children with very severe pneumonia (p=0.957).

Several studies have reported low serum zinc levels in children with pneumonia[10,15,16] and significantly lower values in children with severe pneumonia[12,13,17,18]. According to a cross-sectional hospital-based study by Ibraheem RM *et al*[16], the mean serum zinc level in children 2 months to 5 years of age with ALRI was 18.7 ± 11.8µg/dl which was significantly lower compared to 53.1 ± 18.5µg/dl recorded in the controls (p=0.001). Fifty cases of severe pneumonia and fifty cases of healthy control group of children of same age, sex and nutritional status were compared by Pushpa *et al*[17]; they found that low serum zinc levels were present even in well-nourished children suffering from severe pneumonia (mean = 184.92 ±

44.11µg/dl) as compared to controls (mean = 206.76 ± 47.59µg/dl) (p = 0.004). In a case-control study of well-nourished Bangladeshi children of age group 6-60 months with ALRI, Shakur MS, *et al*[15] found that the mean serum zinc level was low in children suffering from ALRI (90±51µg/dl) when compared to controls (176 ± 98µg/dl), (p<0.05). Similar finding was also reported in the study by Kumar S, *et al* [13] which showed low serum zinc level in children between 2 months to 5 years with pneumonia compared to control group (p= 0.001). Other studies by Hussain AM, *et al*[12] and Paneerselam R, *et al*[10] have also reported significantly low serum zinc levels in children with pneumonia when compared to healthy controls.

One explanation for the low serum zinc levels seen in cases of pneumonia might be an already existing zinc deficiency, which increases the susceptibility of a child to get pneumonia by impairing child's immunity[19]. Another explanation for the low serum zinc levels might be the shift of zinc from plasma to liver, said to be caused by cytokines released during acute phase response to infection[20]. The increased amount of intracellular zinc acts as a toxin to the engulfed pathogens and protects the cell by promoting production of neutralizing reactive oxygen and nitrogen species[21]. The mean serum zinc level (53.0083 ± 11.286 µg/dl) was found to be decreased in the present study which resembles the results of the study by Hussain AM, *et al*[12]. This can be attributed to the mild to moderate zinc deficiency common in developing countries both due to inadequate intake of zinc in the diet as well as the high phytate content in cereal based diets which are popular in these countries which inhibits the absorption of zinc from intestine. A community based cross sectional study by Kapil U, *et al*[22] to estimate the prevalence of zinc deficiency among Indian children 6-60 months of age showed an overall prevalence of 43.8%. Current evidence suggests that there is no role for the prescription of zinc as an adjunctive therapy for paediatric pneumonia. Haider BA, *et al*[23] conducted a systematic review of 4 randomized control trials (RCTs) which analysed the beneficial effects of zinc as adjuvant therapy in addition to antibiotics in children aged 2 to 59 months of age and found that zinc supplementation did not confer any significant benefit on the clinical recovery of patients in terms of time-to-recovery from tachypnoea (respiratory rate >50 breaths per minute) and time-to-recovery from chest indrawing or on the time-to-hospital discharge. However, several studies have reported a beneficial effect of zinc supplementation in preventing paediatric pneumonia[4,24]. A meta-analysis of 10 RCTs comparing the effects of zinc versus placebo on the incidence of ALRI in children <5 years showed that zinc supplementation reduced the incidence of ALRI by 35% (95% CI 18% to 48%)[25]. Further RCTs are needed to identify the target population of children who might benefit from zinc supplementation and its optimal mode of community-based delivery (i.e. fortification, supplementation), dose and duration.

The study had some limitations. The diagnosis of ALRI, including pneumonia, was based on clinical symptoms and pneumonia was categorised further into different grades based on WHO classification only; radiological features were not considered for severity or diagnosis. Correlation between nutritional status, dietary intake and serum zinc levels could not be done in this study.

Conclusions

The mean serum zinc level was low in children with ALRI who developed tachypnoea, tachycardia and low oxygen saturation in room air which are predictors of severity of illness. The mean serum zinc levels were also low in children with different grades of pneumonia when compared to children with WALRI / bronchiolitis and in children with severe pneumonia when compared to those with pneumonia.

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