ORIGINAL RESEARCH

Zinc Supplementation in Preterm Neonates for growth and Neurological Development

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ABSTRACT
Background: Zinc is one of the most important trace elements for the body. It plays a major role in various aspects of physiology, immunity and skeletal growth. Zinc deficiency may be particularly relevant to early development, growth and function of many organ systems, including the neurologic system. Typical clinical manifestations are commonly observed only for conditions of severe zinc deficiency. Increasing data suggest significant subclinical effects of a moderate zinc deficiency in preterm neonate. Thus, this study was done to see the effect of zinc for growth and neurodevelopment in premature babies.
Materials& Methods: The prospective cohort study was conducted in preterm neonate from December 2019 to December 2020 at Department of pediatrics J.L.N. Hospital & attached group of hospital Ajmer, Rajasthan, India. A total of initial 100 premature babies who fulfilled the inclusion criteria, were included in the study. We included infant born preterm (gestational age 30 to < 37 weeks) and low birth weight (birth weight 1000 to <2500 grams) who were admitted to the neonatal intensive care unit of pediatrics department. Zinc was given once daily till 3 months of age in the study group and follow up for 6 months. All 50 preterm neonates receiving Zinc supplementation included in group I. All 50 preterm neonates not receiving Zinc supplementation included in group II.
Results: A total of 100 premature babies were enrolled for study out of which 50 (50%) in group I (zinc) and 50 (50%) in group II (non-zinc). Our study presents the successive p-values for Weight, Length and Head Circumference at Baseline, 1Month, 3 Month and 6Month intervals. Weight was not significant at the enrolment phase but in the first month, three month and six month was significant (P value <0.05) the difference in the means of group I and group II. In the case of Length, at baseline phase, the difference in means was not significant but in length at 1st month age (p-value 0.001), at 3rd month (p-value 0.000), and at 6th month (p-value 0.001) were significantly in group I as compared to group II. The Mean of head circumference at different levels at enrolment (P-value 0.11), at 1st month of age (P-value 0.36), 3rd month (P-value 0.13) and 6th month (P-value 0.0.22) were not significant. However, there was no significant difference between zinc

and control group in head circumference and neurodevelopmental score at age of 6-month.
Conclusion: We concluded that enteral zinc supplementation in preterm infants at the dose of 2mg/kg/day for 3 months resulted in improved weight gain and linear growth till 6 months follow up. However, there was no significant difference between zinc and control group in head circumference and neurodevelopmental score at age of 6-month.
Keywords: Weight, Length, Head circumferences, Neurodevelopment, Zinc.

INTRODUCTION

Zinc is one of the most important trace elements for the body. It plays a major role in various aspects of physiology, immunity and skeletal growth. Its many roles include participation in basic metabolic functions such as cellular respiration, synthesis of many proteins and enzymes, DNA and RNA replication, carbohydrate metabolism, cell division and growth. Normal R.D.A of zinc is 3.5–5 mg/day in normal infants. Zinc may be essential for brain function as well as for growth in the fetus and child.[1] Zinc deficiency may be particularly relevant to early development, growth and function of many organ systems, including the neurologic system.[2,3]

Low zinc concentrations have been observed in the cord blood of low birth weight (LBW) newborn babies (<2500 g) and birth weight has been shown to be highly correlated with cord zinc concentration in India. Studies have shown reduced levels of zinc in low-birth-weight infants[4,5], that may account for increased morbidity and growth failure in such neonates.

Zinc is involved in numerous aspects of cellular metabolism.[6] It was estimated that about 10% of human proteins potentially bind zinc, in addition to hundreds which transport and traffic zinc. It required for the catalytic activity of more than 200 enzymes and it play a role in immune function, wound healing, protein synthesis, DNA synthesis and cell division.[7,8]

Zinc possesses antioxidant properties, which may protect against accelerated aging and help speed up the healing process after an injury.[9] Zinc ions are effective antimicrobial agents even at low concentrations. Gastroenteritis was strongly attenuated by ingestion of zinc and this effect could be due to direct antimicrobial action of the zinc ions into the gastrointestinal tract, or to the absorption of the zinc and re-release from immune cells.[10]

Zinc was played an essential rule in neurodevelopment as zinc-dependent enzymes are involved in brain growth, zinc-containing proteins participate in brain structure and neurotransmission, and finally zinc is involved in the production of neurotransmitters which are involved in brain memory function.[11] About 60% of fetal zinc was acquired during the third trimester of pregnancy, the fetal weight increase three-fold. Preterm infants (<37 weeks gestation) have lower zinc reserve than term infants and because of immaturity, they may be less efficient in absorbing and retaining zinc for growth.[12]

Zinc is the one of the most common hidden health problems in children, since, unlike iron deficiency, zinc was not something for which pediatricians routinely screening. For several reasons, preterm infants have relatively high zinc dietary requirements and face special challenges to meet them. Zinc deficiency has a negative effect on the endocrine system, leading to growth failure among other clinical manifestations.[13] Typical clinical manifestations are commonly observed only for conditions of severe zinc deficiency. Increasing data suggest significant subclinical effects of a moderate zinc deficiency in preterm neonate. Thus, this study was done to see the effect of zinc for growth and neurodevelopment in premature babies.

MATERIALS& METHODS

The prospective cohort study was conducted in preterm neonate from December 2019 to December 2020 at Department of pediatrics J.L.N. Hospital & attached group of hospital

Ajmer, Rajasthan, India. A total of initial 100 premature babies who fulfilled the inclusion criteria, were included in the study. We included infant born preterm (gestational age 30 to < 37 weeks) and low birth weight (birth weight 1000 to <2500 grams) who were admitted to the neonatal intensive care unit of peadiatrics department. Eligible neonates admitted during the study period either to receive elemental zinc or no Zinc. Zinc was given once daily till 3 months of age in the study group and follow up for 6 months. Written informed consent was obtained from the parents. The study was approved by the institutional ethical committee.
All 50 preterm neonates receiving Zinc supplementation included in group I. All 50 preterm neonates not receiving Zinc supplementation included in group II.

EXCLUSION CRITERIA
1. GI surgery during their initial hospital stay.
2. GI malformation or another condition accompanied by abnormal losses of GI juices, which contain high levels of zinc (including, but not limited to, stomas, fistulas and malabsorptive diarrhea.)

METHOD
Zinc was given once daily till 3 months of corrected age in the study group. Syrup zinc was procured from hospital supply and administered by nursing staff till discharge. After discharge from hospital, the mother administered the supplements. Before discharge, the mother was trained to administer the supplements and advised to give a repeat dose if the baby vomited the supplement within 30 minutes of administration. Infants in both groups were given an oral calcium and vitamin D preparation. Iron drops 2 mg/kg body weight daily was started at 4 weeks of postnatal age.[6]
Weight, length and head circumference were measured at the time of admission, age of 1 month, 3 month and 6 month of age. Nude weight was recorded using an electronic weighing scale with an accuracy of 5 g. Length was measured from crown to heel in supine position, using an infantometer, to the nearest of 1 mm. The occipito-frontal circumference was recorded using non-stretchable measuring tape with an accuracy of 1 mm using cross-tape technique.
At each visit, history related to pattern of feeding, diarrhea, respiratory illness, fever, lethargy, vomiting or any other illness in the intervening period was recorded.
Adverse effects of oral zinc supplement (vomiting following administration) were enquired at each visit. All mothers were counseled at each visit about care of infants particularly maintaining temperature, breastfeeding, nutritional supplements, prevention of infections, immunization and date of next follow up. All infants were exclusively breastfed during the entire study period. Compliance to zinc administration was monitored using a compliance sheet given to mother at discharge. Compliance was checked at each visit by entries in the sheet, and also by measuring residual of drug.

RESULTS
A total of 100 premature babies were enrolled for study out of which 50 (50%) in group I (zinc) and 50 (50%) in group II (non-zinc).
Our study presenting the successive p-values for Weight, Length and Head Circumference at Baseline, 1Month, 3 Month and 6 Month intervals. Weight was not significant at the enrolment phase but in the first month, three month and six month was significant (P value <0.05) the difference in the means of group I and group II. In the case of Length, at baseline phase, the difference in means was not significant but in length at 1st month age (p-value 0.001), at 3rd month (p-value 0.000), and at 6th month (p-value 0.001) were significantly in group I as compared to group II. The Mean of head circumference at different levels at

enrolment (P-value 0.11), at 1st month of age (P-value 0.36), 3rd month (P-value 0.13) and 6th month (P-value 0.0.22) were not significant (table 1).

In this study, the children were follow upto six month of age, only six parameters are included of TDSC which are assumed to be measured on Likert Scale of Six parameters. Henceforth, the scale of Neuro development is taken from 0 to 6. The Trivandrum Development Screening Chart (TDSC) is a 51-item assessment of cognitive and motor milestones for children 0-6 years old. The test-gives first assesses the definite age of the child by depicting a vertical line through the chart through their age. If the child can complete any items that are to the left of the line, then there is no delay for that item. If an item lies to the left of the line and the child cannot complete the item, then there is an item delay is assumed. In this study, the children are upto six month of age, only six parameters are included of TDSC which are assumed to be measured on Likert Scale of Six parameters. Henceforth, the scale of Neuro development is taken from 0 to 6 and consequently coded as the same (Figure 1).

The Mean age of Neuro Development at different levels at three month (P Value 0.08) and Six month (P value 0.18) were equal in both Groups. (P Value >0.05) (table 2).

There is only one model with Weight (Ind-WZ), Length (Ind-LC), Head Circumference (Ind-HCZ), Neuro Development (Score-NDZ) as independent variables and overall development (Score-Dev) as dependent variable and for the duration of fitting the regression line no variable was removed and the method was Enter. The ANOVA is given in the Table 3 and the significance value is 0.000 which is less than critical value of 0.05, therefore the Overall Development (Score-Dev) has significantly different mean than Weight (Ind-WZ), Length (Ind-LC), Head Circumference (Ind-HCZ), Neuro Development (Score-NDZ). The Sum of Squares associated with the three causes of variation, Total, Regression and Residual which are possibly explained by the Weight (Ind-WZ), Length (Ind-LC), Head Circumference (Ind-HCZ), Neuro Development (Score-NDZ) (Regression) i.e. 591.020 and the variance which is not explained by the Weight (Ind-WZ), Length (Ind-LC), Head Circumference(Ind-HCZ), Neuro Development(Score-NDZ)(Residual)i.e. 337.547.

Table 1: Weight Gain, Length and Head Circumference (Mean± SD) of the Study Infants

Anthropometric measurements		**Group I (N=50)**	**Group II (N=50)**	**p-value**
Weight	**Baseline**	1801.12±355.93	1789.08±311.81	0.843
	1 Month	2372.46±353.15	2282.72±328.26	0.041*
	3 Month	3494.88±466.66	3316.44±419.43	0.049*
	6 Month	4832.10±520.50	4685.18±518.66	0.036*
Length	Baseline	43.39±2.12	43.08±1.75	0.383
	1 Month	47.13±2.07	45.92±1.59	0.001*
	3 Month	52.94±2.15	51.45±1.77	0.000*
	6 Month	58.93±2.19	57.608±1.78	0.001*
Head Circumference	Baseline	30.85±1.53	30.42±1.09	0.115
	1 Month	33.21±1.61	32.92±1.60	0.369
	3 Month	36.74±1.61	36.29±1.28	0.137
	6 Month	39.90±1.75	39.49±1.41	0.224

Fig. 1: Trivandrum Developmental Screening (Tdsc) Chart For Neuro Development

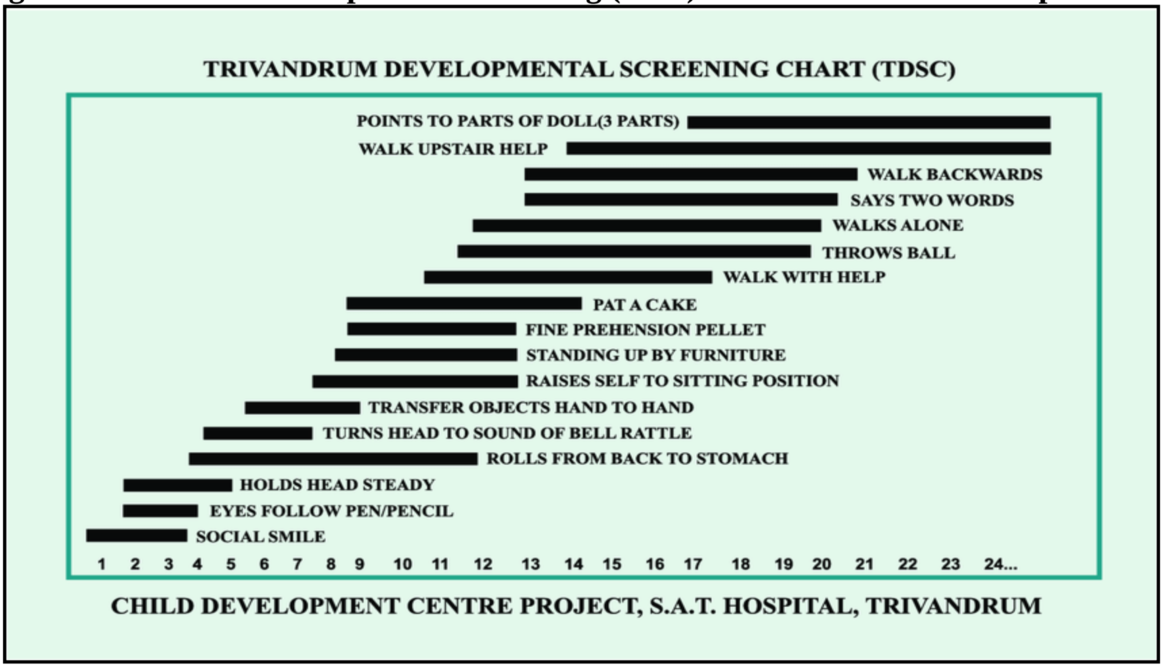

Table 2: Effect of Zinc Supplementation on Neuro Development

Neuro development	Groups	N	Mean	Std. Dev.	Lower Bound	Upper Bound	Min. range	Max. range	Mean difference	t test value	p value	Interpretation
ND at enrolment	Group I	50	0.00	.000	-	-	0	0	-	-	-	Not Significant*
	Group II	50	0.00	.000	-	-	0	0	-	-		
ND at 1st Month	Group I	50	0.00	.000	-	-	0	0	-	-	-	Not Significant*
	Group II	50	0.00	.000	-	-	0	0	-	-		
ND t at 3rd Month	Group I	50	3.86	.452	3.73	3.99	3	5	3.86	60.358	0.083*	Not Significant*
	Group II	50	3.80	.495	3.66	3.94	3	5	3.80	54.297		
ND at 6th Month	Group I	50	5.90	.303	5.81	5.99	5	6	5.90	137.667	0.182*	Not Significant*
	Group II	50	5.84	.370	5.73	5.95	5	6	5.84	111.509		

*95% Level of Confidence

Table3: ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	**Regression**	591.020	4	122.755	16.366	.000b
	Residual	337.527	45	7.501		
	Total	928.547	49			

a. Dependent Variable: Score-Dev

b. Predictors:(Constant), Ind-NDCZ, Ind-LCZ, Ind-HZ, Ind-WZ

DISCUSSION

Preterm infants are likely to have higher zinc deficit and dietary requirements as nearly 60% fetal zinc is acquired during third trimester of pregnancy.[14] Therefore, preterm and low birth weight infants are born with low stores in zinc, which is a vital trace element for growth, cell differentiation and immune function. Preterm infants are at risk of zinc deficiency during the postnatal period of rapid growth also. In the present study, zinc supplementation in preterm infants at the dose of 2mg/kg/day for3 months resulted in improved weight gain and linear growth as compared to the control group. All the preterm infants were followed up to 6 months of age. There was significant improvement in weight and length in subsequent follow-up (p value<0.001). However, there was no significant difference between zinc and control group in head circumference and neuro-developmental score in subsequent follow-up(p value=0.071 and 0.118respectively).

Systematic reviews in the older paediatric population have previously shown that zinc supplementation potentially improves growth and positively influences the course of infectious diseases. Many studies have reported the beneficial effect of zinc supplementation in preterm infants from hospital stay period to discharge and follow-up. Harris enrolled 105 preterm infants in a prospective cohort study and found positive correlation between total enteral zinc intake and weight and head circumference gain at discharge.[15]

One similar RCT from India enrolled 100 consecutive preterm infants and randomized to receive oral zinc at 2 mg/kg/day till 3 months of corrected age (study group) or not (control). The sample size and population were like the present study, and they also looked at growth and neuro development in follow-up although the follow-up was only up to 3months of corrected age as compared to 6 months follow-up in current study. They found no significant difference in gain in weight, length and head circumference between groups which is contrary to the present study. Serum alkaline phosphatase in the zinc group was significantly higher. However, they found significant differences in neuro development. A higher number of zinc supplemented infants demonstrated alertness and attention pattern normal forage compared to non-supplemented infants at 40 weeks post conceptional age, but not at 3 month corrected age. Infants in non-supplemented group were more likely to show signs of hyper-excitability, including insufficient sleep, excessive crying and frequent startling when assessed at 40 weeks and3month corrected age.[16]

So far only a few double blind and randomized controlled trials, three from developed country settings,[17-20] two of which were In premature infants, and seven from developing country settings,[16,21-26] have reported the effects of zinc supplementation during the first months of life on growth of infants born prematurely or small for their gestational age. The dose in these studies varied between 3 mg to 10 mg of zinc per day. Of the 3 studies conducted in developed countries (Spain and Canada), 2 studies among preterm infants showed positive effect on plasma zinc concentrations and linear growth[17,18] and one study[21] on LBW infants showed no effect. However, no significant effect on weight gain was observed in any ofthesestudies.[17-20]

Islam and colleagues studied 100 preterm infants and zinc supplementation was given for 6 weeks in the intervention group. The investigators concluded that zinc supplementation among preterm babies for 6 weeks resulted in improved weight gain and linear growth, enhanced serum zinc status and reduced incidence of diarrhea.[26]

Like the present study they did not find difference in head circumference between the zinc and control group. The current study has longer duration of zinc supplementation upto 6 months which is important to evaluate the long- term effect of zinc supplementation on growth and neuro development in preterm infants. Another RCT from developed country

studied 36 preterm infants and found that the zinc supplementation group had a greater linear growth (from baseline to 3 months corrected age: Delta score deviation standard length: 1.32+/-.8vs.38 +/-.8).[17]
Hoque et al in 2005 in a study of 200 low birth weight infants also found significant effect of zinc supplementation on weight gain like our study. However, authors did not study the effect of Zn on other growth parameters.[22] In contrast to the current study, Friel et al in their study of zinc supplementation on 52 very low birth weight infants for 12 months found significant effect on length only but not on weight gain and head circumference.[13]
An Egyptian study enrolling 60 preterm infants and following upto 6 months of corrected age like our study showed significant increase in weight and length at 6 months of age.[27]The Cochrane systematic review concluded that enteral zinc supplementation probably improves weight gain (SMD 0.46, 95% CI 0.28 to 0.64; 5 studies,481 infants; moderate-certainty evidence); and may slightly improve linear growth (SMD0.75,95%CI0. 36 to1.14, 3 studies, 289 infants; low- certainty evidence), but may have little or no effect on head growth (SMD0.21,95%CI-0.02to0.44, 3 studies, 289 infants; moderate-certainty evidence).[28]This is like the results from current study.
Zinc plays a pivotal role not only in the growth but also in the pathogenesis of many diseases in preterm infants. One RCT from Australia enrolled 193 preterm low birth weight infants and found significant reduction in morbidities (p=0.030), mortality(p=0.006) and necrotizing enterocolitis (p=0.014) in the zinc group ascomparedtothecontrolgroup.[28]
Like this the current study found that the supplementation with adequate doses of zinc also reduces the occurrence and severity of the morbidities typical of prematurity i.e., NEC, brain damage, BPD, infectious diseases, and RO Pin preterm neonates. This result contrasts with the published Cochrane systematic review. The Cochran systematic review concluded that enteral zinc supplementation may have little or no effect on common morbidities such as bronchopulmonary dysplasia (RR 0.66, 95% CI 0.31 to1.40, 1 study, 193 infants; low-certainty evidence), retinopathy of prematurity (RR0.14,95%CI0.01to2.70,1 study, 193 infants; low- certainty evidence), bacterial sepsis(RR1.11,95%CI0.60to2.04,2studies, 293 infants; moderate-certainty evidence), or necrotizing enterocolitis (RR0.08,95%CI0.00to1.33,1 study,193 infants; low- certainty evidence).[28]
Long-term neuro development is the most important outcome in preterm infants. However, the effect of enteral zinc supplementation on long-term neurodevelopmental outcome is lacking. The present study followed up the preterm infants till 6 months and found no significant difference in neuro developmental outcome. Similarly, an RCT from India demonstrated alertness and attention pattern normal for age in zinc supplemented group increased hyper-excitability, including in sufficient sleep, excessive crying, and frequent startling in the control group.[16] The Cochrane systematic review could not conclude because of lack of data on long-term neuro developmental outcome related to enteral zinc supplementation.[28] Strength of this study is longer duration of enteral zinc supplementation and long-term neuro developmental outcome at 6-month follow-up. However, a better measure would be neuro developmental outcome at 18-24 months of corrected age.

CONCLUSION

In conclusion, enteral zinc supplementation in preterm infants at the dose of 2mg/kg/day for 3 months resulted in improved weight gain and linear growth till 6 months follow up. However, there was no significant difference between zinc and control group in head circumference and neurodevelopmental score at age of 6-month.

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