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A STUDY TO EVALUATE EFFICACY OF ZINC SUPPLEMENTATION IN NEWLY DIAGNOSED HIV AFFECTED CHILDREN

Paediatrics

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ABSTRACT

Background: In Indian literature, very few studies are available in the pediatric population evaluating role of zinc in HIV-affected children. Hence this study was undertaken, evaluating the role of zinc on growth, CD4 counts and serious co morbidities in HIV affected children. **Objective:** Aim of this study was to evaluate the role of zinc on growth, CD4 counts and serious co-morbidities in newly diagnosed HIV affected children. **Study design:** Prospective open randomized controlled trial **Participants:** All newly diagnosed HIV affected children **Intervention:** Zinc levels were done at baseline, at 6 months and at 1 year of follow up. Those who were found to be zinc deficient baseline were started on zinc supplement. Children who were not zinc deficient were randomized into two groups, zinc supplementation and no zinc supplementation. Group 1: Zinc deficient (zinc level < 60 µg/dl) Group 2: normal zinc levels given zinc supplementation. Group 3: normal zinc levels and not given zinc supplementation. The subjects were analysed at 6 months and 1year with respect to anthropometrical assessment, serum zinc level and CD 4 counts. **Outcome & Results:** Out of 83 study subjects, 80.1 % (67) were less than 10 years of age with male to female ratio being 0.9:1. 15.66 % (13) patients had zinc deficiency at baseline. Mean weight, height and CD4 improved significantly with zinc supplementation. Frequency of Acute gastroenteritis (AGE) episodes decreased significantly in zinc supplemented group at 1 year. **Conclusions:** Zinc supplementation in HIV affected children has significant impact on nutritional status as well as immunological status.

KEYWORDS

HIV affected children, nutritional status, and Zinc deficiency

INTRODUCTION

AIDS is a global pandemic of this era claiming over 25 million lives in last 30 years. There were an estimated 37.7 million [30.2–45.1 million] people living with HIV at the end of 2020. In 2020, 680 000 [480 000–1.0 million] people died from HIV-related causes and 1.5 million [1.0–2.0 million] people acquired HIV.[1]

In India as per NACO, National adult (15–49 years) HIV prevalence was estimated at 0.22% (0.17%–0.29%) in 2020; 0.23% (0.18%–0.31%) among males, and 0.20% (0.15%–0.26%) among females. The total number of people living with HIV (PLHIV) in India was estimated at 23.19 lakh (18.33 lakh– 29.78 lakh) in 2020. Children (<15 years) accounted for 3.5 %.[2]

Among all the micronutrient abnormalities found in HIV infection, zinc deficiency is most prevalent. Zinc deficiency can cause impaired growth and development in children, immune dysfunction, and increased susceptibility to infection. Low levels of plasma zinc predict a 3-fold increase in HIV related mortality.[3]

Zinc is component of both catalytic and structural protein of HIV.[4]It is required for the activity of reverse transcriptase and causes viral replication through binding to the catalytic site of HIV protease.[4]

In Indian literature, very few studies are available in the pediatric population evaluating role of zinc in HIV-affected children. Hence this study was undertaken, evaluating the role of zinc on growth, CD4 counts and serious co morbidities in HIV affected children.

METHODS

This was a prospective open randomised controlled trial conducted at Paediatric Centre of Excellence (PCOE) for HIV care at a tertiary care hospital from May 2014 to November 2015. Written informed consent was taken from all parents/ guardians and patients(assent). The study was approved by ethics committee of the medical college.

A total of 83 newly HIV diagnosed children, from 6 months to 15 years of age, were included in the study. All patients were followed up for 1 year.

Inclusion criteria

All newly diagnosed HIV affected children from age group 6 months-15 years

Exclusion criteria

HIV affected children already on zinc supplementation or higher than normal zinc level at presentation.

All newly diagnosed HIV affected children attending Pediatric Centre of Excellence (PCOE) for HIV Care fulfilling the inclusion and exclusion criteria were recruited in the study after informed consent/assent. Zinc levels were done for all children at baseline, at 6 months and at 1 year. Those who were found to be zinc deficient were started on zinc supplement. Children who were not zinc deficient were randomized into two groups by simple randomisation method. One of the groups was started on zinc supplement while other group was not given zinc supplements.

Normal serum zinc level [5]:0-10 yrs: 60-120 µg/dl & ≥ 11 yrs: 66-110 µg/dl

Serum zinc levels were estimated by Colorimetric method. Zinc in an alkaline medium reacts with nitro-PAS to form a purple-coloured complex. Intensity of the complex formed is directly proportional to the amount of zinc present in the sample. [6,7]

Detailed history, clinical symptoms, examination finding including anthropometry were noted in a pre-designed Performa. All baseline investigations included complete blood counts, liver function tests, renal function tests and CD4 counts. Along with these baseline investigations, serum zinc levels were also done. In history they were specifically asked for any acute respiratory, gastrointestinal or other co morbidity requiring admission/ hospitalization within 1 year prior to recruitment in study.

Supplementation was given in form of zinc acetate syrup (5 ml=20 mg elemental zinc) in the dosage as per recommended dietary allowance (RDA) for Indian population. 1-3 yrs-5mg/day, 4-6yrs-7mg/day, 7-9yrs-8mg/day, 10-12yrs-9mg/day, 13-15yrs-11mg/day.

The subjects were analysed at 6 months and at 1year follow up with respect to anthropometrical assessment, serum zinc level and CD 4 counts. They were also assessed for any acute respiratory, gastrointestinal or other co morbidity required hospitalization during study period.

Statistical analysis

All the analysis was performed using 10.0 version of statistical

software SPSS. Data were entered in Microsoft Excel and analysed using Stata Version 13. Means and standard deviations were calculated for the linear variables, and proportions for the categorical variables. The means between two groups were compared using the unpaired and paired t-test (for different groups, and pre-and post-means respectively). For more than two groups, we used Analysis of Variance (ANOVA) to compare the means and standard deviations. For data that were not normally distributed, we used Wilcoxon rank sum test and Kruskal-Wallis equality-of-populations rank test. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Total of 83 newly diagnosed HIV affected children were included in the study. Table 1 shows age and gender distribution of patients. 15.66 % (13) patients were having zinc deficiency at baseline out of 83 study subjects.

Table 1: Age and gender distribution of study subjects (n=83)

Age group	< 5 years	5.1 – 10 years	10.1 – 15 years	Total
Males	10 (25%)	24 (60%)	6 (15%)	40 (48.2%)
Females	11 (25.6%)	22 (51.2%)	10 (23.2%)	43 (51.8%)
	21 (25.3%)	46(55.4%)	16 (19.3%)	83

For analysis subjects were divided into 3 groups.

Group 1: Those who were zinc deficient and started on zinc supplement.

Group 2: Those who had normal zinc levels and given zinc supplementation.

Group 3: Those who had normal zinc levels and not given zinc supplementation

Table 2 demonstrates clinical stage wise distribution of all three groups. Mean zinc levels significantly increased over 1 year in all 3 groups (p<0.05). On comparison amongst 3 groups, at 1 year, mean zinc levels were significantly greater in group1 as compared to other two groups. (p<0.05) (Table -2 & Figure 1)

Table 2: Comparison of various parameters in three groups (n=83)

		Group 1 (n=13)	Group 2 (n=38)	Group 3 (n=32)
Mean Zinc levels (µg/dl)	Baseline	39.06 ± 12.66	124.82 ± 47.77	121.11 ± 46.72
	At 6 months	97.52 ± 41.79	160.45 ± 59.23	164.13 ± 105.79
	At 1 year	114.02 ± 58.27	211.49 ± 116.09	200.22 ± 115.31
	p-value	< 0.05	< 0.05	< 0.05
Clinical stage	Stage 1	1 (7.7%)	16 (42.1%)	12 (37.5%)
	Stage 2	1 (7.7%)	16 (42.1%)	20 (62.5%)
	Stage 3	6 (46.1%)	4 (10.5%)	0
	Stage 4	5 (38.5%)	2 (5.3%)	0
Weight in kg, Mean ± SD	Baseline	19.90 ± 7.64	16.88 ± 7.92	19.07 ± 8.52
	At 6 months	21.27 ± 8.07	17.96 ± 7.41	20.50 ± 15.82
	At 1 year	22.01 ± 7.71	18.75 ± 7.11	21.42 ± 9.74
	p-value	< 0.05	< 0.05	> 0.05
Height in cm, Mean ± SD	Baseline	120.53 ± 17.90	105.12 ± 24.45	111.27 ± 28.46
	At 6 months	122.07 ± 17.64	108.01 ± 22.73	114.39 ± 35.67
	At 1 year	123.03 ± 17.25	110.04 ± 21.14	116.67 ± 26.29
	p-value	< 0.05	<0.05	>0.05
Cd4 count/cumm, Mean ± SD	Baseline	402.76 ± 296.96	906.97 ± 701.53	1034.25 ± 797.36
	At 6 months	452.46 ± 228.10	940.07 ± 670.20	1160.28 ± 848.25
	At 1 year	502.07 ± 269.87	990.60 ± 749.73	1279.34 ± 960.13
	p-value	< 0.05	< 0.05	< 0.05

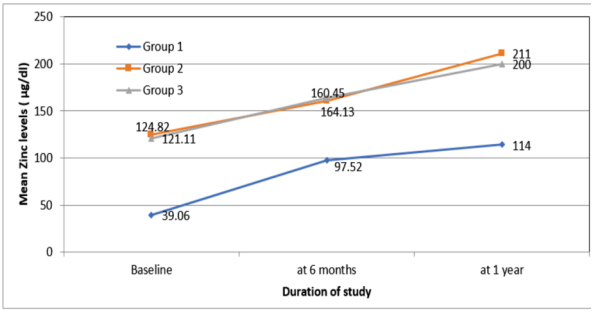

Figure 1: Comparison of mean zinc levels in three groups (µg/dl) (n=83)

Table 2 shows changes in the mean weight, height and CD4 counts in all three groups at 6 months and 1 year, as compared to baseline. In group 1, mean weight increased from baseline value of 19.90 ± 7.64 to 21.27 ± 8.07 kg at 6 months and 22.01 ± 7.71kg at 1 year *(p value <0.05)*. Similarly in group 2, mean weight increased from 16.88 ± 7.92 to 17.96 ± 7.41 kg at 6 months and 18.75 ± 7.11 kg at 1 year of follow up. This improvement was statistically significant in group 1 and group 2 (p value <0.05*)*. In group 3, mean weight increased from 19.07 ± 8.52 to 20.50 ± 15.82 kg at 6 months and 21.42 ± 9.74 kg at 1 year of follow up. (p value >0.05). At 1 year follow up, group 1 and group 2 (zinc supplemented group) had weight gain statistically more significant as compared to group 3, (non zinc supplemented). (p value <0.05)

In group 1, mean height improved from baseline value of 120.53 ± 17.90 to 123.03 ± 17.25 cms at 1 year. *(p value< 0.05)* Similarly in group 2, mean height significantly increased from 105.12 ± 24.45 to 110.04 ± 21.14cm. *(p value < 0.05)* In group 3, mean height increased from 111.27 ± 28.46 to 116.67 ± 26.29 cm (p value > 0.05). However, improvement in height was statistically not significant between three groups. (p value >0.05)

As demonstrated in table 2 and figure 2, in group 1, mean CD4 increased from 402.76 ± 296.96/cumm to 452.46 ± 228.10/cumm at 6 months, which further increased to 502.07 ± 269.87/cumm at 1 year. In group 2, mean CD4 increased from 906.97 ± 701.53/cumm to 940.07 ± 670.20/cumm, which further increased to 990.60 ± 749.73/cumm. In group 3 also, mean CD4 increased from 1034.25 ± 797.36 to 1160.28 ± 848.25 to 1279.34 ± 960.13. This was statistically significant in all 3 groups. (p value <0.05) When compared among all 3 groups, at 1 year follow up, increase in mean CD4 was statistically more significant in group 1 (zinc deficient group) as compared to group 2 and group 3 (*p value <0.05*).

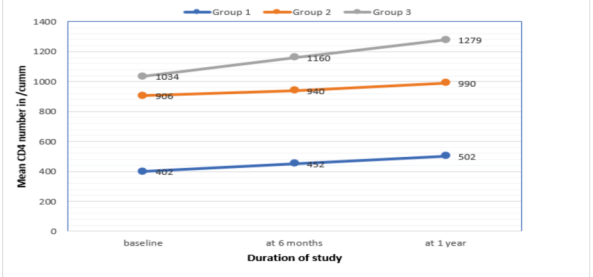

Figure 2: Comparison of mean CD4 counts in three groups (n=83)

The number of episodes of acute respiratory infections (ARI) and acute gastroenteritis (AGE) decreased over 1 year in all 3 groups, however, this was statistically not significant (p>0.05). However, group 1 had more significant decrease in number of AGE episodes as compared to other 2 groups, which was statistically significant. (p value <0.05) (table 3)

Table 3: Comparison of number of episodes of ARI between three groups (n=83)

Number of ARI episodes		1 year prior to enrolment	At 6 months	At 1 years	P value
Group 1 (n=13)	0	1	3	7	> 0.05
	1	11	9	6	
	> 1	1	1	0	

Group 2 (n=38)	0	3	6	18	> 0.05
	1	33	32	20	
	> 1	2	0	0	
Group 3 (n=32)	0	1	2	15	> 0.05
	1	30	29	17	
	> 1	1	1	0	
Number of AGE episodes		1 year prior to enrolment	At 6 months	At 1 years	P value
Group 1 (n=13)	0	3	9	6	< 0.05
	1	6	3	6	
	> 1	4	1	1	
Group 2 (n=38)	0	12	19	20	>0.05
	1	20	14	15	
	> 1	6	5	3	
Group 3 (n=32)	0	11	19	22	> 0.05
	1	20	12	9	
	> 1	1	1	1	

DISCUSSION

Zinc is an essential micronutrient found in every cell of living organism and is necessary for cell growth, wound healing, mucosal epitheliasation, DNA synthesis, and support of a healthy immune system.[8]It may alter appetite control by acting directly on the central nervous system, altering the responsiveness of receptors to neurotransmitters. [9]

In present study, 83 newly affected HIV children attending Pediatric Centre of Excellence (PCOE) for HIV Care were recruited in the study after informed consent.

The male to female ratio was 0.9:1. Gender ratio was similar to a study done in South Western Nigerian population, by Anyabolu et al. [10] In this study, gender ratio was 1:1.3 (p=0.87) in both subjects and controls. Whereas, study done on Nigerian population by Yarhere et al, [11] the male female ratio was 1.3:1.

15.66% (13) patients were having zinc deficiency at baseline out of 83 study subjects. This was different as compared to other studies found in literature. Torsak et al [12] studied associations between Se and Zn level and baseline characteristics of the patients in ART naïve thai children. They found prevalence of zinc deficiency was 32%. Ndeezi et al [13] measured the baseline zinc status of 247 children aged 1-5 years enrolled in a randomised trial for multiple micronutrient supplementation at paediatric HIV clinics in Uganda. Of the 247 children, 134 (54.3%) had low serum zinc (< 10.0 µmol/L). Of the 44 children on highly active antiretroviral therapy (HAART), 13 (29.5%) had low zinc compared to 121/203 (59.6%) who were not on HAART.

This difference can be contributed to difference in study population and also variation in cut off of zinc level to define zinc deficiency in different studies.

Patient with advanced disease (stage 3 & 4) were deficient in zinc as compare to other stages. This finding was similar to other studies. In a Nigerian study by Yehere et al, [11] the mean serum zinc level decreased as the WHO HIV clinical staging worsened.

Similarly, in study done in Uganda, [13] advanced HIV disease (WHO stage III and IV) was associated with low serum zinc. Advanced HIV disease is more likely to be associated with recurrent acute infections and an elevated acute phase response interpreted as low zinc. A similar finding was found in many other studies in children and adults. [3, 10,12,14,15]

Fever was the most common presenting complaints at diagnosis (16.8 % patients) followed by cough (15.6 % patients), diarrhea (9.6 %) and not gaining weight (7.2%).16 (19.2 %) were asymptomatic children, detected on family screening.

In an Indian study done by Gomber et al. [16], Profile of HIV-affected Children from Delhi, common clinical symptom at diagnosis was fever (83%), cough (50.8%) and diarrhoea (38.9%). When baseline characteristics of HIV-affected children aged 1 to 5 years attending pediatric HIV clinics in Uganda was compared, cough was the predominant symptom followed by fever. [13]

As illustrated in table 2, zinc supplemented children had significant increase in mean weight. Also, at 1 year follow up, group 1 and group 2 i.e., zinc supplemented group (zinc deficient as well as normal zinc level group) showed weight gain statistically more significant as compared to group 3 i.e., non zinc supplemented and normal zinc level group. ($p<0.05$)

In the study done on 1-5 years aged children attending clinics in Uganda,[13] zinc supplemented children had significant weight gain. In a randomised controlled trial, that was conducted to determine the safety and efficacy of zinc supplementation (10 mg elemental zinc as sulphate) in HIV-affected children in South Africa (n =96, aged 6-60 months) [14] showed that after 6 months of supplementation, children gained a median of 7% of their body weight when compared to only a 2% gain in children given placebo (P =.02). Study done at Capetown [17] in stable HIV affected children showed similar results.

We did not find any study in the literature correlating improvement in height in HIV affected children with zinc supplementation. However, in HIV non-infected children, zinc supplementation significantly improves linear growth as shown in studies done by Umeta et al,[18] in Ethiopia and Rivera JA et al,[19] in Guatemala.

In our study, the difference in improvement in height was not significant amongst three groups (zinc deficient and normal zinc value group). Probably longer follow up is required for the differences in height to be more significant, as height is a marker of chronic malnutrition.

The increase in CD4 was statistically significant in all 3 groups ($p<0.05$) (Table 2). This can also be contributed to other confounding factors such as HAART and good supportive care. This finding was similar to other studies in literature. In an RCT study done by Baum and coworkers, [20] they found that supplementation of zinc given to HIV infected adults resulted in a fourfold decrease in the likelihood of immunological failure (i.e., CD4 < 200/mm^3) after 18 months of use compared with placebo.

In a study done in Thai children [12] adequate zinc levels were associated with significant increases in CD4 % at 48 weeks after commencement of HAART. Reich et al. [21] did not find short term benefit from oral zinc supplementation in HIV affected children. Only 2 out of 13 subjects had increased CD4+ T-cell numbers, the reason being, probably, small size of subjects. In an Indian study done by Malviya et al. [22]moderate degree of correlation between serum zinc and CD4 cell count ($r=0.6926$, $r^2=0.4797$) was found. Study done by Baum et al. [20] [in] HIV-1 infected illicit drug user adults, it was found that CD4 cell counts were consistently lower over time in the group with low level of plasma zinc.

When compared among the 3 groups, at 1 year, mean zinc levels were significantly greater in group1 as compared to other two groups. This was similar to the RCT study by Baum and coworkers [20]in adults. In this study, at the end of the trial, participants who received zinc supplements had higher plasma zinc level.

In present study, Number of episodes of acute respiratory infections (ARI) and AGE (Acute Gastroenteritis) decreased over time in all 3 groups, however, this was statistically not significant ($p>0.05$). At 1 year follow up, group 1 has more significant decrease in number of AGE episodes as compared to other 2 groups. ($p<0.05$)

This observation is similar to other studies in the literature. In a study done in Ethiopia,[18] they found reduced illnesses due to diarrhoea, cough and fever in supplemented group. Also, Roy et al. [23] in Bangladesh found fewer episodes of diarrheal and respiratory illnesses in zinc supplemented group. Similar results were found in study done in Cape Town.[24] In a study done in South African children by Bobat et al,[14] they found reduced diarrheal morbidity in supplemented group.

CONCLUSION:

Zinc supplementation may help in improving nutritional status and immunological status in the newly diagnosed HIV affected children.

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Declarations:

Ethics clearance: Ethical clearance was obtained from institutional ethics committee LTC/ 374/2015.

Conflict of interest: there is no conflict of interest of the above said article and all the authors have equally contributed in getting the data as well as in writing the manuscript

The authors have no competing interests to declare that are relevant to the content of this article.

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Consent: written informed consent was taken from all the participants

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