

Treatment of Hypophosphatemia in Extreme Low Birth Weight Preterm Infants: A Case Report

Lei J, Liang M, Cao X, Li Q, Gong L and Cai J*

Clinical Pharmacy Department, Central People's Hospital of Zhanjiang, The Second Hospital of Guangdong Medical University, Zhanjiang, China

*Corresponding author:

Jingyue Cai,
Senior Pharmacist, Clinical Pharmacy Department,
Central People's Hospital of Zhanjiang, The Second
Hospital of Guangdong Medical University,
Zhanjiang, China, E-mail: leileijl@126.com

Received: 26 Jan 2023

Accepted: 21 Mar 2023

Published: 29 Mar 2023

J Short Name: AJSCCR

Copyright:

©2023 Cai J, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

Citation:

Cai J. Treatment of Hypophosphatemia in Extreme Low Birth Weight Preterm Infants: A Case Report.

Ame J Surg Clin Case Rep. 2023; 6(8): 1-4

Keywords:

Hypophosphatemia; Preterm infants; Very low birth weight; Case report; Parenteral nutrition

Abbreviations:

MBDP: Metabolic Bone Disease of Prematurity; SMOF: Mixed-Oil Intravenous Lipid Emulsion; PO4: Phosphate; NPT2b: Type IIb Sodium-Dependent Phosphate Cotransport Protein; TPN: Total Parenteral Nutrition

1. Abstract

1.1. Background: Hypophosphatemia has a high incidence in very low birth weight preterm infants and may be related to inadequate intrauterine reserve, poor tolerance of enteral nutrition in the early postnatal period, and insufficient parenteral supplementation. Hypophosphatemia can be corrected by parenteral nutrition. Hypophosphatemia affects the growth and development of the child and may lead to serious sequelae. At present, there are still few reports on phosphorus supplementation for very low birth weight premature infants.

1.2. Case Summary: We report a twin female infant born at 29 weeks of gestation who developed hypophosphatemia while on phosphate-free parenteral nutrition (PN). After administration of calcium with phosphate, the child experienced a persistent decrease in serum phosphorus concentration (P1.25 mmol/L) but normal serum calcium concentration, probably because of the albumin and diuretic infusion at that time. Subsequently, as enteral nutrition was tolerated and the intravenous infusion of calcium with phosphate was discontinued, the patient's serum phosphorus returned to normal levels at 2.22 mmol/L.

1.3. Conclusions: Very low weight, low gestational age preterm infants are prone to hypophosphatemia, which may be overlooked by clinicians, and early active detection and correction of hypophosphatemia is important to prevent metabolic complications and metabolic bone disease in preterm infants. The correction of hypophosphatemia can be done through enteral and parenteral

nutrition, and calcium should be supplemented along with phosphorus supplementation through parenteral nutrition. During the process of parenteral nutrition support containing calcium and phosphorus preparations, attention should be paid to regular monitoring of serum phosphorus, serum cholinesterase, serum calcium and urinary calcium and phosphorus levels.

2. Introduction

Metabolic bone disease (MBDP) in preterm infants is a disease that occurs when the bone mineral content of preterm infants does not meet the needs of normal bone growth and development. Early biochemical changes in the serum of children with MBDP are characterized by hypophosphatemia which may be accompanied by hyperalkaline phosphataseemia and, on imaging, skeletal hypomineralization [1].

The major components of bone are calcium and phosphorus, and 80% of the body's phosphorus and 99% of calcium are found in the bones. Eighty percent of the mineral reserve occurs between 24 and 40 weeks of gestation, with a peak at 34 weeks. Preterm infants born at gestational age <32 weeks have 25% to 70% lower bone mineral than full-term infants, due to insufficient body stores, intolerance to enteral nutrition in the early postnatal period, insufficient parenteral nutrition supplementation, and disease, so the younger the gestational age and lower the birth weight, the higher the incidence and severity of MBDP. Studies have shown that the prevalence of MBDP in very low birth weight preterm infants is 20%-30%, of which 17%-34% can have spontaneous rib

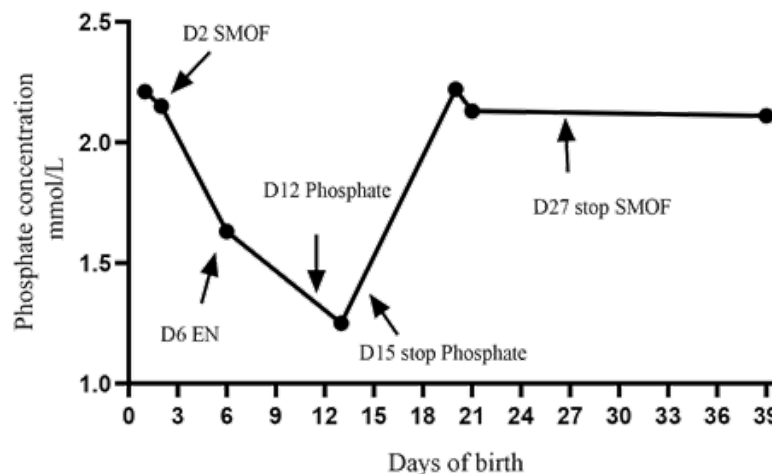
or long bone fractures [2, 3-5]. Very low birth weight preterm infants with birth weight <1.5 kg are at high risk for MBDP, and children with high risk factors should be supplemented with calcium and phosphorus to prevent MBDP [6]. The normal serum phosphorus concentration in preterm infants is 1.9-2.45 mmol/l. Serum phosphorus in the range of 0.3-0.8 mmol/l is considered moderate hypophosphatemia, and <0.3 mmol/l is considered extreme hypophosphatemia [7].

We report the course of treatment of hypophosphatemia in a very low birth weight preterm infant with the aim of discussing the pathogenesis, treatment and prevention given to this group of disorders.

3. Case Presentation

A preterm female infant born at 29 weeks of gestation weighing 1.13 kg with no history of intrauterine distress was asphyxiated at birth with a 1-minute score of 6 and a 5-minute score of 7. She improved after immediate treatment with airway clearance and airbag pressure and oxygen. The child's extremities were slightly bruised, her breathing was irregular, and she was given non-invasive assisted ventilation with a mild inspiratory trismus sign. The child was not yet breast-fed, and a gastric tube was left in place. On day 1 of life, she had a serum phosphorus concentration of 2.21 mmol/L, parenteral nutritional support was given and the formula

was phosphate-free. On the 2nd day of life, 5 ml of mixed-oil intravenous lipid emulsion (SMOF) was added to the parenteral nutrition formula. On the 3rd day of life, the child was started on tube enteral nutrition with 1 ml q4h and SMOF up to 8 ml. On the 4th day of life, the child developed abdominal distension and enteral nutrition was suspended. On the 6th day of life, the child's examination showed plasma phosphorus of 1.63 mmol/L, which continued to decrease (Figure 1), and was re-feeding enteral nutrition 1ml q4h, with SMOF increasing to 11 ml. The pharmacist considering that the target intake of phosphorus in enteral and parenteral nutrition was not reached, potassium phosphate complex injection (PO4 16mg/kg/day) was added to PN on day 12, along with additional calcium supplementation (Ca 5.5mg). Serum phosphorus was rechecked on day 14 and decreased to 1.25 mmol/L (Figure 1), which may be related to the use of albumin, the use of diuretics, so the diuretics and albumin were discontinued. On day 15 enteral nutrition was increased to 5ml q2h, enteral nutrition was tolerated, phosphorus and calcium supplementation was stopped, and SMOF was increased to 20ml. On day 20, enteral nutrition was increased to 8 ml q2h, SMOF was maintained, and serum phosphorus was restored to 2.22 mmol/l, returning to normal range (Figure 1). On the 27th day, parenteral nutrition was stopped. The serum phosphate of the child remained at normal level until discharge.



Supplementary Figure 1: Occurrence and progression of diaphoresis.gif

4. Discussion

Calcium and phosphorus deposition during fetal life occurs mainly in late pregnancy, and preterm infants may miss the optimal reserve period. Small gestational age, low birth weight, delayed enteral feeding and feeding intolerance are all risk factors for hypophosphatemia in preterm infants. In the body, phosphorus is partly bound to calcium and deposited in bones and teeth, and partly present in cells as a component of lipids, proteins and nucleic acids, where it is involved in the conversion of endosomal substances and energy. Therefore, hypophosphatemia in premature babies can affect the development of skeletal muscles and teeth and, in severe cases, lead to MBDP.

The incidence of neonatal hypophosphatemia is high and is more

common in preemie, especially in low birth weight preterm infants, with an incidence of 16% in very low birth weight infants and up to 40% in ultra-low birth weight infants [8], and the incidence of neonatal hypophosphatemia in the ICU is about 30% [9]. After birth, the jejunum is the main site of calcium and phosphorus absorption. The jejunum achieves calcium and phosphorus absorption through the type IIb sodium-dependent phosphate cotransport protein (NPT2b) expressed by intestinal epithelial cells [10]. The kidneys maintain phosphate levels in the body by reabsorbing 80% of phosphate [11]. Premature infants have small gastric contents, immature swallowing function and immature kidney development, resulting in inadequate early enteral feeding, leading to insufficient calcium and phosphorus intake and further leading to the development of hypophosphatemia. Premature infants with inadequate

early enteral feeding should therefore be given additional phosphorus supplementation in a timely manner.

Our child was born at 29 weeks of gestation with a birth weight of 1.13 kg, which is a high risk factor for hypophosphatemia. The child was given phosphate-free parenteral nutrition on day 1 of life and combined enteral and parenteral nutrition was started on day 2 of life. Due to poor tolerance of enteral nutrition, enteral nutrition was discontinued on day 4 of life. After the 6th day of life, the child developed hypophosphatemia with a serum phosphorus of 1.63 mmol/l. This case is further evidence of poor tolerance of enteral nutrition in the early stages of prematurity and inadequate enteral and parenteral supplementation, causing hypophosphatemia.

A certain ratio of calcium to phosphorus needs to be maintained in the body to facilitate skeletal muscle development. For children with MBDP risk factors, the recommended additions to TPN are 40-120mg/kg/d of calcium and 31-71mg/kg/d of phosphorus for 1-2 weeks [12]. There are differences in the recommended amounts of calcium and phosphorus for preterm babies between domestic and international guidelines. Clinical application guidelines [13] recommends a physiological requirement of 0.6-0.8 mmol/kg/d for calcium and 1.0-1.2 mmol/kg/d for phosphorus for preterm infants. ESPGHAN/ESPEN/ESPR/CSPEN guidelines [14] recommend 0.8-2.0 mmol/kg/d (32-80 mg) for calcium and 1.0-2.0 mmol/kg/d (31-62 mg) for phosphorus, and a molar ratio of total Ca to P below 1 (0.8-1.0) in early PN reduces the incidence of early postnatal hypophosphatemia and subsequent hypercalcemia. To prevent MBDP, 24-40 mg/kg/d of calcium and 18-30 mg/kg/d of phosphorus are recommended in the initial TPN for very low birth weight preterm infants [6]. However, in clinical practice, the children are complex and phosphorus supplementation may not be consistent with guideline recommendations. Cubillos C [15] reported a case of a hypercalcaemic hypophosphataemic ultra-low weight preterm infant on parenteral nutrition support with calcium 0.5 mmol/kg/d, phosphate 80 mg/kg/d and a molar ratio of Ca to P of 0.6, with eventual normalisation of blood calcium, blood phosphorus, serum PTH and skeletal muscle profile. Improdan N [16] described the treatment of a very preterm infant with severe hypercalcaemia and hypophosphataemia, who was supplemented with 80 mg/kg/d of sodium glycerophosphate in PN, with a rapid decrease in calcium concentration to 10 mg/dl within 24 hours, followed by the addition of phosphate, with normalization of parathyroid hormone by day 4. Based on the degree of tolerance of enteral nutrition, phosphorus supplementation was discontinued within 3 weeks and the child had no skeletal lesions on x-ray.

Boubred F [17] compared the differences in serum electrolyte levels between small for gestational age preterm and full term infants and found that small for gestational age preterm infants were at high risk of developing hypophosphorous and hypokalemia. In early TPN, the molar ratio of Ca to P was 1:1 in both groups and as a result hypophosphatemia was corrected in the two groups.

Bustos LG [18] made a comparison of the incidence and severity of hypophosphataemia in very low birth weight preterm infants with early (day 1 of life) versus late (48 hours after birth) phosphate supplementation. The results showed that the incidence of hypophosphataemia was significantly lower when phosphate was given early. Tan YL [19] compared changes in serum phosphorus and cholinesterase in the high risk group for hypophosphataemia (very low birth weight preterm infants, dependent on PN for more than 14 days) with those in the control group (very low birth weight preterm infants). Children in both groups were started on SMOF 0.5g/kg/d 24 hours after birth and increased by 0.5g/kg/d every other day to a maximum of 3g/kg/d. Both groups of children were given enteral nutrition as tolerated. The results showed that children in the high-risk group had significantly lower serum phosphorus than the control group with hypophosphatemia after week 2, but returned to the normal range after week 6, indicating that prolonged reliance on parenteral nutrition may be a cause of hypophosphatemia in preterm infants. Zhu [20] reported a case of calcium and phosphorus supplementation in a premature infant, in which only calcium and no phosphorus were supplemented in the early PN of the child, resulting in hypophosphatemia in the child. Subsequently, phosphate was added to PN with a calcium-phosphorus ratio of 0.5, and after the 28th day, the child tolerated enteral nutrition well, and calcium and phosphorus supplementation was stopped, and the child's serum phosphorus increased and approached the normal range.

The child with this case had a birth weight of 1.13 kg, which is a very low weight preterm infant, and is a high risk factor for hypophosphatemia, as well as MBDP. When the child developed hypophosphatemia on the 6th day after birth, we first increased the amount of SMOF in PN. After the clinical pharmacist calculation, the child's phosphate intake did not reach the recommended amount. Thus, on the 12th day of life, phosphate and calcium were added to PN separately, and the calcium-phosphorus molar ratio was maintained in the range of 0.8-1.0. On the 15th day of life, the child tolerated enteral nutrition, and the phosphate and calcium in PN were discontinued. On the 20th day of life, the child's serum phosphorus was 2.2 mmol/l, which returned to the normal range, and there was no recurrence of hypophosphatemia.

5. Conclusion

In conclusion, preterm infants, especially very low weight, low gestational age preterm infants, are prone to hypophosphataemia. Early and active detection and correction of hypophosphatemia can effectively prevent a wide range of complications and prevent metabolic bone disease in pregnant preterm infants. Premature infants should be enterally fed as early as possible, or if early enteral feeding is not possible, calcium and phosphate should be added to the PN to avoid hypophosphataemia. During parenteral nutrition support with calcium and phosphorus preparations, attention should be paid to regular monitoring of blood phosphorus, serum

cholinesterase, blood calcium and urinary calcium and phosphorus levels.

6. Declarations

6.1. Ethics Approval and Consent to Participate

All reports involving human data have been approved by the Clinical Research Ethics Committee of Zhanjiang Central People's Hospital.

All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

The written informed consent was obtained from her legal guardian.

6.2. Consent for Publication

The publication of this case report and its accompanying images has received written informed consent from the child's legal guardian. Availability of data and materials.

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

6.3. Author Contributions

JC: study design and interpretation. JL: manuscript drafting, and figures creation. ML: manuscript review, and editing. XC: data collection and manuscript review. QL: check the data and monitor the change of serum phosphorus. LG: data collection, and editing. All authors contributed to the article and approved the submitted version.

6.4. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6.5. Acknowledgements

The author would like to thank the Laboratory Department of Zhanjiang Central People's Hospital for providing tests for this study.

Reference

- Pieltain C, Halleux V, Senterre T, Rigo J. Prematurity and bone health. *World Rev Nutr Diet.* 2013; 106: 181-8.
- He XR, Liang C, Yu YQ, et al. A national multicenter survey of risk factors for metabolic bone disease in very low/ultra-low birth weight preterm infants. *Chinese Journal of Contemporary Pediatrics.* 2021; 23(6): 555-62.
- Shamir R, Turck D, Phillip M. *Nutrition and Growth (World Review of Nutrition and Dietetics).* Basel: Karger Publishers. 2013; 106: 181-8.
- Gleason CA, Juul SE. *Avery's Diseases of the Newborn.* 10th ed. Philadelphia: Elsevier. 2018; 1347-1350.
- Zhang H, Jia Q, Piao M, Chang Y, Zhang J, Tong X, Han T. Screening of serum alkaline phosphatase and phosphate helps early detection of metabolic bone disease in extremely low birth weight infants. *Front Pediatr.* 2021; 9: 642158.
- Chang YM, Lin XZ, Zhang R, Xi-Hong L, Xiao-Mei T, Ping-Yang C, et al. Expert consensus on clinical management of metabolic bone disease in preterm infants. *Chinese Journal of Contemporary Pediatrics.* 2021; 23(8):12.
- Han D, Zhang W. Progress of research on nutritional hypophosphatemia in preterm infants. *Chinese Journal of Neonatology.* 2021; 6(5): 75-8.
- Rustico SE, Calabria AC, Garber SJ. Metabolic bone disease of prematurity. *J Clin Transl Endocrinol.* 2014; 1(3): 85-91.
- Padelli M, Leven C, Sakka M, Plée-Gautier E, Carré JL. Causes, consequences and treatment of hypophosphatemia: a systematic review. *Presse Med.* 2017; 46(11): 987-99.
- Koumakis E, Cormier C, Roux C, Briot K. The causes of hypoand hyperphosphatemia in humans. *Calcif Tissue Int.* 2021; 108(1): 41-73.
- Bex S, Mollard F, Stirnemann J. Diagnosis and treatment of hypophosphatemia. *Rev Med Suisse.* 2019; 15(667): 1871-5.
- Chacham S, Pasi R, Chegondi M, Ahmad N, Mohanty SB. Metabolic Bone Disease in Premature Neonates: An Unmet Challenge. *J Clin Res Pediatr Endocrinol.* 2020; 12(4): 332-9.
- Cai W, Tang QY, Wang Y, Feng Y, Wu J, Qian LX, et al. Clinical application guidelines for neonatal nutrition support in China. *Journal of Clinical Pediatrics.* 2013; 31(12): 1177-82.
- Mihatsch W, Fewtrell M, Goulet O, Molgaard C, Picaud JC, Senterre T; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium. *Clin Nutr.* 2018; 37(6): 2360-5.
- Cubillos CMP, Mena NP. Hipofosfemia en recién nacidos prematuros: un trastorno bimodal [Hypophosphatemia in preterm infants: a bimodal disorder]. *Rev Chil Pediatr.* 2018; 89(1): 10-17.
- Improda N, Mazzeo F, Rossi A, Rossi C, Improda FP, Izzo A. Severe hypercalcemia associated with hypophosphatemia in very premature infants: a case report. *Ital J Pediatr.* 2021; 47(1): 155.
- Boubred F, Herlenius E, Bartocci M, Jonsson B, Vanpée M. Extremely preterm infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia. *Acta Paediatr.* 2015; 104(11): 1077-83.
- Bustos LG, Soriano-Ramos M, Pinilla Martín MT, Chumillas CS, García Soria CE, Pallás-Alonso CR. Early Hypophosphatemia in High-Risk Preterm Infants: Efficacy and safety of sodium glycerophosphate from first day on parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2019; 43(3): 419-25.
- Tan YL, Tsao PN, Chou HC, Yen TA, Chen CY. Hypophosphatemia as an early metabolic bone disease marker in extremely low-birth-weight infants after prolonged parenteral nutrition exposure. *JPEN J Parenter Enteral Nutr.* 2021; 45(6): 1268-74.
- Zhu K, Wang Y, Hong Y, et al. Pharmacy practice of clinical pharmacist involvement in calcium and phosphorus supplementation in parenteral nutrition for preterm infants. *Parenteral and enteral nutrition.* 2019; 26(5): 3.