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Late and Insufficient Phosphorus Supplementation is Associated with Early Severe Hypophosphatemia in Extremely Low Birth Weight Infants with Early Amino Acid Administration

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Objective: To investigate the incidence of early severe hypophosphatemia, and examine the associated clinical factors and outcomes, in extremely low birth weight infants (ELBWI) who received early amino acid administration.

Methods: Medical records of 82 ELBWI were retrospectively reviewed. Severe hypophosphatemia was defined as a serum phosphate level <2 mg/dL during the first week after birth.

Results: Nineteen ELBWI (23.2%) experienced severe hypophosphatemia. The supplementation of phosphorus was started significantly later in the hypophosphatemia group compared to that in the control group (P=0.036). Small for gestational age infants (SGAI) (P=0.006) and bronchopulmonary dysplasia (P=0.016) were more prevalent in the hypophosphatemia group compared to that in the control group.

Conclusion: Early severe hypophosphatemia is common in ELBWI. Late and insufficient supplementation of phosphorus and SGAI were associated with severe hypophosphatemia.

Key Words: Infant, Extremely low birth weight, Hypophosphatemia, Bronchopulmonary dysplasia

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Introduction

Premature infants, including extremely low birth weight infants (ELBWI) miss the last trimester, which involves rapid intrauterine growth and nutrition accretion.[1] Optimal nutritional support through parenteral nutrition (PN) is important for survival and postnatal growth, as most ELBWI cannot tolerate enteral nutrition. In the last few decades, nutrition guidelines have emphasized early and aggressive PN with high amino acid supplementation immediately after birth, to minimize growth restriction and reduce adverse outcomes due to nutrition deficiency.[2,3]

However, a recent study reported that early aggressive amino acid administration causes hypophosphatemia.[4] A high-protein diet accelerates protein synthesis and tissue anabolism. In addition, the intracellular influx of serum phosphate and synthesis of adenosine triphosphate and creatine phosphate are increased, resulting in serum phosphorus depletion in ELBWI, especially in small for gestational age infants (SGAI).[5-8] Unfortunately, the literature is limited, as wide variations exist in the definition of hypophosphatemia, and assessments regarding the impact of hypophosphatemia on the major outcomes in the neonatal intensive care unit (NICU) are lacking. In addition, few studies have examined whether delayed and lower phosphorus administration causes severe hypophosphatemia in ELBWI who receive

early amino acid administration.[9] Therefore, the present study investigated the incidence of severe hypophosphatemia during the first week after birth, and examined the associated clinical factors (including phosphorus supplementation) and outcomes, in ELBWI who received same policy of early amino acid administration.

Methods

1. Study population

ELBWI (birth weight less than 1,000 g) born at Ajou University Hospital from January 2013 to December 2016 were included. Exclusion criteria included death within seven days after birth and severe congenital malformations, resulting in the exclusion of five of the 87 reviewed ELBWI. Nineteen of the included 82 ELBWI experienced severe hypophosphatemia (serum phosphate level <2 mg/dL) during the first week after birth (hypophosphatemia group); the remaining 63 ELBWI were classified as the control group (Fig. 1). This study was approved by the Institutional Review Board of Ajou University Hospital (M-2017-C0460-00003) and we received permission to waive parental consent.

2. Data collection

Clinical data was collected retrospectively from a medical record review. The collected data included perinatal and neonatal characteristics such as sex, gestational age, birth weight, SGAI status, use of antenatal steroids, whether delivered via caesarean section, Apgar scores at 1 and 5 minutes of life, existence of histologic chorioamnionitis, preterm premature rupture of membrane (PPROM), patent duct arteriosus (PDA) ligation, intraventricular hemorrhage (IVH), sepsis, extrauterine growth retardation (EUGR), necrotizing enterocolitis (NEC), duration of PN (days), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), duration of mechanical ventilation, and mortality. Serum phosphate and calcium levels, and the amounts of amino acid, phosphorus, calcium, and fluid administration during the first week after birth were also collected.

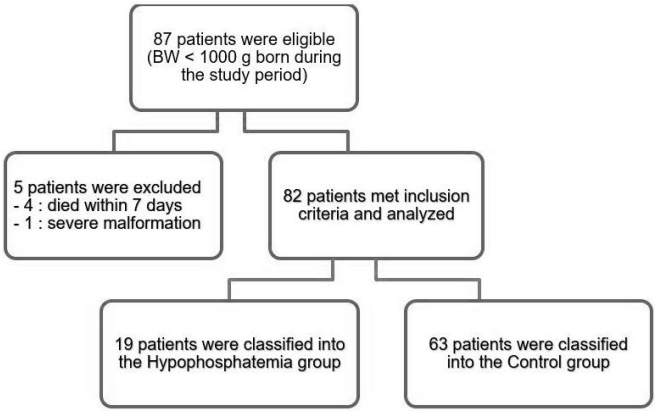

Fig. 1. The patient enrollment flow chart. BW, birth weight.

3. Definitions

Early severe hypophosphatemia was defined as a serum phosphate level less than 2 mg/dL during the first week after birth. Hypercalcemia was defined as a serum calcium level higher than 11 mg/dL. Treatment was performed when hypercalcemia persisted for more than two days or when there was an electrocardiography change.

BPD was defined as the need for supplemental oxygen for at least 28 days after birth, and the severity was graded according to the respiratory support required at 36 postmenstrual weeks or discharge, whichever came first.[10] If the infants died before 36 weeks, they were excluded from the BPD classification. NEC was defined as Bell's stage II or greater.[11] IVH was defined as grade III or IV on a cranial ultrasonography, based on the Papile grading system.[12] ROP was defined using International Classification of Retinopathy of Prematurity criteria.[13] PPROM was defined as a rupture of membranes before the onset of uterine contractions before 37 weeks, SGAI was defined as <10th percentile for gestational age at birth and EUGR was defined as <10th percentile for the corrected gestational age at 36 weeks.[14]

According to our NICU policy, PN was started on postnatal day 1. Carbohydrates were given at a minimum of 4 mg/kg/min on day 1. Amino acids (Primene® 10%; Baxter, Grosotto, Italy) were given at 1 g/kg/day starting on day 1, and were increased 0.5-1.0 g/kg/day daily to a maximum of 3.5-4 g/kg/day on day 7. The amount of administered amino acids was guided by the serum blood urea nitrogen level and the development of severe metabolic acidosis. Lipids (SMOF lipid® 20%; Fresenius Kab, Uppsala, Sweden) were given at a minimum of 0.5 g/kg/day starting on day 1, and were increased to a maximum of 3 g/kg/day. Calcium (Calcium Gluconate Injection®; Daihan Pharm, Seoul,

Korea) infusion was started on day 1 at 60–80 mg/kg/day (1.5–2 mmol/kg/day). Phosphorus supplementation (Phosten Injection®, JW Pharma, Seoul, Korea) began on days 2–4, with consideration of the infants' condition, and were prescribed by the physician at an adequate dose of 15.5–46.5 mg/kg/day (0.5–1.5 mmol/kg/day), as guided by the stability of the PN. Fluid administration was started on day 1 at a rate of 80 mL/kg/day and thereafter was determined by the monitoring of vital signs, urination, and daily weight.

4. Statistical analysis

Data are presented as the median [25; 75 percentile] for continuous variables, and as the number (%) for categorical variables. Group differences were evaluated using the Student's *t*-test or Kruskal–Wallis rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria).[15]

Results

1. Phosphate and calcium levels

The serum phosphate level in the hypophosphatemia group on day 1 did not differ from that in the control group (5.5 [2.9; 6.6] vs. 5.8 [4.5; 6.5] mg/dL, *P*=0.389); however, the levels on days 2, 4, 5, and 7 were significantly lower in the hypophosphatemia group compared to those in the control group (*P*<0.05) (Fig. 2A). The serum calcium level on day 5 was significantly higher in the hypophosphatemia group compared to that in the control group (10.0 [9.7; 10.8] vs. 9.2 [8.6; 9.9] mg/dL, *P*=0.012) (Fig. 2B).

The incidence of hypercalcemia was significantly higher in the hypophosphatemia group (52.6%, 10/19) compared to that in the control group (14.3%) (*P*=0.002). A total of 36.8% (7/19) and 3.2% (2/63) of the infants in hypophosphatemia and control groups, respectively, required treatment for hypercalcemia (such as hydration and systemic steroids), with no significant group difference (*P*=0.55).

2. Demographic characteristics

Demographic characteristics are presented in Table 1. There were no significant group differences in sex, gestational age, birth weight, histologic chorioamnionitis, use of antenatal steroid therapy, caesarean sections, and Apgar scores at 1 and 5 minutes. However, the incidence of SGAI was significantly higher in the hypophosphatemia group (36.8%, 7/19), compared to that in the control group (7.9%, 5/63) (*P*=0.006).

3. Supplementation of amino acids, phosphorus, and fluid

Amino acids were administered at a rate of 1 g/kg/day starting on day 1, with no significant group differences during the first week after birth (*P*=0.95) (Fig. 3A). The supplementation of phosphorus started significantly later in the hypophospha-

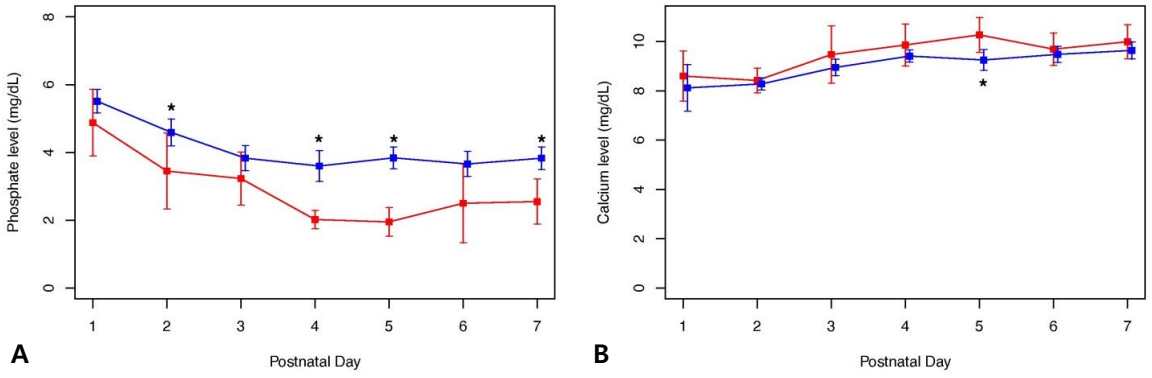

Fig. 2. The serum phosphate and calcium levels during the first week after birth are shown for the hypophosphatemia and control groups. (A) Mean phosphate levels during the first week after birth: there was no group difference in phosphate level on day 1, but there were significant group differences on day 2 (3.5±1.9 vs. 4.6±1.34 mg/dL, *P*=0.015), day 4 (1.9 [1.8; 2.2] vs. 3.5 [2.9; 4.3] mg/dL, *P*<0.001), day 5 (2.0±10.6 vs. 3.8±1.0 mg/dL, *P*<0.001), and day 7 (2.5±1.2 vs. 3.8±1.0 mg/dL, *P*<0.001). (B) Mean calcium levels during the first week after birth: on day 5 (10.0 [9.7; 10.8] vs. 9.2 [8.6; 9.9] mg/dL, *P*=0.012), there was a significant group difference in calcium levels.

temia group compared to that in the control group (73 [61; 88.5] vs. 85 [71.5; 142.0] hours after birth, P=0.036). Although there was no significant group difference in the amount of supplied phosphorus on days 1, 2, and 3, the amount on days 4 and 5 was significantly less in the hypophosphatemia group compared to that in the control group (all P<0.05) (Fig. 3B). There was no significant group difference in the amount of administered fluid during the first week after birth (Fig. 3C).

Table 1. Patient Characteristics

	Control group (n=63)	Hypophosphatemia group (n=19)	*P*-value
Gestational age (wks)	26^{+0} [25^{+0}; 27^{+0}]	25^{+6} [24^{+4}; 28^{+5}]	0.847
Birth weight (g)	850 [720; 920]	710 [650; 905]	0.216
Histological chorioamnionitis	28/63 (44.4)	11/19 (57.9)	0.443
SGA	5/63 (7.9)	7/19 (36.8)	0.006
Antenatal steroids			0.603
None	17/63 (27.0)	3/19 (15.8)	
Incomplete use	25/63 (39.7)	9/19 (47.4)	
Complete use	21/63 (33.3)	7/19 (36.8)	
PPROM	10/63 (15.9)	6/19 (31.6)	0.129
Male	31/63 (49.2)	13/19 (68.4)	0.226
Caesarean section	34/63 (53.9)	12/19 (63.2)	0.657
Apgar score			
1 minutes	3 [2; 5]	4 [3; 5]	0.334
5 minutes	6 [4; 6]	6 [5; 6.5]	0.548

Values are presented as median [25; 75 percentile] or number (%).
Abbreviations: SGA, small for gestational age; PPROM, preterm premature rupture of membrane.

4. Clinical outcomes during the neonatal intensive care unit stay

Clinical outcomes during the NICU stay are provided in Table 2. There were no significant group differences in the rates of PDA ligation, IVH, sepsis, EUGR, NEC, duration of PN, ROP, duration of mechanical ventilation, and mortality. However, the incidence of BPD was greater in the hypophosphatemia group compared to that in the control group (100% [11/11] vs. 59.6% [31/52], P=0.016).

Discussion

The purpose of the present study was to investigate the incidence of early severe hypophosphatemia, as well as the associated risk factors and outcomes among ELBWI who received

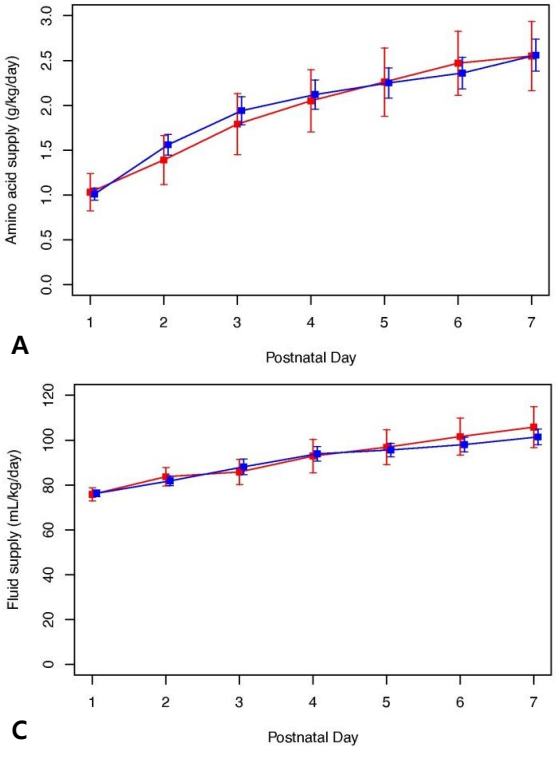

Fig. 3. The supplementation of amino acid, phosphorus, and fluid during the first week after birth is shown for the hypophosphatemia and control groups. (A) Amino acids supplementation during the first week after birth: there was no group difference in the amount of amino acid administration during the first week after birth. (B) Phosphorus supplementation during the first week after birth: there were significant group differences in the amount of phosphorus administered on day 4 (0.0 [0.0; 0.5] vs. 0.6 [0.0; 1.0] mmol/kg/day, P=0.37) and day 5 (0.5 [0.0; 1.0] vs. 1.0 [0.8; 1.0] mmol/kg/day, P=0.017). (C) Fluid supplementation during the first week after birth: there was no group difference in the amount of fluid administration.

Table 2. Clinical Outcomes in the Neonatal Intensive Care Unit

	Control group (n=63)	Hypophosphatemia group (n=19)	*P*-value
PDA ligation	30/63 (47.6)	11/19 (57.9)	0.601
IVH (≥grade III)	11/63 (18.0)	7/19 (36.9)	0.475
EUGR	18/63 (28.6)	7/19 (36.8)	0.688
Sepsis	22/63 (34.9)	11/19 (57.9)	0.128
NEC (≥stage IIa)	8/63 (12.7)	4/19 (21.1)	0.594
Duration of TPN (days)	37 [26; 53]	37 [17.5; 60.5]	0.899
ROP (≥stage I)	24/63 (38.1)	5/19 (36.8)	0.346
BPD (≥moderate)	31/52 (59.6)	11/11 (100)	0.016
Duration of mechanical ventilation (days)	15 [6; 42.5]	20 [9; 62]	0.361
Mortality	11/63 (17.5)	8/19 (42.1)	0.055

Values are presented as median [25; 75 percentile] or number (%).
Abbreviations: SGA, small for gestational age; PPROM, preterm premature rupture of membrane.

same policy of early amino acids administration. The hypophosphatemia group had a later starting time and received a smaller amount of phosphorus supplementation compared to that in the control group. In addition, the hypophosphatemia group showed a higher morbidity of SGAI and incidence of BPD compared to that in the control group.

An absolute level for hypophosphatemia has not been defined for preterm infants. In this study, severe hypophosphatemia was defined as a serum phosphate level <2 mg/dL. Brener Dik et al.[4] defined severe hypophosphatemia in a similar manner and reported that the incidence of hypophosphatemia in very low birth weight infants was 34%, which is higher than that in the present study. This difference may result from differences in amino acid administration policies (3 mg/kg/day starting on day 1 in the previous study). In the present study, supplied amino acids were not increased when the serum blood urea nitrogen level was 30 mg/dL or more. In a study by Boubred et al.,[8] 80% (48/60) of ELBWI experienced hypophosphatemia, defined as a serum phosphate level <1.6 mmol/L (4.95 mg/dL), which corresponds to relatively milder hypophosphatemia compared to that in the present study. Bonsante et al.[16] showed a clear association between high amino acid administration and hypophosphatemia; hypophosphatemia was more frequent in the high amino acid group (12.5%) than in the medium (4.6%) and low amino acid groups (0%). Similarly, in the study of Ichikawa et al.,[7] higher parenteral amino acid administration was associated with hypophosphatemia on day 8. Thus, knowledge regarding the factors that enhance or reduce the risk of hypophosphatemia in ELBWI who receive early amino acid administration is needed. The present results suggest that the timing and amount of phosphorous supplementation is important.

SGAI who faced with chronic malnutrition in the fetal period have metabolic and electrolyte imbalances, which can be explained by the concept of refeeding syndrome.[17] Small for gestational age ELBWI were shown to have lower phosphate levels on day 8 compared to that in ELBWI who were appropriate for gestational age in study by Ichikawa et al.[7] Similarly, Boubred et al.[8] reported that hypophosphatemia is more likely to occur in SGAI among ELBWI who receive high amounts of amino acids. The present results are consistent with results from these studies.

A few previous studies have attempted to define the association between phosphorus administration and hypophosphatemia. For example, Moe et al.[9] compared the incidence of hypophosphatemia in three groups of ELBWI (less than 28 weeks of age) who received three types of PN containing different amounts of phosphorus and amino acids; phosphorus levels were lowest in the group receiving PN containing a low amount of phosphorus and a high amount of amino acids. However, the authors were unable to investigate whether phosphorus administration affected the development of hypophosphatemia regardless of the amount of administered amino acids. In the present study, the time to the start of phosphorus administration and the amount of supplemented phosphorus were associated with the development of hypophosphatemia, in the clinical setting of a shared PN policy among those who did and did not develop hypophosphatemia. There is no consensus on the optimal requirements for phosphorus in preterm infants. In this study, most physicians usually decide to supply phosphorus when preterm infants enter a diuretic phase and recovery of hyperkalemia, and it seems to be later and insufficient than actual demand. An earlier and adequate supply of phosphorus should be considered in the care of preterm infants.

The manifestations of hypophosphatemia may occur in the cardiovascular system, skeletal muscles, nervous system, and hemato-immunologic system in the critical care setting.[18] Hypophosphatemia may increase bone resorption in association with bone metabolism in preterm infants.[9] In the present study,

hypercalcemia, but not treatment for hypercalcemia, was more common in the hypophosphatemia group. Although hypophosphatemia can cause growth retardation in prematurity,[19] there was no significant group difference in EUGR. Hypophosphatemia has been reported as a risk factor for the prolongation of mechanical ventilation and the hospital stay in children and adults.[20,21] In our study, the duration of invasive mechanical ventilation was not different between the two groups; however, the prevalence rate of BPD, duration of oxygen therapy, was higher in the hypophosphatemia group compared to that in the control group. Although the effect of hypophosphatemia on the respiratory system remains unclear, hypophosphatemia may cause or exacerbate respiratory failure by interfering with weaning from the mechanical ventilator and impairing the contractility of the diaphragm.[22-25]

Previous studies have reported that early aggressive amino acid administration causes hypophosphatemia and is associated with small for gestational age. On the other hand, the present study provides meaningful information regarding the relationship between hypophosphatemia and phosphorus supplementation in ELBWI with same policy of early amino acid administration; however, several limitations should be acknowledged. Mainly, the present study involved a retrospective review in a single institution and small study population. Also, we cannot investigate to a direct relationship between hypophosphatemia and BPD. Further studies are needed to explain the relationship between hypophosphatemia and BPD.

In conclusion, early severe hypophosphatemia is common in ELBWI who receive early amino acid administration. Late supplementation of phosphorus and SGAI were associated with severe hypophosphatemia in ELBWI.

Acknowledgments

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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