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Original Article

Linear growth patterns in small for gestational age and preterm infants after zinc supplementation

Caecilia Nancy Setiawan, Gatot Irawan Sarosa, Mexitalia Setiawati

Abstract

Background Low birth weight (LBW) infants are at risk for growth disturbances due to intrauterine zinc deficiency. Zinc supplementation is expected to improve the linear growth of LBW babies.

Objective To assess the effect of zinc supplementation on linear growth in preterm and small for gestational age (SGA) infants.

Methods This quasi-experimental study had a pre- and post-test design. Subjects were LBW infants hospitalized in Kariadi Hospital during March-December 2011, consisted of SGA and preterm neonates. All subjects were given 5 mg of zinc syrup daily for 3 months. Subjects' head circumference, weight, and length were measured monthly. Serum zinc levels were measured before and after supplementation. Data were analyzed with Chi-square test, independent T-test, and general linear model repeated measure.

Results A total of 61 subjects were enrolled consisted of 31 preterm and 30 SGA neonates. Mean serum zinc levels in the preterm group were 168.2 (SD 54.5) μg/dL pre-supplementation and 163.6 (SD 50.7) μg/dL post-supplementation (P=0.049), while mean serum zinc levels in the SGA group were 174.8 (SD 46.6) μg/dL pre-supplementation and 167.4 (SD 49.4) μg/dL post-supplementation (P=0.271). Median percentage preterm weight and length increased from 87.3 to 102.4% in the third month (P<0.001) and from 95.8 to 103.9% in the third month (P<0.001), respectively. Median percentage SGA weight and length increased from 73.5 to 98.3% in the third month (P<0.001) and from 94.5 to 102.2% in the third month (P<0.001), respectively.

Conclusion Both, the preterm and SGA infants exhibit catch-up growth after three months of zinc supplementation. **[Paediatr Indones. 2015;55:23-8.]**.

Keywords: *small for gestational age, preterm, zinc supplementation, growth*

Low birth weight (LBW) is defined as a birth weight of less than 2,500 grams regardless of gestational age.[1] Low birth weight may also be classified as preterm or intrauterine growth retardation (IUGR). Infants with LBW have high mortality and morbidity because of immune system immaturity, and the risk of failure-to-thrive.[2] Zinc, a micronutrient, is required for nucleic acid metabolism and protein synthesis which are important for growth.[4] The prevalence of zinc deficiency has been estimated to occur in 20% of the world population.[5] Zinc deficiency leads to short stature, low immunity, and disturbances in psychomotor development.[6]

Exclusively breastfed LBW infants require zinc supplementation from birth. Mothers who give birth to preterm and LBW infants tend to have low zinc levels in their breast milk.[7] Neonates with 26-30 weeks gestational age often have low serum zinc and copper levels. This condition may be due to high fecal loss, low deposits at birth, or a high requirement for fast growth.[7] Several studies have noted that zinc

From the Department of Pediatrics, Diponegoro University Medical School/Dr. Kariadi Hospital, Semarang.

Reprint requests to: Dr. Caecilia Nancy Setiawan, Department of Pediatrics, University of Diponegoro Medical School/Dr. Kariadi Hospital, Jl. Dr. Sutomo 16, Semarang, Indonesia 50231. Tel. +6224 8453708 Fax. +6224 8453708. E-mail: doktercaecilia@gmail.com.

supplementation increased linear growth of preterm infants.[2,8,9]

The objective of this study was to assess the effect of zinc supplementation on the linear growth of preterm and SGA infants.

Methods

This quasi-experimental study with pre- and post-test design was done in the Neonatology Ward and the Growth and Development Clinic at Kariadi Hospital from March to December 2011. This study was approved by the Ethics Committee of the Health Research-Medical Faculty of Diponegoro.

Subjects were low birth weight infants in the Neonatology Ward at Kariadi Hospital. Inclusion criteria were newborns with birth weights of 1,500-2,499 grams, well being baby at birth, had no congenital anomalies that disturbed dietary intake or growth, and whose parents provided informed consent. Severely ill infants requiring hospitalization during study were excluded. Subjects were consisted of two groups consecutively, based on gestational age: the SGA group (gestational age ≥ 37 weeks) or the preterm group (gestational age < 37 weeks)

The following subjects' data was collected: gender and anthropometric data (birth weight, length, and head circumference). We also collected 3 mL of venous blood from subjects to examine early serum zinc levels. Parents in both groups were given one bottle of zinc syrup (100 mL) with a measuring spoon monthly. Parents gave 5 mg (2.5 mL) to their infants daily for three months.

We used the Fenton 2003 growth chart to assess growth in IUGR and preterm infants.[10] The growth chart assembles infant weight, length, and head circumference from the 22nd to 50th weeks of gestational age. The median percentages was used to evaluate growth of infants within three months of study. Median percentage is the percentage of infants' weight, length, and head circumference divided to median's value according to gestational age in Fenton 2003 growth chart. For example, a baby born at 37 week gestational age, with birth weight 1750 gram. Weight median's value (50th percentile) for 37 week gestational age in Fenton 2003 growth chart is 3000 gram. Therefore, the median percentage of the baby is 1750/3000 x 100% = 58.33%. We provided zinc supplementation for the first three months of life because this is a period of fast growth.

Subjects from both groups were evaluated by home visits to assess signs of infection, milk consumption, volume of zinc syrup consumed, weight, length, and head circumference every two weeks in the first month, then monthly in the second and third months. At the end of third month, 3 mL of venous blood were taken to evaluate serum zinc levels after supplementation. Serum zinc examinations were done collectively with an atomic absorption spectrophotometer in the Central Laboratory-Faculty of Medicine Diponegoro University. Normal serum zinc levels were considered to be in the range of 80-110 μg/dL.

For data analysis of a comparative hypothesis test, we used unpaired T-test. Serial analyses for median percentages of weight, length, and head circumference between groups were performed with GLM repeated measure. Serum zinc levels pre- and post-supplementation were analyzed with Wilcoxon signed rank test.

Results

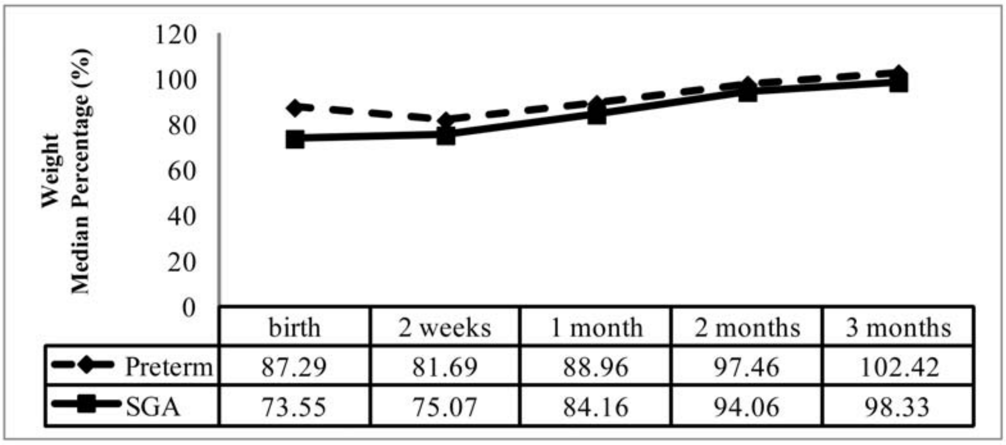
At the end of third month, there were 61 subjects, consisting of 31 infants in the preterm group and 30 infants in the SGA group. In the SGA group, 14 subjects at 50-53 weeks gestational age during the third month monitoring, was plotted to the 50-week gestational age in Fenton growth chart. Those subjects was born at 38-41 weeks gestational age. This was due to the maximum 50 weeks monitoring in the chart. Subjects' characteristics were similarly distributed between 2 groups as shown in **Table 1**.

Figure 1 shows increased weight median percentages in both groups using serial measurements, with statistically significant differences ($P<0.001$). The preterm median weight median percentage increased from 87.3% at birth to 102.4% at the third month ($P<0.001$). The SGA median weight percentage increased from 73.6 % at birth to 98.3% at the third month ($P<0.001$).

Figure 2 shows the increased median length percentages in both groups, which were statistically significantly different between birth and the third

Table 1. Demographic characteristics of subjects

Description, n (%)	Preterm n=31	SGA n=30	Total N=61
Gender			
Male	18 (58)	14 (46.7)	32 (52.45)
Female	13 (42)	16 (53.3)	29 (47.55)
Maternal disease			
Preeclampsia/eclampsia	5 (16.1)	4 (13.3)	9 (14.75)
Twin pregnancy	1 (3.2)	2 (6.7)	3 (4.91)
Heart disease	1 (3.2)	0 (0.0)	1 (1.64)
Other	8 (25.8)	2 (6.7)	10 (16.4)
None	16 (51.7)	22 (73.3)	38 (62.3)
Exclusively breastfed			
Yes	13 (42)	13 (43.3)	26 (42.62)
No	18 (58)	17 (56.7)	35 (57.38)
Infection			
No	16 (51.6)	16 (53.3)	32 (52.46)
Yes	15 (48.4)	14 (46.7)	29 (47.54)

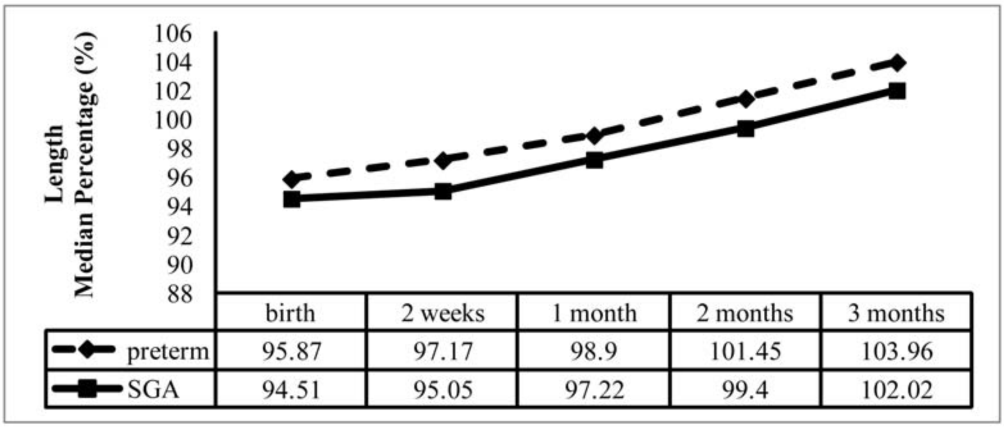


Preterm : P<0.001*
SGA : P<0.001*
p <0.001**

Figure 1. Weight median percentage analysis of the preterm and SGA groups

* within group analysis using GLM repeated measure analysis

** between group analysis using GLM repeated measure analysis



Preterm : P<0.001*
SGA : P<0.001*
p <0.001**

Figure 2. Length median percentage analysis of the preterm and SGA groups

* within group analysis using GLM repeated measure analysis

** between group analysis using GLM repeated measure analysis

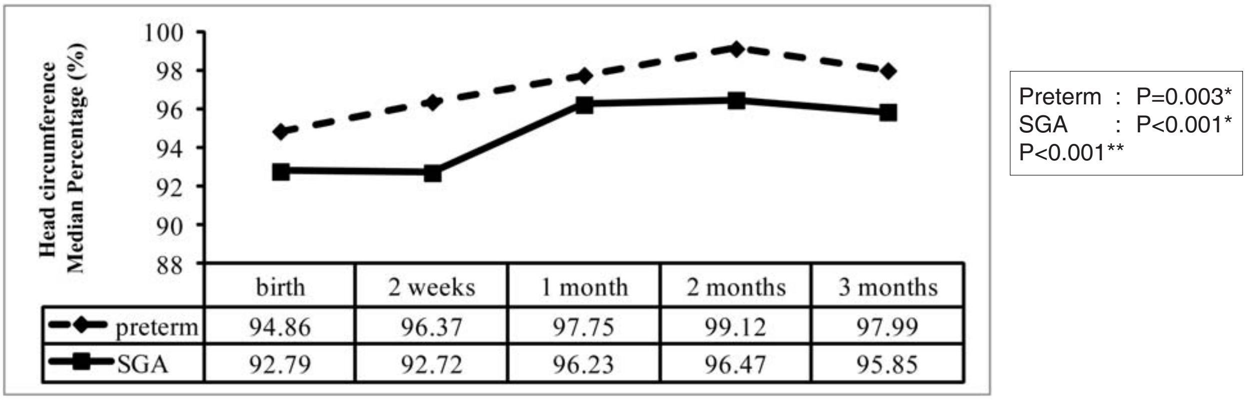


Figure 3. Median head circumference percentage analysis of the preterm and SGA groups

* within group analysis using GLM repeated measure analysis

** between group analysis using GLM repeated measure analysis

Table 2. Serum zinc analysis pre- and post-supplementation

Group		Mean (SD) , μg/dL	P value*
Preterm	Pre-supplementation	168.21 (54.5)	0.049*
	Post-supplementation	163.62 (50.7)	
SGA	Pre-supplementation	174.75 (46.6)	0.271*
	Post-supplementation	167.44 (49.4)	

*Wilcoxon signed rank test

month (P<0.001). Median length percentage increased in the preterm group from 95.9 % at birth to 103.9 % the third month (P<0.001). Median length percentages increased in the SGA group from 94.5 % at birth to 102.2% at the third month (P<0.001).

Figure 3 shows that median head circumference percentages increased in both groups. Median head circumference percentage in the preterm group increased from 94.8% at birth to 98% at the third month (P=0.003). Median head circumference percentage in the SGA group increased from 92.8% at birth to 95.9% at the third month (P< 0.001).

As shown in **Table 2**, the post-supplementation serum zinc levels were not different compared to pre-supplementation within each group.

Discussion

This study was done in low birth weight infants from birth to three months of age. There were no significant differences between the preterm and SGA groups in terms of gender distribution, maternal diseases, or infant infection. In addition, for the combination of the two groups, 42.6% of the infants were breastfed exclusively for the three-month study period, and there was no statistically significant difference in exclusive breastfeeding rates between the groups (P=0.921). Zinc absorption from breastmilk is higher compared to that of infant formula.[11,12]

Infection occurred in 48.3% of subjects in the preterm group and 46.7% of subjects in the SGA group. During the three months observation, 19/61 (31.1%) infants had infections once and 10/61 (16.4%) infants had infections twice. Cough and flu infections were reported by parents at home visits which were treated at primary health care centers. Recurrent acute or chronic infection could delay growth in infants. However, we observed no chronic nor recurrent acute infections in our subjects.

Pre-supplementation serum zinc levels in both groups were above normal levels (168.21 μg/dL in the preterm group and 174.75 μg/dL in the SGA group). The maximum tolerated serum zinc level for 0-6 month-old infants is 4,000 μg/dL per day.[5] Zinc toxicity may be detected by clinical manifestations such as nausea, epigastric pain, diarrhea, lethargy, and muscle pain.[13] Serum zinc levels in subjects remained below the maximum daily level and there were no toxicity clinical manifestations in subjects during monitoring.

From the 61 subjects, one infant in the preterm group had a low serum zinc level of 49.5 μg/dL. After zinc supplementation, the serum zinc level increased to 253.3 μg/dL. Other subjects showed no difference in serum zinc levels post-supplementation compared to pre-supplementation. The lower serum zinc levels after supplementation shows that there was an increased requirement for zinc during the catch-up growth period which occurs during the first months of life. While physiologically serum zinc levels also decrease in 0 to 6-month-old babies due to the decreasing amounts of zinc in breast milk, while less zinc is stored in the body.[8,13] This result differed from other research conducted by Diaz-gomez et al,[8] in which 5 mg zinc supplementation was given to preterm infants. After three months of supplementation, the serum zinc level increased significantly from 69 (SD 20) μg/dL to 113 (SD 25) μg/dL ($P=0.003$).

Median weight percentages increase in the SGA group was better compared to the preterm group after three months of zinc supplementation. Preterm infants have gastrointestinal immaturity, low zinc stores in the body, and postnatal catch-up growth. As such, preterm infants given zinc supplementation may grow better than the SGA group. Similarly, previous research on infants aged less than 6 months who were given 8 weeks of zinc supplementation, had linear mean weight increase from the start of follow-up to the 8th week of evaluation. But no significant differences in the monthly weight for age *z*-score changes were observed between the zinc and placebo groups.[14]

Median length percentages in both groups increased after three months of zinc supplementation with statistically significant differences. However, length percentage increase in preterm babies is higher than SGA. Similarly, Sur *et al.* gave zinc supplementation to LBW infants and found greater length gain in supplemented infants, but the statistically significant difference was only at the end of 1 year ($P<0.001$).[2] The linear growth pattern between the supplemented and non-supplemented groups was comparable until 10 months of age.[2] In this study, median head circumference percentages increased in the both group was statistically significant, but the percentage increase in preterm was higher compared to the SGA group.

A limitation of our study was the growth of several SGA babies at 50-53 weeks gestational age during the third month monitoring was plotted at the 50-week gestational age in Fenton growth chart. Second limitation was all serum zinc measurements had to be done at the same time, so it was difficult to look at serum zinc level for each infant before giving zinc supplementation.

In conclusion, in preterm and SGA infants, median percentages of weight, length, and head circumference increase after three months zinc supplementation. Median weight percentages increase in the SGA is higher compare to the preterm group after zinc supplementation. Median length and head circumference percentages increase are higher in the preterm group than in the SGA group after zinc supplementation.

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