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CORRELATION OF SERUM ZINC LEVEL WITH SEVERITY OF DIARRHEA IN CHILDREN UNDER 16 YEARS OF AGE: A CROSS-SECTIONAL OBSERVATIONAL STUDY

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ABSTRACT

Acute diarrhea is one of the commonest cause of hospitalization in children and it can vary from self limiting course to severe diarrhea requiring hospitalization and can cause severe morbidity and occasionally mortality if not treated accordingly. Zinc deficiency can cause impaired immunity thereby increasing the infections including acute diarrhea. It is thus biologically plausible that zinc deficiency may increase the incidence and duration of acute diarrhea in children. WHO has recommended supplementation of zinc for each episode of diarrhea irrespective of zinc status of the child. Zinc and its association with diarrhea in school going children (5 -16yrs) has not been established. In this study, we attempted to analyse if zinc has its role in this age group in causing diarrhea. **AIM:** To study the correlation between serum zinc level and severity of diarrhea in children of age 6 months-16 years. 450 children were assessed for eligibility and 400 met the inclusion criteria who were studied. **Results:** Mean serum zinc levels and zinc deficiency were not associated with severity of diarrhea, severity of dehydration or length of stay in hospital. Zinc levels were lowest in upper lower socio-economic status (SES).

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INTRODUCTION

Acute diarrhea is a leading cause of emergency department visits and hospitalizations causing a significant economic burden.[1] The clinical spectrum of diarrheal disease range from a self-limiting disease with the potential of short hospitalization for few days up to more prolonged disease that may be complicated by severe dehydration, malnutrition, and death.[2] Zinc is considered as an essential trace element required for normal intestinal mucosal integrity, sodium and water transport and immune function.[3] Unfortunately, 30% of the world's population is zinc deficient.[4] Zinc deficiency is among the 10 most important factors that lead to increased morbidity and mortality in developing countries. Zinc deficiency results in impaired immunity, which may increase the risk of infections, including diarrhea and pneumonia. It is thus biologically plausible that zinc deficiency may increase the incidence and duration of acute diarrhea in children. WHO has recommended supplementation of zinc for each episode of diarrhea irrespective of zinc status of the child.[5] Zinc has a direct effect on intestinal villus, brush-border disaccharidase activity, and intestinal transport of water and electrolytes. It also has a marked effect on T-cell function and its supplementation improves immunity. Thus, it might also reduce the severity of diarrhea.[6]

The role of zinc level and its association with the outcome of acute pediatric diarrhea has been studied over the last years in both developing and developed countries showing a potential effect of zinc in reducing complications and mortality rates.[7] Hence this study was undertaken to estimate serum zinc level in children with acute diarrhea and its correlation with the severity of diarrhea estimated by Vesikari Scoring System[8] which is a clinical severity scoring system for grading of acute gastroenteritis (Table 1).

Need for the Study: There are many studies proving role of zinc supplementation in diarrhea, but there are very few studies regarding correlation of serum zinc and severity of diarrhea in children in India. Zinc deficiency based on socioeconomic status has not been frequently reported. Zinc and its association with diarrhea in school going children (5 -16yrs) has not been established. In this study, we attempted to analyse if zinc has its role in this age group in causing diarrhea.

Aims and Objectives

Aim: To study the correlation between serum zinc level and severity of diarrhea in children of age 6 months-16 years.

Objectives

Primary Objective: To correlate serum zinc levels with severity of diarrhea at the time of presentation to hospital in children of age 6 months-16years.

Secondary Objective

1. To determine the prevalence of zinc deficiency with respect to socioeconomic status.
2. To determine the association of serum zinc level with duration of hospital stay for hospitalised children with acute diarrhea.

MATERIALS AND METHODS

Study area: Department of Pediatrics, NICE Hospital for Women, Newborns and Children.

Study Design: Cross sectional study.

Study population: All children under 16 years of age, who presented to hospital with acute diarrheal illness (both in- patients and out-patients)

Study sample: All consecutive cases were considered for enrollment to achieve the required sample size.

Study Period: September 2020 till September 2022 (2 years)

Inclusion criteria: Children of age group 6months- 16years with acute diarrheal illness.

Exclusion criteria

1. Children with known intestinal disorders leading to chronic diarrhea.
2. Children with diarrhea more than 2 weeks (persistent diarrhea)
3. Children who have already been supplemented with Zinc during the current illness
4. Children whose parents have refused consent to participate in the study

Primary Outcome*:* Measurement of serum zinc levels in children with acute diarrhea and correlation between the serum zinc level and severity of diarrhea in children of age group 6months-16years.

Secondary Outcome: Measurement of serum zinc level in hospitalized children suffering from acute diarrhea and its association with duration of hospital stay and estimation of prevalence of zinc deficiency with respect to socioeconomic status.

METHODOLOGY

Institutional ethical committee clearance was obtained prior to beginning of the study**,** all children fulfilling the inclusion criteria were enrolled in the study.

Sample size: Sample size was calculated using the following formula:

$n= 4pq/d^2$

p= prevalence of zinc deficiency in children below 5 years of age
q= 100-p
d= Allowable error of 5% with 95% confidence limits.

So, assuming 95% confidence interval, 43.8% as prevalence[9] of zinc deficiency in children below 5 years of age and 5% allowable error, the required sample size was 398.

Statistical Analysis: Collected data were entered in the Microsoft excel 2016 for further analysis of data. Qualitative data were represented by using frequency and proportions while quantitative data were represented using mean and standard deviation. Association between the qualitative variable were assessed with the help of chi-square test and mean difference between different variable were assessed using ANOVA and T-test. To know the correlation between the variables pearson correlation test was used. P-value less than 0.05 were considered as statistically significant at 5% level of significance.

Data collection methods

- Written informed consent and Child assent (where applicable) for participating in the study was obtained from those fulfilling the inclusion and exclusion criteria.

Acute diarrhea was defined as caregiver's report of ≥ three loose or watery stools in a 24-hour period.

- At Out Patient Department (OPD) and in the ward, relevant history taking and clinical examination was done and blood samples were drawn for laboratory tests.
- Relevant history was obtained as follows:
  - Duration of diarrhea, Stool frequency, blood in stool
  - Duration and frequency of vomiting
  - H/o chronic diarrhea and any intestinal disorders
- Duration of diarrhea was defined as time in days from the first episode of diarrhea till sample collection.
- Socioeconomic status was assessed using Modified Kuppuswamy scale
- At the initial presentation, child's dehydration status was documented and scored as per Vesikari scoring system[8] into 3 groups – mild, moderate and severe as shown below:

Table 1. Vesikari Scoring System[8]

Parameter	Score 1	Score 2	Score 3
Diarrhea			
Maximum number of stools per day [a]	1-3	4-5	>/6
Diarrhea duration (days) [b]	1-4	5	>/6
Vomiting			
Maximum number of vomiting episodes/ day [c]	1	2-4	>/5
Vomiting duration [d]	1	2	>/3
Temperature [e] (^{0}C)	37.1-38.4	38.5-38.9	>39.0
Dehydration [f]	N/A	1-5%	>6%
Treatment [g]	Rehydration	Hospitalisation	N/A

Severity Category: Mild: <7, Moderate: 7-10, Severe: >/11; Maximum Score: 20

Sample collection*:* Three ml blood venous sample was collected and centrifuged in zinc free tubes (BD trace element tubes) within one hour of enrollment before administering zinc therapy.

Testing Method: Serum zinc was measured using colorimetric method by Erba CHEM-7 analyzer and expressed as mcg/dl.

Diarrhea was managed according to the standard WHO guidelines, including oral rehydration therapy (ORT) with WHO low osmolarity oral dehydration solution (ORS) and zinc. Zinc was given in form of oral suspension (20mg/5ml) at the dose of 10mg once a day for 14 days for children under 6 months and dose of 20mg once a day for 14 days for children above 6 months of age. Children were monitored till cessation of diarrhea or till 7 days. Severity scoring system was correlated with serum zinc levels.

In our study, normal serum zinc level was defined as 60-120 mcg/dl with reference to the study done by Barman N et al [10] During the study period 450 children with acute diarrheal illness were studied for eligibility. However 50 children were excluded from the study as they fulfilled the exclusion criteria (Figure 1).

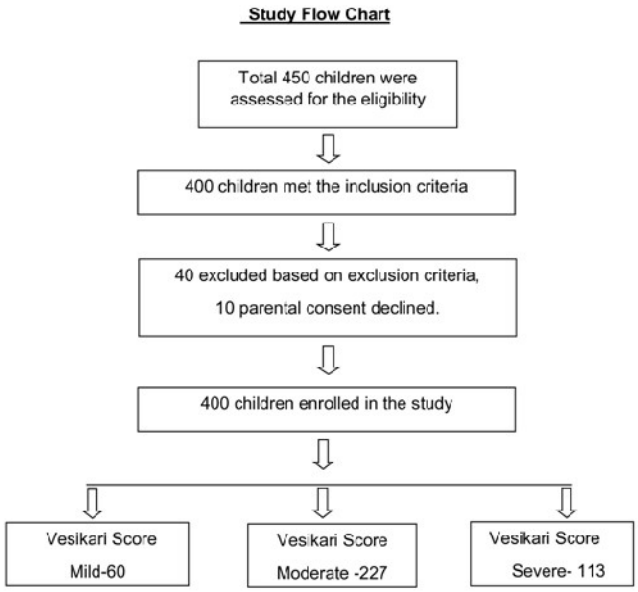

Figure 1. Study Flow Chart

Table 2. Comparison of mean serum zinc levels in different groups based on Vesikari severity rating

Severity Rating	N	Serum Zinc (mcg/dl)				T-test	p-value
		Mean (mcg/dl)	Standard Deviation	Minimum	Maximum		
Mild	60	79.97	18.128	46	121	2.85	0.059
Moderate	227	86.37	19.237	48	138		
Severe	113	83.67	19.429	42	140		
Total	400	84.65	19.22	42	140		

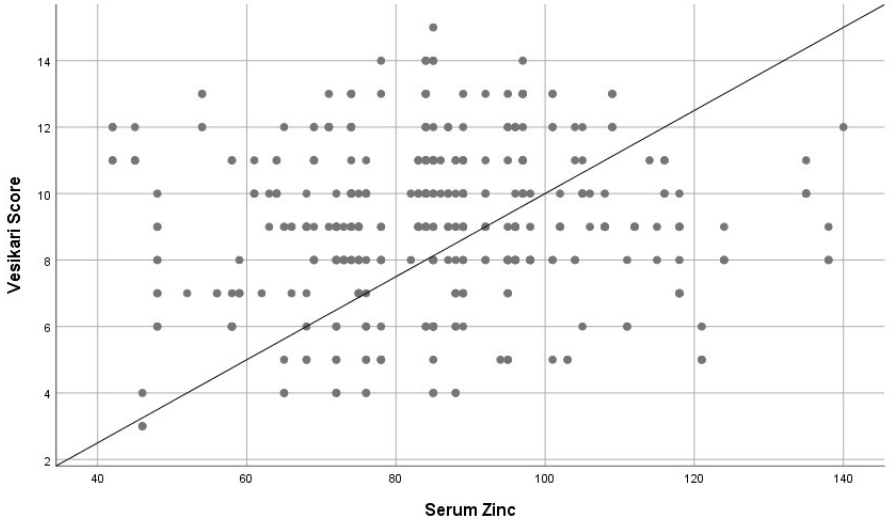

Figure 2. Scattered diagram showing correlation between Serum zinc level and Vesikari score

Table 3. Association of serum zinc level and socioeconomic status

Socioeconomic Status	Serum zinc levels (mcg/dl)				Chi-square	p-value
	≤60	61 - 120	≥121	Total		
Lower	6(11.5%)	42(80.70%)	4(7.6%)	52(100%)	23.73	0.001
Lower Middle	9(6.25%)	131(90.97%)	4(2.7%)	144(100%)		
Upper Lower	15(18.29%)	62(75.6%)	5(6.0%)	82(100%)		
Upper Middle	8(9.6%)	75(90.3%)	0(0%)	83(100%)		
Upper	0(0%)	35(89.74%)	4(10.2%)	39(100%)		
Total	38	345	17	400		

RESULTS

- Out of the total study sample of 400, males and females were 216 (54%) &184 (46%) respectively, males outnumbering females.
- 124 children were of 6 months -1year, 252 children were in age group 1-5 years and 24 children were in 5-10 years age group.
- Out of the total study sample, 115 children (28.7%) had no dehydration, 245 children (61.3%) had some dehydration, 40 children (10%) had severe dehydration based on WHO assessment of dehydration.

- As per modified Kuppuswamy Scale, in our study, lower middle class population (36%) was highest followed by upper middle (20.8%) , upper lower (20.5%) and the least was upper class (9.8%).
- In our study, 105 children had serum zinc levels between 81-90 mcg/dl , 86 children had zinc levels between 71-80 mcg/dl, 50 children had zinc levels between 90-100 mcg/dl. Seventeen children had zinc level >120 mcg/dl (above upper limit of normal), 38 children had zinc level <60 mcg/dl (below normal). The mean serum zinc level in the entire study group was 84.6 mcg/dl.
- Mean serum zinc values in mild, moderate and severe grading of Vesikari were 79.97, 86.37, 83.67 mcg/dl respectively. The difference was not statistically significant (p value was 0.059).

Correlation between Serum zinc level and Vesikari score: There was no correlation between serum zinc level and Vesikari score. (Pearson correlation coefficient- 0.069, p- value: 0.17). (Figure 2)

Association of serum zinc level and socioeconomic status: Serum zinc levels <60mcg/dl was found highest in upper lower class followed by lower class. Serum Zinc level >120mcg/dl was found highest in upper class than in other groups and this difference was statistically significant (Table 3).

Serum zinc levels and duration of hospital stay: Mean serum zinc levels were 82.1 mcg/dl, 86.1 mcg/dl, 83.6 mcg/dl, 86.2 mcg/dl and 83 mcg/dl in children admitted for 1, 2, 3, 4 and 5 days respectively. There was no significant association of serum zinc levels with duration of hospital stay (p value is 0.779).

DISCUSSION

Most of the studies of role of zinc in diarrhea had been from African states, where they proved that zinc has a significant role in the treatment of diarrhea. There are very few studies on zinc levels in children with diarrheal illnesses in India. This study was done to determine the correlation of serum zinc with severity of diarrhea in children of age group 6 months to 16 years, conducted in the department of Pediatrics of a tertiary care hospital over a period of 2 years. In this study severity of illness was assessed with Vesikari Scoring system (VSS) and serum zinc levels were measured in all the children presented with acute diarrhea. Based on the Vesikari Score, children were grouped into mild, moderate and severe grading. Most of the children in our study had some dehydration, whereas in the study done by Eskander et al[8], out of 80 studied cases, 66 children (82.5%) suffered from dehydration. Out of them, 27 (40.9%) child had mild dehydration, 27 (40.9%) child had moderate degree of dehydration while 12 children (18.2%) suffered from a severe degree of dehydration with 9 cases requiring ICU admission. In our study, 15 % had mild grading, 56.7 % had moderate grading and 28.2 % had severe grading of illness as per Vesikari score. In the study by Eskander et al[8], 87.5% had severe grading, with 12.5% in the moderate category. The mean serum zinc level in our entire study sample was 84.65 mcg/dl. Eskander et al[8] reported in their study that mean serum zinc levels was 65 ± 13.5 mcg/dl, which was similar to the levels seen in the study by Afolabi et al.[11] In a study done by Rerksuppaphol et al,[12] in children with acute diarrhea in Thai children, the mean serum zinc level in the study was 69.2 mcg/dl. The higher mean serum zinc levels in our study could be attributed to difference in the socio-economic and nutritional status of our study population. In our study, the proportion of children with zinc deficiency, i.e zinc levels below normal (< 60 mg/dl) was 9.5% (38 /400). Prevalence of zinc deficiency has been variously reported in India. Kapil et al[11] in their large survey on prevalence of zinc deficiency among under-5 children in five Indian states (sample size: 1655 children) found that 43.8% were zinc deficient. Agarwal et al[5] reported that 34% of 198 children with acute diarrhea in their study were zinc deficient.

Our study had lower prevalence of zinc deficiency probably due to its urban setting in a tertiary care hospital with better socioeconomic status among the study population. In our study, mean serum zinc levels were 79.9, 86.3 and 83.6 mcg/dl respectively in the three groups of mild, moderate and severe illness, as categorized by Vesikari score. This difference was not statistically significant. Our findings are in contrast to the findings of Eskander et al[8] and Agarwal et al[5]. Eskander et al[8] reported that there was significant negative correlation between zinc levels and Vesikari score (Pearson correlation - 0.496); and zinc levels and severity of dehydration (Pearson correlation - 0.429). Our study evaluated serum zinc levels in relation to duration of hospital stay. There was no significant difference in serum zinc levels among children with varying duration of hospital stay of 1-5 days. Similarly, in the study by Agarwal et al,[5] total duration of diarrhea did not correlate with serum zinc levels. However, Eskander et al[8] found significant negative correlation of duration of hospital stay with serum zinc levels. Patel A et al[7] in a meta-analysis of zinc supplementation in acute diarrhea concluded that mean duration of diarrhea decreased by 19.7% with zinc supplementation.

CONCLUSION

Mean serum zinc levels and zinc deficiency were not associated with severity of diarrhea, severity of dehydration or length of stay in hospital. Zinc levels were lowest in upper lower SES. These findings suggest that there is a need to re-evaluate the need for administering zinc supplements to all children with acute diarrhea in all clinical settings. Prevalence of zinc deficiency needs to be widely estimated among children in our country and randomized control studies are required to establish the beneficial role of zinc supplementation in children with diarrhea.

Limitations of the study

1. Our study was conducted in an urban tertiary care pediatric hospital and is representative of a limited section of the population. The findings cannot be extrapolated to the community, which requires different studies.
2. The study was conducted during the Covid pandemic period, during which use of zinc and multivitamin supplementation was rampant among the general population including children. This may have led to higher mean serum zinc levels in our subjects. The baseline zinc levels of the study population was not known.
3. This was a cross-sectional observational study and was limited by the absence of control group, which would have been a better study design to show the association of zinc levels and diarrhea.
4. Many parents were hesitant to revel their family income, which may have altered the grading of their socioeconomic status.

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