Original Research Article

Serum zinc levels in acute diarrhoea and pneumonia in children aged 6 months to 6 years

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Abstract

Background & Objectives: To compare serum zinc levels in children suffering from acute gastroenteritis, pneumonia (malnourished and normal) with a control group. To study the effects of zinc in reducing the frequency and duration of diarrhea and pneumonia & its impact on the further recurrence of these infections. **Methods:** One hundred thirty (130) children in the age group of 6 months to 5 years were included. The Blood samples were drawn for zinc assay from all children at initial presentation and supplement with adjuvant oral zinc for 14 days. The duration of hospital stay and symptom resolution and the effect of supplementation over the next six months on these children was studied. **Results:** The mean serum zinc levels were significantly lower in children with AGE and Pneumonia as compared to that of the children in the control group which was very highly significant (71.39, 69.45, 81.65 mcg/dl respectively). Also, the malnourished children in both the AGE & LRTI groups had a mean zinc level that was significantly lesser than the adequately nourished children (67.77:73.85 in the AGE group & 57.52: 75.62 in the LRTI group). In the follow-up period for six months, children with undernourishment and those who had low zinc levels at initial presentation had significantly more recurrences **Conclusions:** Children with AGE and LRTI have a reduced serum zinc level when compared to controls. Zinc supplementation reduces the duration of symptoms in both AGE and LRTI children with low zinc levels and who were undernourished had frequent recurrences.

Keywords: Acute diarrhea, Low zinc levels, Lower respiratory tract infection, Undernourished

Introduction

Zinc is an essential mineral which has "exceptional biologic, public health importance". Zinc deficiency affected two billion people in the developing world and associated with many diseases [1]. In children it causes infection susceptibility growth retardation, diarrhea, and delayed sexual maturation, contributing to the death of about 4, 77,293 of under-five children worldwide per year [2].

The global prevalence of zinc deficiency was 31%, range from 4–73% across sub-region. Based on these estimates, zinc deficiency was estimated to cause 176000 diarrhea deaths and 406000 pneumonia deaths [3]. Zinc supplementation is useful for preventing diarrhea and pneumonia in children [4]. When used as adjuvant therapy for acute or persistent diarrhea, zinc reduces the duration of the episode as well as its severity and complications [5]. The results are more limited about zinc supplementation as an adjuvant therapy to pneumonia. A significant reduction in the duration of LRTI was seen with adjuvant zinc treatment in children in Bangladesh and India but only in boys [6]. Another study in Tamil Nadu, south India showed no significant benefits [7].

There are numerous studies on the beneficial effects of zinc supplementation in children with gastroenteritis and pneumonia but limited and inconclusive studies with the same comparison between malnourished and normally nourished. This study is a comparison between the effects of zinc supplementation with gastroenteritis and pneumonia with the comparison of zinc values in between malnourished and normally

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nourished children with that of age-matched asymptomatic children. This study is also intended to compare resolution and future recurrences of these children who have low zinc levels and normal zinc levels at initial presentation.

Materials and Methods

Type of study and setting: The present study was a single centre, prospective study. At least 50 cases of acute diarrhea and pneumonia respectively along with 30 age and sex-matched controls randomly selected in the department of pediatrics NRI general hospital, Chinnakakani, Guntur between November 2016 to April 2018 for determination of serum zinc levels.

Inclusion Criteria: The study includes

- Fifty children in the age group of 6 months to 5 years with acute diarrhea.
- Fifty children in the age group of 6 months to 5 years with pneumonia.
- 30 age and sex-matched controls.

Exclusion Criteria: The study excludes

- Infants less than six months and children more than five years of age.
- Those with the clinical diagnosis of, allergic diseases or asthma, CHD, co-morbid states.
- Those with zinc supplementation.
- Those with documented parenteral antibiotic intake before indoor admission for current illness

All children after admission were further divided into well nourished and undernourished groups.

Methodology: Blood samples for the measurement of serum zinc concentrations collected at enrolment by using a disposable syringe and needle. The samples were transferred to a zinc-free polypropylene tube and centrifuged at 3500 rpm for 10 min. The serum was separated immediately by using a disposable Pasteur pipette and stored in a zinc-free polypropylene tube at -20 °C until analysis. Measurement of the serum zinc concentrations was carried out by using a fully automated calorimetric method done on RANDOX IMOLA

Zinc supplementation was in the form of oral zinc acetate syrup (5 ml = 20 mg). Children less than one year received 10 mg of zinc acetate once daily while children above one year received 20 mg of zinc acetate once daily which continued for 14 days

At the time of enrolment, information collected on demographics, illness, and history of respiratory diseases for each subject. All physical findings, anthropometric data, chest X-ray finding, complete blood count results, and baseline serum zinc concentrations recorded**.** The diagnosis of pneumonia, diarrhea, and under nutrition was based on WHO guidelines [8].

Prior informed consent taken from the parents before drawing of blood

Statistical analysis: Statistical analysis was done by using both descriptive and analytical statistics. Qualitative data was presented with percentages. Mean and standard deviation were calculated for quantitative data. Z test of difference between two means was used to compare mean Zinc levels between malnourished and nourished, low zinc and normal zinc level groups' test of proportions was used to test the difference in portions of children with symptoms between nourished and malnourished. Micro soft office Excel and Medcal C soft ware version 17.2 free version was used to analyze the data

Ethical consideration: Permission was taken from the ethical committee of the institute before starting the study. Written consent was taken from the parents of all participants before starting study.

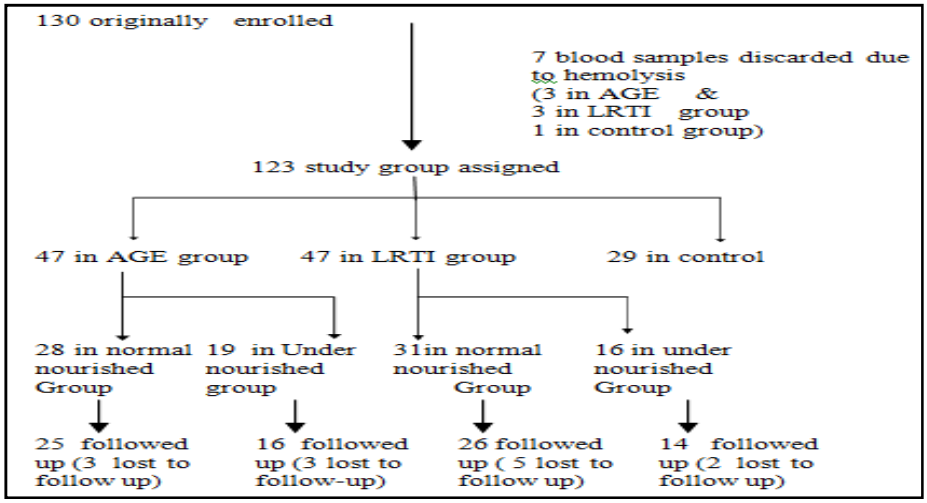

Figure 1: Flowchart depicting study design

Results

The children selected in this study were in the age group of 6 months to 5 years with a mean age of 24.06, 28.06 and 30.08 months in the AGE, LRTI and Control groups respectively.

Table-1: Sex distribution in LRTI and AGE study groups.

Gender Distribution						
Sex	**No (AGE)**	**%**	**No (LRTI)**	**%**	**Controls**	**%**
Males	26	55.32	22	46.81	7	25
Females	21	44.68	25	53.19	21	75
Total	**47**	**100.00**	**47**	**100.00**	**28**	**100**

There were 55.32% males in AGE group, 46.81% males in LRTI group and 25% males in the control group.

Table-2: The table is showing a comparison of serum zinc levels in the AGE, LRTI and Control group.

	Zinc levels		**P-Value**
	Mean	**SD**	
Control	81.65	16.95	
AGE	71.39	21.37	0.03
LRTI	69.45	19.9	0.007

The serum zinc levels were significantly lower in children with AGE and LRTI as compared to that of the children in the control group which was very significant with LRTI than with AGE group. Also, a considerable number (13 out of 29) in the control group who were otherwise asymptomatic had low serum zinc levels.

Table-3: Table showing Mean serum zinc level in malnourished and normally nourished children with AGE. And LRTI.

	Zinc levels				**P-Value**
	Malnourished (n=35)		**Normal (n=28)**		
	Mean	SD	Mean	SD	
AGE (n=47)	67.77	11.46	73.85	26.41	0.35 NS
LRTI(n=47)	57.52	16.61	75.62	18.98	0.02

Out of the 47 children in the LRTI group, 16 children were found to have undernutrition. The malnourished children were found to have a statistically significant lower level of zinc than their adequately nourished. Out of the 47 children in the AGE group, 19 children were found to have undernutrition. The malnourished children were found to have a lower level of zinc than their adequately nourished counterparts, but that was statistically not significant.

Table-4: Table is showing a comparison between malnourished and adequately nourished children in the AGE group concerning the resolution of symptoms.

Acute gastroenteritis	Malnourished (n= 19)		Well-nourished (n=28)		P-Value
	Mean	SD	Mean	SD	
Symptom duration	4.8	0.9	3.9	1.3	0.01
Symptom relief - Tx	3.6	0.7	2.5	1.1	0.0004

The undernourished children in the AGE group had an average duration of symptoms that was slightly more than that of the adequately nourished children, and relief of symptoms with adjuvant zinc therapy in undernourished was significantly more than that of the adequately nourished

Table-5: Comparison of symptom resolution (in days) in the AGE group with low and normal zinc levels

Acute gastro enteritis	Zinc low (n=27)		Zinc normal (n=20)		P-Value
	Mean	SD	Mean	SD	
Symptom duration	5.0	0.9	3.4	0.9	0.0001
Symptom relief - Tx	3.7	0.7	2.0	0.7	0.0001

The AGE group with low zinc levels had both average duration of symptoms and relief of symptoms with supplementation with zinc that was significantly more than that of the adequately nourished children.

Table-6: Table showing a comparison between malnourished and adequately nourished children in the LRTI group concerning the resolution of symptoms.

LRTI	Malnourished (n= 16)		Well-nourished (n=31)		P-Value
	Mean	SD	Mean	SD	
Symptom duration	8.8	1.62	6.6	1.5	0.0001
Symptom relief - Tx	5.81	1.11	4.4	2.1	0.01

The undernourished children in the LRTI group had an average duration of symptoms that was significantly more than that of the adequately nourished children, and relief of symptoms with adjuvant zinc therapy in undernourished was slightly more than that of the adequately nourished children.

Table-7: Comparison of symptom resolution (in days) in the LRTI group with normal and low zinc levels.

LRTI	Zinc Low(n = 25)		Zinc Normal(n=22)		P-Value
	Mean	SD	Mean	SD	
Symptom duration	8.68	1.44	5.9	1.0	0.0001
Symptom relief – Tx	6.52	0.82	3.0	0.8	0.0001

The LRTI group with low zinc levels had both average duration of symptoms and relief of symptoms that were significantly more than that of the children with normal zinc levels with LRTI even with zinc adjuvant therapy Taking undernourishment as criteria in LRTI group, more than three fourth showed the persistence of symptoms till six days even with adjuvant zinc therapy, in contrast with normally nourished majority showed symptom relief by the 3rd day after admission.

Follow up- In AGE group (47) on follow up for further recurrences, next 6months 9 had one episode, and 6 had two episodes among 19 undernourished, and 9 had one episode, and six had two episodes and one had3 episode among 28

normally nourished. These differences between normal and malnourished in the occurrence of one or more episodes of AGE over the next six months was not statistically significant.

In LRTI group (47) on follow up for further recurrences, next 6months 10 had one episode, and 1 had two episodes among 16 undernourished, and only 5 had one episode among 31 normally nourished. These difference between normal and undernourished in the occurrence of one or more episodes of LRTI over the next six months is highly significant In LRTI group (47) on follow up for further recurrences next six months in children with low and normal zinc levels, 12 had one episode, and 1 had two episodes among children with low zinc level (25), and only 4 had one episode among children with normal zinc levels (22).

Discussion

There are some studies on the beneficial effects of zinc on the morbidity associated with conditions like pneumonia and gastroenteritis. Most of the studies and reports of the past are universally of the opinion that zinc has a beneficial effect in gastroenteritis and diarrhea. [5,6,7]. In this study, children with gastroenteritis and pneumonia were found to have a reduced zinc level when compared to asymptomatic children. This study is comparable with Khalili et al [8] and Black R.E [9] who had reported the prevalence of micronutrient deficiencies including zinc and vitamin A in children with these infections.

The study also demonstrates the vicious cycle of increased prevalence of these infections in children with micronutrient deficiencies. Another study which supports this is a case-control study performed by Kumar S et al [10] in a referral & teaching hospital in North India on children aged two months to five years, to compare serum zinc levels in 50 cases of severe acute pneumonia and 50 age, sex, nutritional status matched controls. Mean Zinc levels in cases and controls was 376.1 ug/dL + 225.73 and 538.52 ug /dL ±228.0 respectively (P value 0.0003).

Also, in this study, asymptomatic children without AGE or LRTI also had lowered zinc levels when compared to the reference range. These were the children not suffering from either diarrhea or pneumonia. They were the ones randomly picked up when coming for immunization or the children admitted in the pediatric ward without LRTI or AGE. The low zinc level in the asymptomatic children too suggests an underlying zinc deficiency in children in this part of the district.

This low zinc level is possible as in southern Asia, macronutrient malnutrition and micronutrient deficiencies, especially deficiencies of zinc, are common in young children [7]. This hypozincemia problem attributed to dietary insufficiency, limited nutrient bioavailability from local diets, and excretion of nutrients during recurrent episodes of infection [7]. Baqui A. Het al [11] in their study observed that serum zinc was low in 44% of healthy children with diarrhea. Olmez et al[12] in their prospective study on the mean serum zinc levels in children in the age group of 2-24 months found that although the control group (n = 41) were asymptomatic, still 39% of children in this group had a mean zinc level that was below the normal standards for age [12]. In the present study among AGE, group means zinc levels in undernourished were less than mean zinc levels but it is not statistically significant may be because of the small sample size in this study.

Similar findings found in Study done by Olmez et al[12] in a total of 82 children (41 children suffering from acute gastroenteritis of < 7 days duration along with 41 age and sex-matched controls) showed that the baseline characteristics in the mean zinc levels in both the groups of children were the same with no statistical difference [12]. Among LRTI group of present study mean zinc levels in undernourished were less than mean zinc levels which are significant statistically.

This study is comparable with the study done by Md. Salim Shakur et al [13] by Both control and ALRI groups matched for age, sex and anthropometry shows that serum zinc significantly lower in the Acute LRTI group than control (OR = 6; CI 95%: 1.83, 19.62; P<0.05) Serum zinc concentration in Acute LRTI ranged from 40 µg/dL to 130 µg/dL and in control 90 µg/dL to 220 µg/dl [13].

The undernourished children in the AGE group even with adjuvant zinc therapy had the resolution of symptoms was significantly longer than that of the adequately nourished children. In the study done by Tomkins et al [14] On average, the duration of diarrhea appears longer in undernourished children and clinically ill with diarrhea 13.6% of the time compared with 7.6% of the time for the better-nourished children (P < 0.01)The undernourished children in the LRTI group

with adjuvant zinc therapy had an average duration of symptoms that was significantly longer than that of the adequately nourished children, and resolution of symptoms is seen clinically but not as significant as compared to the total duration of LRTI . This study is comparable with the findings of Caulfield S.E et al [15] and Fishman S.M et al [16] who state that under-nutrition is known to associated with greater severity of pneumonia, a higher frequency of complications, more prolonged episodes of infection, and higher case fatality rates.

The AGE group with low zinc levels had both average duration of symptoms and resolution of symptoms was significantly more than that of the adequately nourished children. As per the study of Polat TB et al [17]. the mean duration of diarrhea was shorter and the children with consistent diarrhea for more than 3-7 days was lower in the study subgroups 40 subjects with low zinc levels (Group 1a) and 52 subjects with normal zinc levels (Group 1b) than in the control subgroups.

Prolonged diarrhea was present in 12% of children in the study group, and in 44% and 37% of children in the hypozincemia and normoglycemic control subgroups, respectively [17].

Zinc supplementation in AGE and children with normal zinc levels have a shorter mean duration of symptoms due to diarrhea. Similar seen As per Marzia Lazzerini [18] et al In children older than six months of age, zinc therapy may shorten the average duration of diarrhea by around half a day (MD −11.46 hrs, 95% CI −19.72 to −3.19; 2581 children, 9 trials, low certainty evidence), and reduces the number of children with diarrhea persists until day seven (RR 0.73, 95% CI 0.61 - 0.88; 3865 children, 6 trials, moderate certainty evidence) [18] The LRTI group with low zinc levels had both average duration of symptoms and relief of symptoms that was significantly longer than that of the children with normal zinc level with LRTI.

Bikha Ram Devrajani et al [19] did the study; the mean age of the 118 patients in the study was 25.64±6.53 years. The mean serum zinc level was 8.279±2.77 mmol/L, while the mean serum zinc levels in patients having low and normal levels was 6.740±1.47mmol/L and 13.243±1.52 mmol/L respectively ($p<0.001$) Out of 77 (65%) hypozincaemia patients, 69(90%) recovered, while 08(10%) failed to recover) during their hospital stay ($p<0.33$). Of the 69 who recovered, 29 (42%) patients did so in less than two weeks, while 40 (58%) patients recovered in more than 02 weeks [19].

Follow– Up Period- Some studies showed zinc supplementation in both AGE and LRTI decreases further episodes on follow up and reduce in morbidity and mortality in these children None of the studies conducted previously in both AGE and LRTI with zinc supplementation showed the comparison with low zinc levels at initial presentation and further recurrences of episodes of AGE and LRTI.

Conclusions and Recommendations

1.Supplementation of zinc reduces duration of symptoms of pneumonia and diarrhea and hence must be administered to all cases.

2.Zinc supplementation reduces the frequency of recurrences especially in malnourished children.

What this study adds to the existing knowledge?

Present study shows that zinc supplementation in both AGE and LRTI decreases recurrences in a period of six months of both the conditions. Dose of zinc supplementation in LRTI is same as that of AGE can be used.

Contribution by authors

- Data collection done by **Dr. Vinay Kumar**
- Analysis and manuscript preparation done by **Dr. Vinay Kumar** and **Dr. Nalluru Lakshmi Sravanthi**,
- All research work done under the guidance of **Dr. B. Vijaya Lakshmi**, and **Dr. Kantha Kumari**.

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