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Original Article

Benefits of Providing 2 mmol Calcium/kg/day in Parenteral Nutrition for Premature Infants: A Cohort Study on Biochemical Markers of Metabolic Bone Disease of Prematurity

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Abstract ***Objective:*** To evaluate the benefit of providing approximately 2 mmol Calcium/kg/day in parenteral nutrition for premature infants less than 1200 grams. ***Methods:*** This was a retrospective study of two historical cohorts. The Low Calcium group was from 2008 to 2012 when inorganic phosphate was used as ingredients for preparing parenteral nutrition. Parenteral nutrition provided 1.3 mmol Calcium/kg/day and 1.3 mmol Phosphorus/kg/day. The High Calcium group was from 2015 to 2017 when sodium glycerophosphate (organic phosphate) was used. Parenteral nutrition provided approximately 2 mmol Calcium/kg/day (1.8-2.2 mmol/kg/day) and 1.7 mmol Phosphorus/kg/day. ***Results:*** Fewer infants had radiological evidence of metabolic bone disease of prematurity in the High Calcium group than in the Low Calcium group (0/40 versus 6/47, p=0.02). There were significantly fewer cases of hyperphosphatasia as defined by peak alkaline phosphatase (ALP) level more than 800 IU/L in the High Calcium group than the Low Calcium group. Hypophosphataemia (serum phosphate level <1.33 mmol/L) lasting longer than 2 weeks was less common in the High Calcium group than the Low Calcium group. ALP levels were significantly lower and serum calcium and phosphate levels were significantly higher across week 0 to week 12 in the High Calcium group than the Low Calcium group. There was drop in z-score for length from birth to 37 weeks. The drop in z-score was not significantly different between the two cohorts. ***Conclusion:*** The proxy measures of metabolic bone disease of prematurity (high ALP and low phosphate level) are improved and radiological evidence of metabolic bone disease of prematurity is reduced by the prescription of higher doses of calcium and phosphate in parenteral nutrition.

Key words *Glycerophosphate; Hyperphosphatasia; Hypophosphataemia; Parenteral nutrition; Organic phosphate*

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Introduction

Metabolic bone disease (MBD) of prematurity is characterised by decreased bone mineral content of premature infants. Initially X-ray reveals osteopenia. At advanced stage, rachitic change and fractures occur.

The foetal accretion rates are 3.5 mmol/kg/day for calcium and 2.4 mmol/kg/day for phosphorus in the third trimester.[1] Currently premature infant formulas contain 1331 mg to 1826 mg of calcium (33 mmol to 46 mmol) and 670 mg to 1014 mg (22 mmol to 34 mmol) of phosphorus per liter.[2] These premature infant formulas provide daily intake of calcium and phosphorus exceeding foetal accretion rate. This is also true for expressed breast milk supplemented by human milk fortifier.[2] On the other hand, before full enteral feeding is established, premature infants receive parenteral nutrition, which has so far been unable

to match the foetal accretion rate. For example, one can provide 1.6 mmol Calcium/kg/day and 1.4 mmol Phosphorus/kg/day by parenteral nutrition according to a guideline in Australia.[3] This is the physiological basis for metabolic bone disease of prematurity. Organic phosphate has high compatibility with calcium salts.[4-8] As a result of the licensed use of organic phosphate in some parts of the world, higher doses of calcium and phosphates can be delivered in parenteral nutrition than the doses limited by the use of conventional formations containing calcium gluconate and inorganic phosphates. To date, the highest prescription doses are 2 mmol Calcium/kg/day and 2 mmol Phosphorus/kg/day as stated in a national practice guideline.[9] From a physiological point of view, it is sound to provide higher doses of calcium and phosphate by parenteral nutrition with the use of organic phosphate. However, studies on the advantage of parenteral formulations containing organic phosphate providing higher doses of calcium and phosphorus over the conventional formulations containing inorganic phosphate are scarce in the literature. We identified two such studies in the literature.[10,11] Parenteral nutrition admixtures with higher concentration of calcium and phosphate resulted in higher calcium and phosphorus retention[10,11] and increased bone mineral contents.[10] Therefore, we carried out yet another study in the hope of providing further evidence in support of using parenteral nutrition with higher concentration of calcium and phosphate achieved by using organic phosphate.

Methods

This was a retrospective study of two cohorts of premature infants with birth weight less than 1200 grams in our hospital. Non-survivors were excluded from this study as most neonatal death was in early life before MBD of prematurity developed. Besides, infants transferred to another hospital mainly for surgical management were also excluded as the difference in dosing of calcium and phosphate in parenteral nutrition in that hospital was an important factor that could contribute to the variation of bone health of the infants. This was an observational study of two periods when there was change of practice in the prescription of calcium and phosphorus contents in parenteral nutrition. The first cohort (Low Calcium group) was from the years 2008 to 2012. During this period, calcium gluconate (organic calcium) and potassium phosphate (inorganic phosphate) were the ingredients used in preparing parenteral nutrition admixtures. Calcium and phosphorus provision was started at 0.6 mmol/kg/day and stepped up gradually to 1.3 mmol/kg/day in one week with the molar ratio of calcium and phosphate 1:1. The second cohort (High Calcium group) was from the years 2015 to 2017. During this period, calcium gluconate and sodium glycerophosphate (organic phosphate) were the ingredients used in preparing parenteral nutrition admixture. Calcium and phosphorus provision was started at 1.3 mmol/kg/day and 1-1.3 mmol/kg/day respectively and then stepped up. By day 10, calcium was provided at 1.8-2.2 mmol/kg/day and phosphorus at 1.7 mmol/kg/day. The doses of calcium and phosphate as described were the amount of calcium and phosphate delivered by the parenteral nutrition admixtures when the premature infants received full parenteral nutrition and did not take any milk. When these infants took milk, the volume of milk ingested was taken into account and the volume of parenteral nutrition admixtures was reduced on pro rata. Therefore the calcium and phosphate doses in mmol/kg/day were per design of the parenteral nutrition admixtures and not the actual doses of calcium and phosphate intravenously given when oral feeding was concomitantly taking place.

In these two periods, the dose of vitamin D was the same: 160 IU/kg/day provided by adding 4 ml Vitalipid/kg/day into the entire parenteral nutrition admixtures. Similarly intravenous dose of vitamin D actually delivered was reduced in the same proportion to the reduction of volume of parenteral nutrition admixtures given as a result of advancement of oral feeding. The ever breastfeeding rates during these two periods were similar (95%). Before full enteral feeding was achieved, during these two periods, premature infants were fed either premature infant formula (when expressed breast milk is not available) or expressed breast milk from their own mothers.

Alkaline phosphatase (ALP) and serum phosphate levels are proxy measures of MBD of prematurity. ALP level greater than 700 IU/L at 3 weeks of life has a sensitivity of 73% and specificity of 74% for the occurrence of osteopenia in X-ray of forearm taken at term.[12] According to a committee report of the American Academy of Pediatrics, MBD of prematurity is unlikely to occur for neonates having ALP level less than 800 IU/L.[13] Otherwise radiological evaluation should be done for premature infants with ALP level exceeding 800 IU/L. Serum phosphate level lower than 1.33 mmol/L is associated with low phosphorus status in neonates.[13] Therefore, we had two definitions for hyperphosphatasia: ALP level >700 IU/L[12] at three weeks of life and peak ALP level >800 IU/L.[13]

We defined hypophosphataemia as serum phosphate level <1.33 mmol/L.[13] The incidence of hyperphosphatasia and hypophosphataemia was compared between the two cohorts according to the definitions used. The weekly levels of ALP, serum calcium and serum phosphate were compared between these two cohorts from birth to week 12.

Premature infants often have impaired growth in length in early weeks of life. A study showed length z-scores had a deficit progressively worsened in the first 30 days of life of premature neonates.[14] The growth chart of premature infants showed that length often fell below 3rd centile before term.[15] The growth in length of premature infants is the result of lengthening of bones. Bone is mainly made up of calcium, phosphorus and protein. Besides, peak ALP higher than 1200 IU/L was associated with MBD of prematurity and reduced length at 9 and 18 months.[16] Therefore, we hypothesised that length growth might be improved in the High Calcium group. We evaluated the length at birth and at 37 weeks when most premature infants were still in the hospital and growth parameters were mostly available. The z-scores of the High Calcium group and that of the Low Calcium group were compared.

Confounding factors that increase the risk of MBD of prematurity were also evaluated and compared between the two cohorts: birth weight, gestation, use of frusemide, use of dexamethasone, incidence of bronchopulmonary dysplasia, the duration of parenteral nutrition provided.[1] Bronchopulmonary dysplasia was defined as requirement of supplementary oxygen at 36 weeks.

In our centre, we have a powerful search engine for patient data named CDARS (Clinical Data Analysis and Reporting System), which generates data according to the request put into this search engine. By means of CDARS, we obtained the database of all neonates with birth weight less than 1200 grams in these two periods, survivors and non-survivors, results of the laboratory data as requested including ALP, serum calcium and phosphate levels, and drug data for dexamethasone and frusemide. We went through the medical records to find out if infants were still on supplementary oxygen/ventilator support at 36 weeks for the sake of diagnosis of bronchopulmonary dysplasia.

We adopt the Student's t-test for the comparison of continuous variables and Pearson's chi-squared test for categorical variables between the Low Calcium group and High Calcium group. To account for the dependency arising from repeated measurements from each individual over time, we applied the MANOVA for repeated measures to each of the levels of ALP/Phosphate/Calcium datasets. The method is an overall test for testing whether the time, Calcium groups (low/high), or their interaction effects are significant after adjusting for the repeated measurement structure of the dataset. The level of significance is set to be 0.05 for the statistical analysis of this paper. Missing data will shrink the numerator and dominator of proportion calculated and will be mentioned in the following section.

Results

There were 76 neonates with birth weight less than 1200 grams born in the period from 2008 to 2012. Twenty-two of them died. Among these 54 survivors, seven of them were transferred to another hospital with paediatric surgery service in the first 12 weeks of life because of surgical indications. These seven infants were excluded from the study leaving 47 premature infants in the Low Calcium group for analysis. There were 60 neonates with birth weight less than 1200 grams born in the period from 2015 to 2017. Eleven of them died. Among these 49 survivors, nine of them were transferred to another hospital with paediatric surgery service in the first 12 weeks of life because of surgical indications. These nine infants were excluded from the study leaving 40 premature infants in the High Calcium group for analysis. The median time of death of all the non-survivors was 1 day. The demographic data and risk factors predisposing to MBD of prematurity were compared between the two groups (Table 1). There was no statistical significant difference in gestation, birth weight, sex distribution, proportion of small for gestation age and Apgar score ≤3 at 5 minutes of life. There were more cases of maternal diabetes or impaired glucose tolerance in the High Calcium group. There was no difference in occurrence of risk factors such as bronchopulmonary dysplasia, prescription of dexamethasone and frusemide, duration of parenteral nutrition. Only missing data was duration of parenteral nutrition in eight of the infants in the Low Calcium group.

Review of clinical records showed that in the Low Calcium group one infant had fracture of long bone and six infants had radiological features of MBD of prematurity: osteopenia, fraying of metaphysis, periosteal reaction. In the High Calcium, group no infants had fracture or radiological features of MBD of prematurity. The difference in the occurrence of radiological features of MBD of prematurity was significant (Table 2).

Hyperphosphatasia was less often encountered in the

High Calcium group than the Low Calcium group according to the definition of peak ALP level >800 IU/L (Table 2). The High Calcium group and the Low Calcium group had similar incidence of hypophosphataemia that had ever occurred. However, hypophosphataemia tended to be of shorter duration in the High Calcium group than the Low Calcium group.

The serial ALP levels, serum phosphate levels and serum calcium levels of the two cohorts were plotted against time (Figure 1). To account for the dependency arising from repeated measurements from each individual over time, we applied the MANOVA for repeated measures to each of the ALP/Phosphate/Calcium datasets. Our results showed that for all three datasets provided, the time, the two Calcium groups and their interaction effects were all significant (all with p-values <0.0001). In general, the average values of ALP/Phosphate/Calcium vary significantly across the two calcium groups over the twelve weeks.

There was impaired length growth in both the High Calcium group and the Low Calcium group. The average z-score for length at birth of the High Calcium group was -0.892 (0.94), which further went down to -2.368 (1.39) at 37 weeks. The average z-score for length at birth of the Low Calcium group was -0.932 (1.40), which further went down to -2.492 (1.73) at 37 weeks. The drop in length (in terms of z-score) from birth to 37 weeks of the High Calcium group was 1.476 (1.08). The drop in length (in terms of z-score) from birth to 37 weeks of the Low Calcium group was 1.56 (1.09). When we compared the drop in length of the two groups, there was no significant difference (p=0.288).

Table 1 Demographic data and risks factors for MBD of prematurity in the two cohorts

	Low Calcium group n = 47	**High Calcium group n = 40**	**P value**
Birth weight, grams (mean ± SD)	914 ± 200	964 ± 169	0.107
Gestation, weeks (mean ± SD)	27.51 ± 2.46	27.60 ± 2.10	0.429
Sex: Male/Female	19/28	24/16	0.0688
Small for gestational age	13 (27.7%)	9 (22.5%)	0.581
Mothers with diabetes or impaired glucose tolerance	1 (2.13%)	8 (20%)	0.00673
Apgar score at 5 minutes ≤3	3 (6.38%)	2 (5%)	0.782
Number of infants receiving dexamethasone	1 (2.13%)	0	0.540
Number of infants receiving frusemide	9 (19.15%)	8 (20%)	0.921
Duration of parenteral nutrition, days (mean ± SD)	28.2 ± 20.2	33.3 ± 15.6	0.106
Bronchopulmonary dysplasia	21 (44.68%)	11 (27.5%)	0.0977

Table 2 Occurrence of clinical fracture, radiological features of MBD of prematurity, hyperphosphatasia and hypophosphataemia in two cohorts

	Low Calcium group n = 47	**High Calcium group n = 40**	**P value**
Fracture	1 (2.13%)	0	0.54
Radiological evidence of MBD of prematurity	6 (12.77%)	0	0.02
ALP >700 IU/L at 3 weeks	6 (12.77%)	1 (2.5%)	0.0794
Peak ALP >800 IU/L	9 (19.15%)	2 (5%)	0.0478
Any occurrence of serum phosphate <1.33 mmol/L	32 (68.09%)	25 (62.5%)	0.5849
Occurrence of serum phosphate <1.33 mmol/L in more than 1 week	27 (57.45%)	15 (37.5%)	0.0635
Occurrence of serum phosphate <1.33 mmol/L in more than 2 weeks	20 (42.55%)	3 (7.5%)	0.0002
Occurrence of serum phosphate <1.33 mmol/L in more than 3 weeks	14 (20.79%)	1 (2.5%)	0.0008

Discussion

The 'gold standard' for detecting osteopenia is bone mineral density measured by Dual-energy Absorptiometry (DEXA) scan.[17] However, DEXA scan is not available as a standard service in most hospitals. In addition, the normal range of bone density in normal population at different gestational age and corrected age is not available. Therefore, DEXA scan does have its own downside in the study of MBD of prematurity.

In our study we used ALP level and serum phosphate level, which are the proxy measures of MBD of prematurity. The limitation of ALP level and serum phosphate level is that their sensitivity and specificity for MBD of prematurity is less than 90%.[17] In other words, abnormal ALP and serum phosphate levels are not sufficient for the diagnosis of MBD of prematurity for individual patients in clinical practice. However, in our study, our purpose was not making clinical diagnosis of MBD of prematurity for individual patients. These proxy measures reflected the general bone health of the cohorts as a group and served the purpose of comparing the bone health of two cohorts. In addition, the definition of hyperphosphatasia we employed did carry clinical meaning. For example, in accordance with an American guideline, radiological investigation in search of MBD of prematurity should be carried out for infants having peak ALP level higher than 800 IU/L.[13] Using peak ALP of 800 IU/L as the cut-off for defining hyperphosphatasia, we managed to show that the need for radiological investigation in our NICU was significantly reduced in the High Calcium group. This result is of clinical significance. In fact, high ALP levels in the Low Calcium cohort could have led to radiological investigation for MBD of prematurity, which was present in six infants in the Low Calcium group. 12.8% of infants in the Low Calcium group had ALP levels higher than 700 IU/L at three weeks while 2.5% of infants in the High Calcium group did. The difference is not significant with p-value of 0.0794, which might be accounted for by the small sample size of our study.

The design of the study did not include specific investigations to confirm safety. The hazard of high

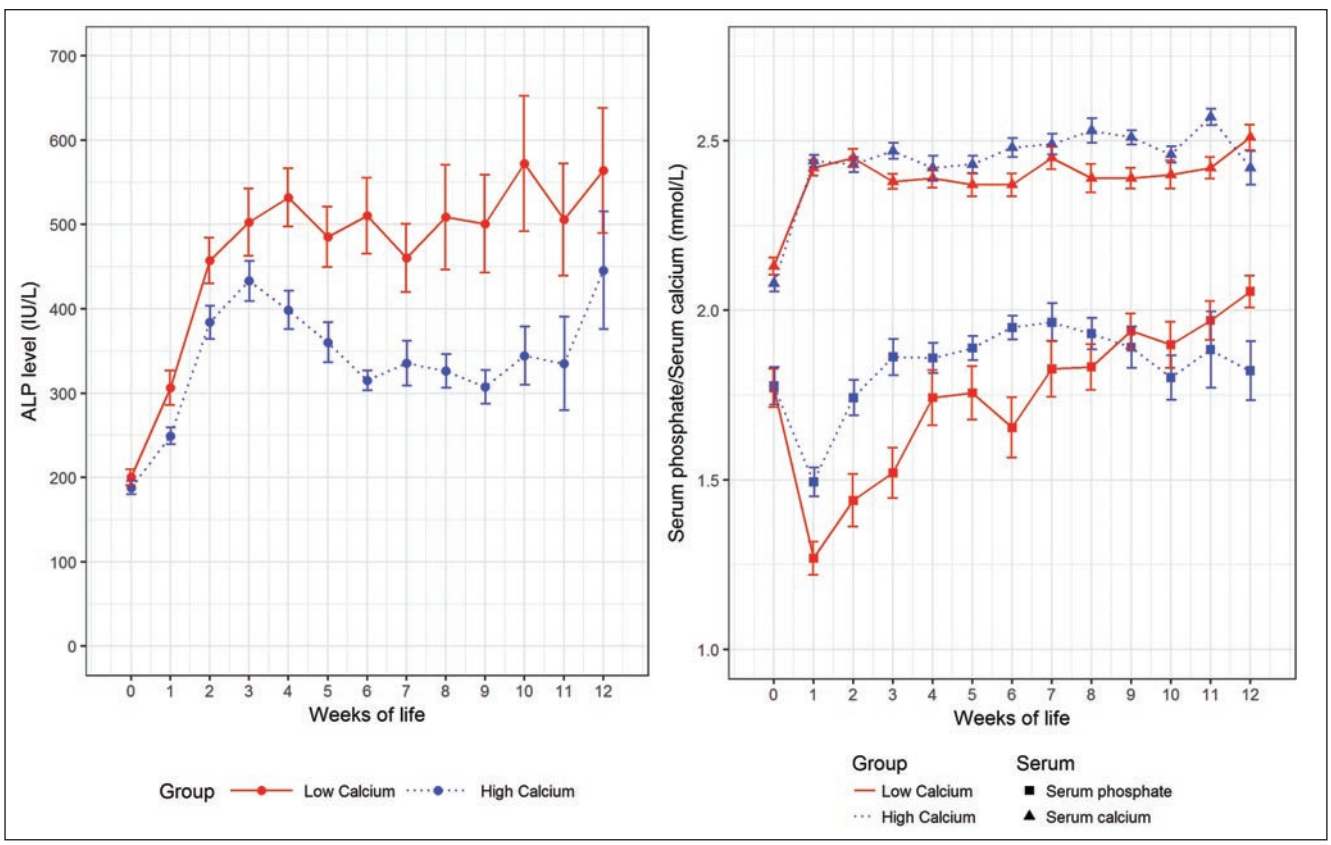

Figure 1 Average ALP, serum phosphate, serum calcium levels (1 standard error) in the first 12 weeks of life of the High Calcium group and Low Calcium group. The main and interaction effects have p-values <0.0001 by MANOVA for all the three plots.

calcium and phosphate concentrations in parenteral nutrition is precipitation, which could lead to fatality.[18] This complication has been reported in the use of inorganic phosphate. This should not be an issue in the High Calcium group because studies showed that with the use of organic phosphate, there was no precipitation even at concentrations much higher than that used in the High Calcium Group.[6,8] Another theoretical risk is ectopic calcification, which could occur in the kidney resulting in nephrocalcinosis. However, in a study, in which calcium and phosphate concentrations in parenteral nutrition admixtures were higher than those of the High Calcium group in our study, calcium retention was high and measured urine calcium was low.[10] Therefore, nephrocalcinosis was unlikely to happen. In addition, prescribing calcium at a dose of 2 mmol/kg/day is currently a standard practice in the United Kingdom.[9] Therefore, in our study we did not feel obliged to perform ultrasound kidney for nephrocalcinosis. Perhaps in future study when calcium and phosphate are prescribed at doses markedly higher than the doses of 2 mmol/kg/day will the performance of ultrasound kidney be necessary.

The limitation of our study is the retrospective nature and small sample size. Even given such a small sample size, there was marked difference of the biochemical markers of bone health and significant difference in the occurrence of radiological features of MBD of prematurity. It is quite convincing that increasing calcium and phosphate doses in parenteral nutrition does make a difference.

The foetal accretion rates are 3.5 mmol/kg/day for calcium and 2.4 mg/kg/day for phosphorus. Organic calcium and organic phosphate are compatible at the concentrations of 5 mmol/dL of each element.[6] In theory, it is now possible to make parenteral nutrition admixtures meeting the fetal accretion rate using organic calcium and organic phosphate. In our study in the High Calcium group, the maximum calcium provision was 2.2 mmol/kg/day, which was still behind the fetal accretion rate. However, we already achieved marked reduction of hyperphosphatasia and hypophosphataemia. The only thing we still observed was that there was no improvement of stunted growth in length during hospitalisation of these premature infants despite high calcium and phosphorus contents in the High Calcium group. Further studies are necessary to find out whether further increasing calcium and phosphorus contents in parenteral nutrition results in additional clinical benefit such as the prevention of stunted growth.

In our study, in the Low Calcium group, calcium and phosphorus provided by parenteral nutrition was restricted by the low compatibility of inorganic phosphate with calcium salts. This is in fact the situation of USA nowadays where licensing of organic phosphate is not yet approved. Under such circumstances, it was reported that up to 31% of extreme low birthweight infants had radiological evidence of MBD of prematurity and 10.4% had spontaneous fracture.[19] Therefore, we reiterate the importance of providing higher calcium and phosphorus concentration by means of using organic phosphate, as the difference is marked when we compare the experience of our hospital with that of the situation in USA.

Despite our small sample size, proxy measures of MBD of prematurity are significantly improved when per design of parenteral nutrition admixtures deliver 2 mmol/kg/day Calcium obviating radiological investigation for MBD of prematurity. Our results are in agreement with two similar studies of improved bone health in terms of higher calcium and phosphorus retention[10,11] and increased bone mineral contents.[10] The recommended dose of 2 mmol Calcium/kg/day is already in a national guideline. We hope to bring this message to centres, which are prescribing calcium at lower doses.

Conclusions

We recommend providing approximately 2 mmol Calcium/kg/day in parenteral nutrition for premature infants with birth weight less than 1200 grams. The use of organic phosphate as ingredient makes this possible.

Ethical Consideration

This study was approved by the Hospital Ethical Committee. Consent from patients was exempted since it was a retrospective and observational study with anonymity of the patients. The reference number is: HKECREC-2017-088.

Conflicts of Interest and Funding

There are no conflicts of interest. There is no funding for this study. All the work is done out of the authors' own interest and carried out after work. The authors do not have personal business due with the pharmaceutical companies selling the ingredients of parenteral nutrition.

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