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Effects of calcium and phosphorus supplementation on metabolic bone disorders in premature infants

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Abstract
Introduction: Every year, 15 million babies are born prematurely around the world of which more than 1 million die as a result of prematurity. Premature infants are considered to be at high risk for developing osteopenia due to their reduced bone mineral content. Mothers milk containing 25-35 mg/dl of calcium and 10-15 mg/dl of phosphorus simply does not contain enough minerals to support skeletal growth of growing premature infants. Supplement of calcium and phosphorus along with breast milk can reduce the rate of osteopenia and improve the growth of premature infants.
Objective of the study: To determine the efficacy of calcium and phosphorus supplementation for prevention of metabolic bone disease and improvement of growth in preterm infants.
Methodology: A randomized clinical trial study was conducted at Department of Neonatology, BSMMU, from 16th August 2016 to 27th August 2017. It involved monitoring 50 premature neonates over a period of six weeks. The babies who were fed with breast milk were randomly divided into two equal groups. One group received supplement of calcium and phosphorus along with breast milk. Serum calcium, phosphorus and alkaline phosphatase levels as well as growth parameters (including weight, length, and head circumference) were measured at enrollment and at 6 weeks post birth. At the end of 6 weeks, wrist X-ray was done for evaluation of osteopenia. Data was analyzed using SPSS 20.
Results: Radiological and biochemical evidence of metabolic bone disease were found in 6 (28%) supplemented group and 7 (35%) non-supplemented group (p=0.45). S. calcium, S. inorganic phosphate and S. alkaline phosphatase level were comparable at enrollment between two groups. At 6 weeks S. calcium, S. inorganic phosphate level were more and S. alkaline phosphatase level were less in supplemented group but no significant change was observed between two groups. The mean of weight, length and head circumference were also comparable at enrollment between two groups. At 6 weeks' growth velocity considering weight, length and head circumference were more at supplemented group but no significant change were observed between two groups.
Conclusion: Infants of supplemented group showed better growth velocity and lower incidence of metabolic bone disorders than non-supplemented group. But this difference between supplemented group and non-supplemented group were not statistically significant. However, his study does not provide any evidence to suggest the effectiveness of supplementary calcium and phosphorus in osteope

Keywords: calcium, phosphorus, metabolic bone disorders, premature infants

1. Introduction

Every year, 15 million babies are born prematurely around the world of which more than 1 million die as a result of prematurity (Blencowe *et al.*, 2012). However, the continuous developments in intensive care of premature newborns have led to a progressive decline in mortality. The achievement in the survival through an intensive care is not always ensured a favorable long-term outcome of premature newborn**.** Prematurity is the greatest risk factor for metabolic bone disease because most calcium and phosphorus deposition occurs during the third trimester (Abrams *et al.*, 2006). In preterm newborn with gestational age below 32 weeks, the mineral content of bone is 25%-70% less than term neonates (Valentina *et al.*, 2009). Metabolic bone disease is characterized by a reduction in bone mineral content (osteopenia), with or without rachitic changes. It presents between 6 and 12 weeks of age but may remain asymptomatic for weeks until overt rickets or fractures develop (Vachharajani *et al.*, 2009). Symptoms may include poor weight gain, faltering growth, and respiratory difficulties or failure to wean off ventilatory support due to excessive chest wall compliance. Fractures may manifest as pain on handling.

A combination of phosphorus less than 4.6 mg/dL (<1.49 mmol/L) and S. Alkaline Phosphatase greater than 900 IU/L yielded a sensitivity of 100% and a specificity of 70% for low bone mineral density (Backström *et al.*, 2000). Experts recommend radiography of the wrist and/or knee because these regions are of high metabolic activity. There is also a grading system for assessing radiological severity (Koo *et al.*, 1984).

Mothers milk containing 25-35 mg/dl of calcium and 10-15 mg/dl of phosphorus simply does not contain enough minerals to support skeletal growth of growing premature infants. Bangladesh is among the top 10 countries with the highest numbers of preterm birth. The number has been

increasing along with the global rise of incidence (Blencowe *et al.*, 2012). In Bangladesh, Prevalence of osteopenia is high (28%) in premature infants (Nadia *et al.*, 2015). Another study which was conducted in Neonatology department of BSMMU, Dhaka showed rate of osteopenia is also high (46%) (Jahan *et al.*, 2016). So, supplement of calcium and phosphorus along with breast milk in premature infants may prevent metabolic bone disease and improve the growth of premature infants.

2. Objectives

To observe the efficacy of calcium and phosphorus supplementation for prevention of metabolic bone disease and improvement of growth in preterm infants.

3. Methodology and Materials

The study was conducted in the department of neonatology, Bangabandhu Sheikh Mujib Medical University from 16th August 2016 to 23rd July, 2017. This was a randomized clinical trial where 25 preterm babies were enrolled in supplement and non-supplement group, so total 50 babies. But one in supplement group and two in non-supplement group lost follow up. Two patients in supplement group and one in non-supplement group died. One in supplement group and two in non-supplement group developed feeding intolerance. At 6 weeks 21 patients in supplement and 20 patients in non-supplement group were available for analysis. After collection, data were entered into a personal computer and were edited, analyzed, plotted and were in graphs and tables. Data were analyzed by chi square test, and student's t test using the statistical package for social sciences (SPSS) version 20.

4. Result

During the study period, 187 preterm infants ≤ 34 weeks' gestation were admitted in the Neonatal Intensive Care Unit. Of them 62 neonates meet inclusion criteria. After taking informed written consent from parents of the selected neonates to participate in the study a total of 50 neonates were enrolled. They were divided into two groups (Supplemented and non-supplemented group) by lottery method. At 6 weeks 21 patients in supplement and 20 patients in non-supplement group were available for analysis. Demographic characteristics of studied infants are presented in table 1. Mean gestational age, birth weight, length and Occipito frontal circumference of supplemented group were 33.7 ± 2.2 weeks, 1353 ± 206 grams, 39.7 ± 2.8 cm and 28.6 ± 1.5 cm respectively. Mean gestational age, birth weight, length and OFC of non-supplemented group were 33.1 ± 2.7 weeks, 1405 ± 263 grams, 39.2 ± 2.9 cm and 28.0 ± 1.7 cm respectively. Gender distribution reflects slight male predominance in non-supplemented group. But there was no statistical significant difference between two groups.

Table 2 shows S. Calcium, S. alkaline phosphatase and S. inorganic phosphate value of infants of two groups at enrollment. There was no statistical significant difference between two groups.

Of the 41 infants, 13 (32%) developed evidence of osteopenia considering biochemical and radiological abnormality (Table 3). Out of 13 patient 12 had radiological evidence of osteopenia and 1 patient had osteopenia by biochemical evidence only 6 patients had both biochemical and radiological evidence of Osteopenia Among the radiological evidence 11 (92%) had grade 1 and 1 patient (8%) had grade 2. (Table-3)

At 6weeks of age S. Calcium and S. inorganic phosphate and S. Alkaline Phosphatase value of supplemented group were 9.5±0.4 mg/dl, 4.8±1.1mg/dl and 357±253 U/L respectively. At 6weeks of age S. Calcium and S. inorganic phosphate and S. Alkaline Phosphatase value of non-supplemented group were 9.4±0.5 mg/dl, 4.4±1.2mg/dl and 538±271 U/L respectively. There was no statistical significant difference between two groups (Table 4).

Infants of supplemented group showed better growth velocity considering weight, length and Occipito frontal circumference but there was no significant difference between two groups (Table 5).

Table 1: Comparison of demographic data between two groups (n=50)

Parameter	Supplemented group	Non-Supplemented group	p Value
Sex			
Male	11	11	0.55
Female	10	9	
Gestational age of the neonate (week)Mean ±SD	33.7 ± 2.2	33.1 ± 2.7	0.28
Body Weight of the neonate (Gram) Mean ±SD	1353.81±206	1405±263	0.37
Body length of the neonate (cm) Mean ±SD	39.7±2.8	39.2±2.9	0.48
OFC of the neonate (cm) Mean ±SD	28.6±1.5	28±1.7	0.72

Table 2: Comparison of serum calcium, alkaline phosphatase and inorganic phosphate level in supplemented and Non-Supplemented group at enrollment (n=50)

Parameter	Supplemented group	Non-Supplemented group	P value
S. Calcium (mg/dl) (mean ± SD)	8.8 ± 0.6	8.8 ± 0.7	0.2
S. ALP (U/l) (mean ± SD)	211 ± 55	226 ± 64	0.4
S. inorganic phosphate (mg/dl) (mean ± SD)	4.8 ± 1.3	4.8 ± 1.8	0.09

Table 3: Comparison between radiological and biochemical evidence of osteopenia in preterm neonates in supplemented and Non-Supplemented group at 6th week of age (n=50)

Parameter	Osteopenia		P value
	Present	Absent	
Supplemented group N (%)	6 (28%)	15 (72%)	0.45
Non-Supplemented group N (%)	7 (35%)	13 (65%)	

Table 4: Comparison of serum calcium, alkaline phosphatase and inorganic phosphate level in supplemented and Non-Supplemented group at 6 weeks where (n=50)

Parameter	Supplemented group	Non-Supplemented group	P value
S. Calcium (mg/dl) (mean ± SD)	9.5 ± 0.4	9.4 ± 0.5	0.6
S. ALP (U/l) (mean ± SD)	357.5 ± 253	538.2 ± 271	0.39
S. inorganic phosphate (mg/dl) (mean ± SD)	4.8 ± 1.1	4.4 ± 1.2	0.5

Table 5: Comparison of values of weight, length and head circumference in premature neonates receiving supplements and in the Non-Supplemented group group at 6th weeks. (n=50)

Parameter	Supplemented group	Non-Supplemented group	P value
Body Weight of the neonate (Gram) Mean ±SD	2326.7 ± 602	2301 ± 721	0.3
Body length of the neonate (cm) Mean ±SD	46.2 ± 3.6	44.6 ± 5.5	0.14
Occipito frontal circumference Mean ±SD	33.7 ± 2.2	33.1 ± 2.6	0.28

5. Discussion

This study tried to determine effects of calcium and phosphorus supplementation on radiological and biochemical characteristics of osteopenia and growth in premature infants. Total 13 patients out of 41 patients had evidence of osteopenia Of prematurity (Rate 32%). Out of 13 patients 12 had radiological evidence of osteopenia and 1 patient had osteopenia by biochemical evidence only. 6 patients had both biochemical and radiological evidence of osteopenia. Among the radiological evidence 11(92%) had grade 1 and 1(8%) patient had grade 2.

Normal | Loss of dense white line Grade 1 Osteopenia | Loss of dense white line & cupping Grade 2 Osteopenia

Fig 1

Patients of supplemented group showed better growth velocity and lower incidence of MBD though was not statistical significant change.

This study showed that adding supplement of calcium and phosphorus in premature infants did not have a significant effect on the rate of osteopenia. Some studies have shown similar results [1-3]. Lapillonne A *et al*., in their study showed Compared with control subjects, infants fed the experimental formula had 25% and 40% higher intakes of calcium and phosphorus, respectively. Serum calcium, phosphorus, osteocalcin, and alkaline phosphatase concentrations and urinary collagen type I cross-linked N-telopetide concentrations were not significantly different between the groups at any time point. The bone mineral content of infants fed the experimental formula was 23% (P=0.039) and 35% (P=0.002) higher at hospital discharge and expected term, respectively (Lapillonne A *et al*., 2004) [4]. In this study, the weight and linear and head growth of the intervention infants was s higher at the sixth week of the study. However, the trial had no significant effect on growth parameters. In agreement with current study, another study found that supplement of calcium and phosphorus intake in premature breast-fed infants led to a significant increase in the length and head circumference, but did not have any significant effect on the mean weight or crown-heel length.14 Still, there are several studies that do not support the effectiveness of supplementary feeding on growth parameters [5, 6].

However, there were several studies that demonstrated the beneficial effects of supplementary feeding on the reduction of osteopenia and improvement of bone mineral contents [7-11]. Lapillonne A *et al*., in their study showed Compared with control subjects, infants fed the experimental formula had 25% and 40% higher intakes of calcium and phosphorus, respectively. Serum calcium, phosphorus, osteocalcin, and alkaline phosphatase concentrations and urinary collagen type I cross-linked N-telopetide concentrations were not significantly different between the groups at any time point. The bone mineral content of infants fed the experimental formula was 23% (P=0.039)

and 35% (P=0.002) higher at hospital discharge and expected term, respectively (Lapillonne A *et al*., 2004).
These results might be due to the prescription of different doses of supplements or minerals or the age of neonates at the time of study or other environmental factors.
In this study all the three expired patient was diagnosed as a case of late onset neonatal sepsis. One was Acinetobacter sp. And another one was Klebsiella sp. positive. Third one was diagnose as a case of late onset sepsis by clinically and positive septic screening. Total three patients developed feeding intolerance which managed by nil per os for 5 days and then restart feeding gradually.

6. Limitations of the study
Our study wasn't a blinded study so patient bias was present along with observer bias in subjective recording and the small sample size, single center study, blinding was not done, short follow up period.

7. Conclusion and recommendations
Infants of supplemented group showed better growth velocity and lower incidence of metabolic bone disorders than non-supplemented group. But this difference between supplemented group and non-supplemented group were not statistically significant. However his study does not provide any evidence to suggest the effectiveness of supplementary calcium and phosphorus in osteopenia of prematurity and growth of infants.

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