RESEARCH PAPER

Effect of Oral Zinc Supplementation on the Growth of Preterm Infants

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Received: July 7, 2009; Initial review: August 7, 2009; Accepted: November 5, 2009.

Objective: To compare the effect of oral zinc supplementation on growth of preterm infants.

Design: Randomized controlled trial.

Setting: Dhaka Shisu Hospital (Tertiary care hospital).

Subjects: 100 appropriate for date preterm infants weighing between 1000 to 2500g were randomized to receive zinc and multivitamin supplement (Group I; *n*=50) or only multivitamin supplement (Group II).

Intervention: Zinc supplementation was given 2mg/kg/day for 6 weeks along with multivitamin in Group I and only multivitamin to Group II.

Primary outcome variable: Increment of weight and length.

Results: At enrollment, serum zinc (62.1±12.4µg/dL in Group I and 63.1±14.6µg/dL in Group II) and hemoglobin levels (14.9±2.4g/dL in Group I and 14.4±1.7g/dL in Group II) were almost similar in both groups. Serum zinc levels were in lower limit of normal range. After supplementation, serum zinc and hemoglobin levels were significantly higher in Group I (105±16.5µg/dL) than Group II (82.2±17.4µg/dL) (P<0.05). Weight, length and head circumference were comparable in both groups at enrollment. Significant differences in weight gain and increment in length were found in first and second follow up between two groups but OFC increments were not significant (P>0.05). Reduction of morbidity was apparent in zinc supplemented group. No serious adverse effect was noted related to supplementation therapy.

Conclusion: Zinc supplementation for preterm low birth weight babies is found effective to enhance the growth in early months of life.

Key words: *Infants, Preterm, Supplementation, Zinc.*

Research No: BICH/2006/384

Published online: 2010 Jan 15. PII:S097475590900473-1

Zinc deficiency is common in young infants in the developing world and is associated with reduced immunocompetence and increased rates of serious diseases(1). Low zinc concentrations have been observed in the cord blood of low birthweight (LBW) newborn babies (<2500 g) and birthweight has been shown to be highly correlated with cord zinc concentration in India(2,3). For several reasons, preterm infants have relatively high zinc dietary requirements and face special challenges to meet them. About 60% of fetal zinc is acquired during the third trimester of pregnancy, when fetal weight increases three-fold. Preterm infants (<37 weeks gestation) have lower zinc reserves than term infants and because of immaturity, they may be less efficient at absorbing and retaining zinc for growth(4). Zinc deficiency has a negative effect on the endocrine system, leading to growth failure, among other clinical manifestations. Zinc plays an important role in gene transcription and is also one of the most prevalent trace elements in the brain(5).

Zinc supplementation has been shown to reduce the rates of diarrhea and pneumonia, and to enhance physical growth of young infants(6). Several studies conducted in various parts of the world have shown beneficial effect of zinc supplementation in early growth of preterm babies (7,8). No study has been conducted in Bangladesh to evaluate the effect of zinc on growth of preterm babies. We conducted this study to evaluate the efficacy of oral zinc on growth of preterm infants.

METHODS

This randomized controlled trial was conducted in the Neonatal Special Care unit of Dhaka Shishu (Children) Hospital between January 2006 and May 2007. According to the incidence of low birthweight, the assumed targeted proportion was 0.03 (UNICEF, 2005)(9), the degree of accuracy was 0.05 and with 5% level of significance, the targeted sample size was 323 for population size equal or more than 10,000. However, during the study period of 16 months, there were only 160 population cases, and the estimated sample size was 107. As seven cases were not enrolled due to their parent's unwillingness to participate in the study, 100 cases were included and randomized to supplemented group (n=50) and control group (n=50). Randomization was done by lottery method of selection cards, which were equal in number for each group in sealed opaque envelopes. Principal investigator and data analyzer were blinded to the allocation of the treatment groups.

We included preterm infants below 37 weeks, weighing 1000 g to <2500 g and appropriate for gestational age. Those with major birth defect or congenital deformities, unstable vital signs, or with parents unwilling to participate, were excluded. The study protocol was approved by ethical review committee of Dhaka Shishu Hospital. Informed written consent was obtained from the parents before enrollment of the patient in the study.

Immediately after registration of the patient, detailed history was taken from mothers or relatives and physical examination was performed. Gestational age was determined by maternal record and by New Ballard Score system. Before intervention weight was measured by an electronic weighing scale (Scale–Tronix Pediatric Scale, USA), which was accurate to 5g and was calibrated before each measurement. Weighing was carried out with the baby nude and before feeding. Occipito–frontal circumference (OFC) was measured with a non-elastic standard plastic measuring tape (1cm wide) to the nearest 1mm. Baseline serum zinc level and hemoglobin estimation were done in both the groups, before giving supplementation, within 7-21 days of postnatal age. Determination of serum zinc concentration was carried out in the laboratory of chemistry division of Atomic Energy Centre, Ramna, Dhaka, Bangladesh. Serum zinc level was measured by flame atomic absorption spectrophotometry method. At the same time, blood sample was sent for hemoglobin estimation and hemoglobin level was assayed within half an hour of blood collection, using the cyanmethemoglobin method.

When the neonates were 7 to 21 days old, before discharge from the hospital, mother was given two bottles of supplement containing zinc and instructed to feed her baby at a dose of 2 mg/kg/day orally with other multivitamins for 6 weeks (Group I). Control group (Group II) was instructed to take only the multivitamins (0.3mL daily, each mL containing vitamin A 1500 IU, vitamin D 300 IU, thiamin hydrochloride 0.48mg, riboflavin 0.3mg, pyridoxine hydrochloride 0.3mg, nicotinamide 3mg, calcium D pantothenate 1.5mg and ascorbic acid 15mg) for the same duration. Mothers were advised to attend the follow up clinic after six weeks. Information was obtained about diarrhea, respiratory illness, presence of fever or vomiting, pattern of feeding during these six weeks. Anthropometric measurements were also recorded.

Blood samples for serum zinc and hemoglobin estimation were obtained again from the babies of both the groups. Mothers of both the groups were advised to visit again after six weeks. This time no zinc supplementation was given but iron supplementation was added at a dose of 2.5 mg/kg/day along with multivitamin. During the second follow up, anthropometric measurements and related history were obtained again.

Statistical analyses were done by SPSS. Independent samples t test and Chi-square test were used to evaluate the significance of differences between the groups and considered significant at $P<0.05$.

RESULTS

We enrolled 100 preterm appropriate for gestational age neonates; 50 in zinc and multivitamin supplemented group (Group I) and 50 in multivitamin group (Group II). Seven infants were lost to follow-up in Group I (3 at 1st follow up and 4 at 2nd follow-up) and eight infants were lost to follow-up in Group II (3 at 1st follow-up and 5 at 2nd follow-up). These 15 infants were excluded from analysis of growth. 43 infants in Group I and 42 infants in Group II completed follow-up till 12 weeks of age for growth monitoring. The two groups were comparable for age at enrollment, sex distribution, feeding practices, maternal age, regularity of antenatal visits, and birth order. Mean serum levels of zinc and hemoglobin are depicted in ***Table* I.** Serum zinc level increased in both the groups after supplementation but the increase was more marked in the zinc supplemented group. Hemoglobin level decreased in both the groups.

***Table* II** shows that weight, length and OFC were almost similar in both the groups at enrollment. Gain in weight and height were significantly more in zinc supplemented group both at first and second follow up ($P<0.05$). There was no difference between the groups for head circumference even after supplementation.

TABLE I SERUM ZINC AND HEMOGLOBIN (MEAN±SD) OF THE STUDY INFANTS AT ENROLLMENT AND AFTER SUPPLEMENTATION

	Group I *n*=50	Group II *n*=50	*P* value
Serum zinc (µg/dL)			
Baseline	62.1±12.4	63.1±14.6	0.458
After supplementation	105.8±16.5	82.2±17.4	0.001
Hemoglobin (g/dL)			
Baseline	14.9±2.4	14.4±1.7	0.259
After supplementation	10.2±1.4	11.6±1.8	0.403

Group I: Zinc supplementation group; Group II: Control group.

During the follow-up, only two children (4%) in zinc supplemented group had diarrhea as compared to 8 (16%) in multivitamin group. Thus, the incidence of diarrhea was significantly less in the zinc group. However, there was no significant difference in children developing ARI in the zinc (*n*=1) and vitamin (*n*=3) groups. There was no statistically significant difference between the two groups in terms of side effects. Vomiting and loose stools were noted in 6 and 4 children in zinc group, 5 children each in multivitamin group, respectively.

DISCUSSION

Zinc supplementation to preterm babies for 6 weeks resulted in improved weight gain and linear growth and also helped in reducing incidence of diarrhea. There were no significant side effects of the

TABLE II WEIGHT GAIN, LENGTH AND OCCIPITO-FRONTAL CIRCUMFERENCE (MEAN±SD) OF THE STUDY INFANTS

		Group I *n*=50	Group II *n*=50	*P* value
Weight (g)	Baseline	1736.4±446.7	1632.8±321.7	0.19
	1st follow-up	2343.8±540.3	2060.2±396.3	<0.001
	2nd follow-up	2779.0±638.7	2474.6±441.8	<0.001
Length (cm)	Baseline	42.1±3.3	41.9±2.6	0.06
	1st follow-up	46.9±2.6	44.1±2.8	<0.001
	2nd follow-up	50.3±2.8	47.4±3.2	<0.001
OFC (cm)	Baseline	30.0±1.2	30.1±1.5	0.78
	1st follow-up	32.5±1.7	32.2±1.4	0.40
	2nd follow-up	34.4±1.1	34.1±1.5	0.42

1st Follow-up: After 6 weeks of supplementation, 2nd follow-up: 6 weeks after 1st follow-up;OFC: Occipeto-frontal circumference.

WHAT IS ALREADY KNOWN?

- Zinc supplementation reduces rates of diarrhea and pneumonia in young infants.

WHAT THIS STUDY ADDS?

- Zinc supplementation to preterm low birthweight babies enhances their growth.

supplements. These findings could have important implications for child health survival program in developing countries with high incidence of preterm low birth infants.

The strengths of this study included its randomized, double-blind design and minor differences in initial anthropometric status. The groups were similar at baseline, thus any differences in study outcomes were likely due to the supplements that were provided. Follow-up was given by highly trained observers and no significant differential loss to follow-up between the groups was observed. Compliance with supplementation was good. Limitations of the study included: single center study, supplementation was given for shorter duration, surveillance was not conducted daily and long term follow-up was not done due to difficulty in communication, and fund limitation.

Baseline serum zinc levels and hemoglobin levels were seen in both the groups. Altigani, *et al*.(10) reported serum zinc concentration approximately 65µg/dL in low birth weight babies in their study. Itabashi, *et al*.(11) found mean serum zinc concentration 54±14.4µg/dL in their study. A similar serum zinc level (62.4 ± 27.5µg/dL) was found in Bangladeshi preterm babies(12). Our findings corroborated the findings of these studies(10-12). Baseline hemoglobin levels were within normal level but gradually hemoglobin level reduced. Reduction of hemoglobin was due to prematurity(13). Lind, *et al*.(14) found similar result in their study. We provided 2mg/kg/day elemental zinc to the patients. Significant improvements were noted in serum zinc values in the zinc supplemented group and not in the control group. This indicated that zinc supplemen-tation was successful in improving the zinc status of these infants ($P<0.001$). Other studies found similar results(8,15,16).

There were no significant difference in weight, length and OFC at enrollment but a significant difference were found at 6 weeks and 12 weeks follow up ($P<0.05$). This is understandable as zinc has profound role on cellular growth and proliferation and performs various metabolic functions. Castillo- Duran, *et al*. demonstrated improved growth of low birthweight babies in their study, significantly greater weight for age and length for age were found in the zinc supplemented group(17). Lira, *et al*.(18) found that growth was enhanced in low birthweight babies by giving 5 mg/day zinc. Sur, *et al*.(1) showed improved weight gain of low birth weight baby after long time supplementation of zinc. Osendarp, *et al*.(8) found similar results, but others found no significant weight gain after zinc supplementation to preterm babies in their studies(15,16). OFC was increased in both the groups after supplementation at 1st and 2nd follow-up. The difference was not statistically significant. This result was consistent with the results of Lind, *et al*.(14) and Diaz-Gomez, *et al*.(16).

Morbidity pattern of both the groups were observed in this study and significant difference in morbidity was found between two groups. Osendarp, *et al*.(8) observed significant reduction of morbidity after zinc supplementation among young infants who were zinc deficient at baseline. Sur, *et al*.(1) demonstrated that zinc supplementation was effective in reducing diarrhea incidence in their study. Our findings are comparable with these studies. Thus, zinc supplementation can be recommended along with other vitamins and minerals to preterm low birth weight infants for their growth and developments. Large scale multicenteric studies are required to confirm our results.

Contributors: All authors contributed to the study design, collection of data, analysis and drafting the manuscript.

Funding: Partial funding by Bangladesh Medical Research Council (BMRC). Orion laboratories, Bangladesh supplied zinc syrup.

Competing interests: None stated.

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