Prevention of Metabolic Bone Disease of Prematurity by Optimizing Calcium and Phosphate Contents in Parenteral Nutrition for Premature Infants

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Abstract

Metabolic bone disease (MBD) of prematurity is mainly caused by inadequate amount of calcium and phosphate in parenteral nutrition admixtures given to premature infants in early days of life before full enteral feeding is established. According to published guidelines/survey of parenteral nutrition for premature infants in Australia, USA and Europe, it is still a common practice to prepare parenteral nutrition admixtures with calcium and phosphate concentration not high enough to achieve the fetal accretion rate. Therefore, as these bones of premature infants grow without adequate supply of calcium and phosphorus, they are under-mineralized. MBD of prematurity is still prevalent worldwide. Solubility of calcium and phosphate has been a limiting factor for provision of adequate amounts of calcium and phosphate in parenteral nutrition. However, this is no longer true because for more than a decade there have already been studies on the use of organic phosphate and organic calcium in parenteral nutrition showing their compatibility at high concentration, which if provided could achieve the fetal accretion rates. In addition, several studies have shown that these organic forms of calcium and phosphate at such high concentrations are mostly retained. The retention rates vary from 80% to 97% across these studies. Therefore we advocate the use of organic phosphate and organic calcium in preparing parenteral nutrition for premature infants. We recommend: for infants less than 1.2 kg administer calcium and phosphate at 2.2 and 1.7 mmol/kg/day when they are growing. At this rate MBD of prematurity could be minimized.

ABBREVIATIONS

MBD: Metabolic Bone Disease; BPD: Broncho Pulmonary Dysplasia; ESPGHAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition; ELBW: Extremely Low-Birth Weight; USA: United States of American

INTRODUCTION

Metabolic bone disease (MBD) of prematurity occurs in premature infants whose growing bones are under-mineralized. In the last trimester, the fetal accretion rate of calcium is 2 mmol per 10 grams of newly grown body weight. The fetal accretion rate of phosphorus is 1.52 mmol per 10 grams of newly grown body weight [1]. For a 1 kg baby having growth of 20 grams per day, the fetal accretion rates are 4 mmol/kg/day and 3.04 mmol/kg/day for calcium and phosphorus respectively [1]. This fetal accretion rate was proposed as the reference mark for parenteral nutrition according to a guideline published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [1]. This fetal accretion rate is hard to meet by parenteral nutrition for premature infants. For example, in Australia [2], in the standard parenteral nutrition formulations for premature infants the calcium and phosphate concentrations are 1.2 mmol / 100 ml and 1 mmol / 100 ml respectively. These standard formulations are provided to premature infants at 135 ml/kg/day. Therefore, these premature infants are provided 1.62 mmol calcium/kg/day and 1.35 mmol phosphate/kg/day, which is far lower than the fetal accretion rates of 4 mmol/kg/day and 3.04 mmol/kg/day as calculated for a 1 kg baby. Amongst 23 neonatal intensive care units in Portugal [3], administration of calcium ranged from 1 mmol/kg/day to 1.75 mmol/kg/day. Again these administration rates of calcium are far below the fetal accretion rate. Similarly the parenteral nutrition in the United States of America (USA) [4] contains insufficient amount of calcium and phosphate because inorganic phosphate approved for use in USA has low compatibility with calcium limiting the concentrations of calcium and phosphate in parenteral nutrition admixtures. Not surprisingly MBD of premature still occurs worldwide. The bones of these growing premature infants are
under-mineralized as they continue to grow in their extra-uterine life on parenteral nutrition in the current standard of care.

There is less cause for concern in terms of under-provision of calcium and phosphorus and under-mineralization of bones for premature infants on full enteral feeding. Calcium retention of 60-90 mg/kg/day (1.5-2.25 mmol/kg/day) ensures appropriate mineralization and decreases the risk of fracture [5]. Therefore, for enteral nutrition the recommended calcium and phosphate intake by the ESPGHAN [6] is not the fetal accretion rate but intake that results in calcium retention of 60-90 mg/kg/day.

Either formulae designed for preterm infants or human milk with added human milk fortifier is able to achieve calcium retention of 90 mg/kg/day [7]. Besides, intrauterine bone mineralization was approximated [8,9].

**PRESENTATION AND NATURAL COURSE OF MBD OF PREMATURITY**

MBD of prematurity is not simply a radiological finding of osteopenia. It can produce significant symptoms. It can present with respiratory distress between 5 and 11 weeks of life due to softening and / or fractures of ribs [10]. The time for osteopenia to be apparent in X-ray is 7-8 weeks [11,12] and fractures on average occur at 14 weeks [11]. Fractures classically take place in ribs and long bones. Physical signs include deformity of the skull (diastasis of the suture, enlargement of sagittal fontanelle and frontal bosses, craniotabes), thickening of the chondrocostal junctions of the wrists and ribs [13].

The long-term effects on bone health in late childhood and early adulthood are unclear as studies show inconsistent results [14-17]. However, evidence speaks for the notion that this is a self-limiting disease [5,18]. The severity of osteopenia improves by 15 weeks of life [10]. Bone mineral density catches up by post-conceptional age of 6 months [5]. At 6 months corrected age, spine and total bone mineral density, corrected for anthropometric values, are in the range of normal term newborn infants [19]. It is because the demand of calcium and phosphorus by corrected gestational age at term is far less than that in the third trimester. The demand of calcium and phosphorus by gestational age at term is easily met by usual milk formula [18].

**INCIDENCE OF MBD OF PREMATURITY**

MBD of prematurity was prevalent among premature infants three decades ago. In an article published in 1989 [20], among 78 infants with birth weight less than 1500 grams, by day 88 fractures along with rickets were present in 12 of the 78 infants. It is almost 30 years but recent studies still show high incidence of MBD of prematurity among extremely low-birth weight (ELBW) infants [11,12]. In an article published in 2014 [11], it was found that among ELBW infants, 71 out of 230 (31%) still had radiological evidence of MBD of prematurity and 24 of these 71 infants (38%) developed spontaneous fractures.

**RISK FACTORS OF MBD OF PREMATURITY**

As the pathogenetic mechanism of MBD of prematurity is requirement of minerals of premature infants not being met by postnatal provision in parenteral nutrition, birth weight remains the most important factor for development of MBD of prematurity [20]. As explained while oral intake of milk in current standard provides adequate calcium and phosphorus for bone mineralization in premature infants, parenteral nutrition that is commonly used today provides insufficient calcium and phosphophate. Therefore, the duration of parenteral nutrition before enteral feeding is established is the second most important factor for the development of MBD of prematurity [18]. Other factors for development of MBD of prematurity include systemic steroids, diuretics, bronchopulmonary dysplasia (BPD) and cholestatic jaundice [18].

**STRATEGY FOR THE PREVENTION OF MBD OF PREMATURITY**

The prevention of MBD of prematurity starts with the prevention of prematurity. However, prematurity is not often preventable. Certainly prevention of BPD in theory removes an adverse factor for the development of MBD of prematurity. Neonatologists today have been trying to prevent BPD as far as possible and the prevention of BPD is out of the scope of this review. Efforts should be paid to avoid the use of diuretics and systemic steroids as far as possible. However, prescriptions of these drugs are sometimes justified after balancing the risk-and-benefit ratio. Therefore what remains we can do to prevent MBD of prematurity is optimization of calcium and phosphate in parenteral nutrition admixtures to catch up with fetal accretion rate. The fetal accretion rate of calcium and phosphorus is known and it is set as the target for postnatal supply of the minerals in parenteral nutrition in Europe [1] and USA [4] alike. However, meeting this target remains a dream not yet realized [4]. As already mentioned in previous sections, contents of calcium and phosphorus in parenteral nutrition admixtures commonly used nowadays are often far below the fetal accretion rate, [2-4] which is the major cause for MBD of prematurity.

For more than a decade, studies have proven that organic phosphate and organic calcium are compatible at high concentration in parenteral nutrition admixtures [21-24]. Glucose-1-phosphate and glycerophosphate are examples of organic phosphates and calcium gluconate is an example of organic calcium. The use of organic phosphate greatly enhanced compatibility of calcium and phosphate whereas the use of organic calcium just marginally enhanced compatibility [22]. There was no precipitation of calcium phosphate at concentration of 5 mmol/ 100 ml of each mineral in parenteral nutrition admixtures when glucose-1-phosphate was mixed with either organic or inorganic calcium salts [22]. In another study, when sodium glycerophosphate was mixed with calcium gluconate in parenteral nutrition admixtures, they were still compatible at concentrations at as high as 5 mmol/ 100 ml of each mineral [24]. At this concentration of calcium and phosphate, the formidable task of meeting the fetal accretion rate of calcium and phosphate could be achieved. According to the ESPGHAN guideline on paediatric parenteral nutrition published in 2005 [1], the recommended daily amount of calcium and phosphate provided by parenteral nutrition is the same as the fetal accretion rate of 2 mmol of calcium and 1.52 mmol of phosphate per 10 grams of weight gain.

Despite all these studies showing compatibility of organic phosphate and calcium, thus the feasibility of preparing parenteral

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calcium and phosphate contents in parenteral nutrition for as there is a sign that the world is moving towards optimizing infusion rate was 80% to 97%. Previous studies [27-29] on mineral retention for admixtures containing high concentration of organic phosphate and calcium gluconate [25] even though sodium glycerophosphate was actually in use in the preparation of parenteral nutrition. Calcium and phosphate concentration in parenteral nutrition admixtures remained way too low. Therefore, we carried out yet another study on the compatibility of calcium gluconate and sodium glycerophosphate and only after this study were we allowed to prescribe higher concentration of calcium and phosphate. In this study [26], we confirmed the compatibility of glycerophosphate and calcium gluconate at the concentration of 3 mmol of calcium per 100 ml and 2.3 mmol of phosphate per 100 ml in parenteral nutrition admixture. In our experiment, we pushed the chemical situations to the limit in such a way that precipitation of calcium and phosphate could be favored. We did it by decreasing the acidity of the parenteral solution admixture using lower amino acid concentration and lower dextrose concentration than usual. This is important from the point of view of quality and safety because in our hospital, we do not have standard parenteral nutrition formula. We prescribe parenteral nutrition tailor-made to individual infants. Low amino acid concentration and low dextrose concentration might be prescribed in face of glucose intolerance. Inborn errors of metabolism and in face of glucose intolerance respectively. Even under these extreme chemical situations favoring precipitation, the admixtures were still compatible.

There is no doubt to the in-vitro compatibility of these admixtures containing organic phosphate and organic calcium. However, in vivo whether calcium and phosphorus thus provided could be retained is important. Otherwise, if calcium and phosphate are not retained but lost in urine, under-mineralization of bones of premature infants still occurs no matter how high the contents of calcium and phosphate are in parenteral nutrition admixtures. Previous studies [27-29] on mineral retention for subjects provided with high concentration of organic phosphate and calcium in parenteral nutrition were encouraging. The retention rate was 80% to 97%.

In April 2016, the British Association of Perinatal Medicine published a guideline for parenteral nutrition. For premature infants the recommendation is to give calcium at 1.5 to 2 mmol/kg/day [30]. Parenteral nutrition providing 2 mmol calcium/kg/day is the highest ever appearing in local guidelines for parenteral nutrition in premature infants. This is encouraging as there is a sign that the world is moving towards optimizing calcium and phosphate contents in parenteral nutrition for premature infants.

### RECOMMENDATION FOR CALCIUM AND PHOSPHATE ADMINISTRATION IN PARENTERAL NUTRITION

According to the ESPGHAN guideline of parenteral nutrition, the recommended rates of calcium and phosphate should be the same as the fetal accretion rate. For a 0.5kg fetus gaining weight at 20 grams per day, the fetal accretion rates were 8 mmol calcium/kg/day and 6.08 mmol phosphorus/kg/day. Although it is possible to prepare compatible parenteral nutrition admixtures meeting these recommended doses of calcium and phosphate by the use of organic phosphate, prescribing calcium and phosphate for example at 8 mmol/kg/day and 6 mmol/kg/day looks daunting as provision as such has not been reported in human studies. This exceedingly high concentration of calcium and phosphate only happened in an animal study of piglets [28], in which piglets received calcium and glycerophosphate at the rate of 15 mmol/kg/day.

It is imperative to assume calcium and phosphorus requirement in preterm infants should match the fetal accretion rate and the ESPGHAN actually recommended prescription of calcium and phosphate at the fetal accretion rate [1,4]. A revised calcium and phosphorus recommendation [5] has been proposed suggesting a smaller requirement of the minerals in premature infants, which is less than the fetal accretion rate. In the context of this article, it was meant for design of enteral nutrition but there is no reason why the argument for enteral nutrition could not be applied for parenteral nutrition. The argument for a lower calcium and phosphorus requirement is as follows. In postnatal life bone resorption is more active than in fetal life due to the decrease in mechanical stimulation to bones because these infants have less resistance to moving their limbs after birth. Bone resorption itself provides a part of the mineral requirement necessary for postnatal bone turnover. Therefore, the postnatal calcium and phosphate requirement might be lower than the fetal accretion rate. In addition, mild degree of under-mineralization might be tolerated as long as symptoms of rickets of prematurity and fractures do not occur. It is because MBD of prematurity is a self-limiting disease and in the long run, there is spontaneous mineral catch-up growth for the osteopenic bones of premature infants. Therefore, the target of postnatal bone mineralization for premature infants might not necessarily be equivalent to the same degree of mineralization as happening in fetus. Since there is evidence that calcium retention of 1.5 to 2.25 mmol/kg/day suppresses the risk of fracture and clinical symptoms of osteopenia [5], the calcium and phosphorus contents in parenteral nutrition should be designed in such a way that calcium retention rate of 1.5 to 2.25 mmol/kg/day is achieved. Assuming a calcium retention rate of 90%, the calcium should be prescribed at 1.7 mmol to 2.5 mmol/kg/day to achieve calcium retention rate of 1.5 to 2.25 mmol/kg/day. The dose of phosphate should be calculated so that the molar ratio of calcium and phosphate is 1:3:1 [31]. In our experience, hypercalcemia might ensue if high dose of calcium is prescribed before the growth of these infants is optimal. Therefore, we recommend calcium and phosphate prescription in total parenteral nutrition taking consideration of the size of premature infants and days of life of premature infants when growth should begin to pick up (Table 1).
CONCLUSION

MBD of prematurity is still prevalent in the world. The target of preparing parenteral nutrition to meet the fetal accretion rate of calcium and phosphate has been well recognized. The more recent guideline in Britain is beginning to advance calcium and phosphate rates in parenteral nutrition getting closer to this goal [30]. We advocate the target end-point of preparing parenteral nutrition is the prevention of osteopenia and fractures rather than chasing the fetal accretion rate. Thereby, we recommend preparing parenteral nutrition admixtures with doses of calcium and phosphate higher than the usual doses mostly used in the world but lower than the fetal accretion rate. The use of organic phosphate and organic calcium makes this feasible. We suggest further studies to evaluate the efficacy of our recommendation in the amelioration of MBD of prematurity. In addition, we also suggest further studies to find the optimal doses of calcium and phosphate in parenteral nutrition with end-points in terms of prevention of osteopenia and fractures.

REFERENCES


Table 1: Calcium and phosphate prescription in total parenteral nutrition.

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<td>Premature infants</td>
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<td>1.2/0.9</td>
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