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ORIGINAL ARTICLE

Nutrition

High protein intake can lead to serious hypophosphatemia and hypokalemia in growth restricted preterm newborns

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Abstract

Objectives: High protein parenteral nutrition (HPPN) in the early postnatal period is a recommended strategy for very low birth weight (VLBW) infants. However, limited data is available on electrolyte changes when HPPN strategy is utilized. We investigated the impact of HPPN on the development of hypophosphatemia and hypokalemia in preterm VLBW newborns.

Methods: A retrospective, single-center study investigated the levels of phosphate and potassium in VLBW infants who received HPPN (amino acids intake up to 3.5 g/kg/day) during the first week of life. Preterm infants were divided into two subgroups: appropriate for gestational age (AGA) and small for gestational age (SGA) newborns. Clinical data were obtained from hospital database and medical records.

Results: Overall, 170 VLBW infants were included for the study analysis: 41 SGA (mean birth weight 752 ± 39 g) and 129 AGA infants (mean birth weight 994 ± 23 g). Phosphate and potassium levels were significantly lower in the SGA infants compared to AGA infants (Phosphate: 0.97 ± 0.07 mmol/l vs. 1.44 ± 0.04 mmol/l, $p < 0.001$; Potassium: 3.0 ± 0.1 mmol/l vs. 3.6 ± 0.1 mmol/l, $p < 0.001$).

Conclusions: Repeated measurement of serum phosphate and potassium is recommended when HPPN strategy is utilized in preterm SGA infants where significant hypophosphatemia and hypokalemia might have serious clinical consequences.

KEYWORDS

parenteral nutrition, refeeding syndrome, small for gestational age newborns, very low birth weight infants

1 | INTRODUCTION

Very low birth weight (VLBW) infants usually require early parenteral nutrition to promote satisfactory growth equivalent to fetal development, avoid postnatal catabolism and significant weight loss.[1,2] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends amino acid intake of at least 1.5 g/kg/day (to prevent a negative nitrogen balance) and phosphate intake of at least 1.0 mmol/kg/day during the first days of life in preterm infants.[3,4] The parenteral amino acid intake from postnatal day 2 onwards should be 2.5–3.5 g/kg/day and should be accompanied by nonprotein intakes >65 kcal/kg/day and adequate micronutrient intakes.[3,4] Furthermore, high protein parenteral nutrition (HPPN) minimizes the risk of nonoliguric hyperkalemia by inducing intracellular influx of potassium to promote cell anabolism.[1]

In contrast many studies observed severe metabolic disturbances when HPPN strategy was

administered.[5,6] It was suggested that HPPN with restricting principal electrolytes (phosphate, potassium) during the early postnatal phase may imitate refeeding syndrome (RFS) that is known from critically ill adults.[7] Pathophysiology of RFS involves insulin secretion, promotion of anabolism and intracellular redistribution of phosphate and potassium.[8] The resulting serum hypophosphatemia and hypokalemia may lead to cardiopulmonary and neuromuscular impairment, a decrease in oxygen delivery and increased mortality in critically ill patients.[9]

Metabolic disturbances are significantly dependent either on gestational age or birth weight.[6,10] Limited data is available on complex biochemical changes specifically in small for gestational age (SGA) preterm infants.[11] The aim of this study was to analyze electrolyte changes and neonatal outcome between preterm SGA and appropriate for gestational age (AGA) infants receiving HPPN during the first week of life.

What is Known

- High protein parenteral nutrition (HPPN) is a common nutritional strategy for very low birth weight (VLBW) infants in the early postnatal period.
- Limited data is available on electrolyte changes when HPPN is used in VLBW infants.

What is New

- Repeated measurement of phosphate and potassium is needed when HPPN strategy is utilized in growth restricted preterm infants who are endangered by serious electrolyte deficiencies.
- Early and optimal phosphate and potassium supplementation may prevent biochemical changes that might have serious clinical consequences in high–risk VLBW infants.

2 | METHODS

2.1 | Patients

This retrospective study was conducted in a neonatal intensive care unit at the Institute for the Care of Mother and Child in Prague. The study was done in accordance with the principles outlined in the Declaration of Helsinki and the protocol was approved by the Institutional Review Board and Ethics Committee. VLBW infants (birth weight <1500 g) were considered for the study and data from the period of January 2019–March 2021 were analyzed. The exclusion criteria were: known serious congenital abnormality, birth below the limit of viability (not resuscitated in the delivery room), outborn patients and incomplete data. Overall, the analysis included 170 newborns–the study flowchart is shown in Figure 1. Neonatal anthropometric characteristics were obtained in accordance with Intergrowth-21. SGA infants were considered those with birth weight <10%.[12] Neonatal morbidities were based on the Vermont Oxford Network definitions.[13]

2.2 | Parenteral nutrition

According to the local protocol, initial parenteral nutrition (PN) bags were prepared by the hospital pharmacy and used upon admission of a newborn to the intensive care unit. The initial PN provided protein intake 2.5–3.5 g/kg/day (*Amiped by B. Braun*). Thereafter, patients received customized PN with 3.0–3.5 g/kg/day of protein (*Amiped by B. Braun*), 2.5–3.0 g/kg/day of lipids (*SMOFlipid by Fresenius Kabi*) and 1.0–1.5 mmol/kg/day of phosphate (*Glycophos by Fresenius Kabi*) by the third day of life. Glucose infusion rate was based on the individual glucose tolerance. All electrolyte disturbances were treated by the individualized PN as required. For potassium supplementation, 7,45% potassium chloride (*Kaliumchlorid 7.45% Braun by B. Braun*) or potassium malate (*Kalium–L–malat Fresenius 1 Molar by Fresenius Kabi*) were used. Thiamine was provided from the first day of life (*Soluvit N by Fresenius Kabi*) at standard dose of 0.32 mg/kg/day to all infants. There were no special considerations in parenteral nutrition protocol for SGA infants. The individualized PN was calculated and ordered using targeted NeoDiet software (*Infantools*).

2.3 | Enteral nutrition

No enteral electrolyte supplements were administered and only mother's milk was used as enteral nutrition during the first week of life. In general, enteral feeding (≤30 mL/kg/day) was not counted towards the overall protein intake. The SGA subgroup was more restrictive in enteral feed advancements to minimize potential gastrointestinal problems and after a period of trophic feeding (first three days of life) we advanced feeds usually by 10–20 mL/kg/day. The AGA patients received trophic feeding for the first 2 days of life. Afterwards, the enteral nutrition was advanced by 20–30 mL/kg/day based on the clinical status and feeding tolerance. According to our local protocol, we aimed to keep the overall (enteral and parenteral) protein intake at 3.0–3.5 g/kg/day to achieve consistency.

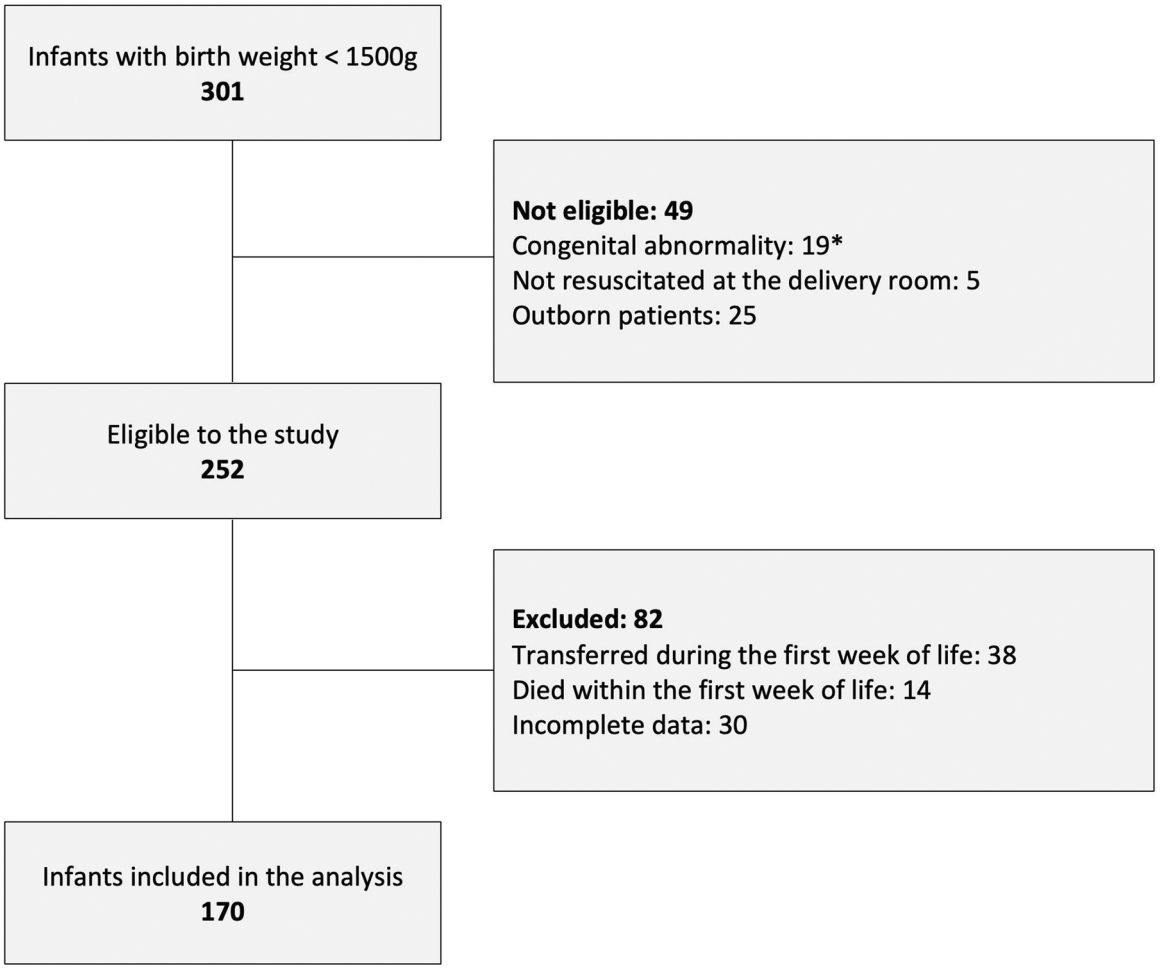

FIGURE 1 Study flowchart. *List of congenital abnormalities: complex malformations (4); coarctation of aorta (3); pulmonary stenosis (1), sacrococcygeal teratoma (2); severe chylothorax and hydrops with pulmonary hypoplasia (1); bilateral hydronephrosis (1); posterior urethral valve with microcolon (1); anal atresia (1); severe limb malformations (1); cleidocranial dysplasia (1); Muenke syndrome–FGF-R3 associated coronal synostosis (1); nephrocutaneous syndrome (1); ichthyosis (1).

2.4 | Electrolytes

The electrolytes were measured using blood gas analysis (*ABL90 FLEX Blood gas analyzer, Radiometer Medical ApS*) or indirect ion-selective electrode method (*Cobas 6000, c501 module, Roche Diagnostics*). The blood was drawn from umbilical or peripheral arterial line (60 μL of blood for blood gas analysis and 500 μL of blood for complete biochemistry panel). Complete biochemistry panel was done based on clinical judgment. Invalid samples (hemolysis, inadequate volume, clot formation) or samples that might have been significantly influenced by acid/base balance (pH < 7.20 or pH > 7.50) were excluded from analysis. Serum phosphate measurements between Day 4 and 7 of life were considered for the analysis. Potassium levels were obtained before initiation of PN (Day 1) and then on a per day basis (days 2–7). The lowest values of phosphate and potassium were included in the analysis. Hypophosphatemia and severe hypophosphatemia were defined as phosphate level <1.5 mmol/L or <1.0 mmol/L, respectively. Hypokalemia and severe hypokalemia were defined as potassium level <3.5 mmol/L or <3.0 mmol/L, respectively.

2.5 | Statistical analysis

The study group was divided into two subgroups: SGA and AGA infants. Continuous data were expressed as the mean ± standard error and categorical variables as counts and percentages. Independent samples and Pearson's chi-squared tests were used to compare variables. One–way ANOVA was used to determine 95% confidence intervals for mean. The statistical tests were two-tailed with $p < 0.05$ being statistically significant. The analysis was performed with Statistical Package for Social Sciences (*SPSS 26.0; SPSS Institute*).

3 | RESULTS

3.1 | Population characteristics

Overall, 170 preterm VLBW newborns were included in the study analysis. The comparison between study subgroups (41 SGA infants and 129 AGA infants) is shown in Table 1. The SGA patients had significantly lower birth weight and significantly higher gestational age than the AGA group ($p < 0.001$). The two subgroups were otherwise comparable in terms of perinatal characteristics and neonatal morbidities.

3.2 | Hypophosphatemia and hypokalemia

The SGA infants had substantially lower values of the serum phosphate and potassium ($p < 0.001$) when compared to AGA infants (Table 2). No statistically significant difference was observed in sodium and chloride levels. Hypokalemia (<3.5 mmol/L) was not observed in 47% of AGA infants, while in SGA infants it was only 14%. Similarly, no hypophosphatemia (<1.5 mmol/L) was detected in 50% of AGA infants and only in 10% of SGA newborns. On the contrary,

TABLE 1 Population characteristics.

	SGA infants ($n = 41$)	AGA infants ($n = 129$)	p value
Gestational age (weeks)	28.3 ± 0.3	27.0 ± 0.2	<0.001
Birth weight (grams)	752 ± 39	994 ± 23	<0.001
Male gender, no. (%)	20 (49%)	69 (54%)	0.599
ANS, no. (%)	39 (95%)	107 (83%)	0.051
C–section, no. (%)	40 (98%)	97 (75%)	0.002
Placental transfusion, no. (%)	17 (42%)	54 (42%)	0.964
Admission temperature (°C)	36.2 ± 0.1	36.4 ± 0.1	0.137
Mechanical ventilation, no. (%)	24 (59%)	93 (72%)	0.103
Mechanical ventilation (days)	7.6 ± 2.0	9.5 ± 1.5	0.498
RDS, no. (%)	41 (100%)	129 (100%)	N/A
BPD, no. (%)	17 (42%)	37 (29%)	0.126
PPHN, no. (%)	6 (15%)	8 (6%)	0.087
Pulmonary hemorrhage, no. (%)	4 (10%)	18 (14%)	0.485
PDA treatment, no. (%)	9 (22%)	32 (25%)	0.710
Hypotension (first 72 h), no. (%)	10 (24%)	39 (30%)	0.472
NEC, no. (%)	2 (5%)	15 (12%)	0.209
PIVH grade 3–4, no. (%)	4 (10%)	6 (5%)	0.226
PVL, no. (%)	0	3 (2%)	0.325
ROP requiring therapy, no. (%)	6 (15%)	16 (12%)	0.711
EOS, no. (%)	5 (12%)	13 (10%)	0.701
LOS, no. (%)	10 (24%)	47 (36%)	0.155
Parenteral nutrition (total days)	20 ± 3	18 ± 2	0.674
Hospitalization (days)	74 ± 5	73 ± 3	0.894
Mortality, no. (%)	1 (2%)	5 (4%)	0.664

Abbreviations: AGA, appropriate for gestational age; ANS, antenatal steroids; BPD, bronchopulmonary dysplasia; C–section, Caesarean section; EOS, early onset sepsis; LOS, late onset sepsis; NEC, necrotizing enterocolitis; PDA, persistent ductus arteriosus; PIVH, peri/intraventricular hemorrhage; PPHN, persistent pulmonary hypertension of newborn; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SGA, small for gestational age.

severe hypokalemia (54% vs. 13%) and severe hypophosphatemia (46% vs. 14%) were significantly more prevalent among SGA newborns in comparison to the AGA subgroup (Figure 2). Development of potassium levels during the first week of life can be seen in Figure 3. SGA infants had significantly lower potassium on days 2–6 when compared to AGA newborns. Postnatal days 2–4 revealed the most substantial distinction between the subgroups ($p < 0.001$). There was no difference in time (postnatal days) at which lowest values were recorded for SGA and AGA infants (Phosphate: 5.1 ± 0.2 vs. 5.2 ± 0.1, $p = 0.602$; Potassium: 3.3 ± 0.2 vs. 3.5 ± 0.1, $p = 0.374$). Sub analysis of extremely preterm ($n = 92$) and very preterm ($n = 78$) infants revealed no difference in the incidence of severe hypophosphatemia and hypokalemia between the groups (Phosphate: 25% vs. 19%, $p = 0.368$; Potassium: 20% vs. 26%, $p = 0.343$).

TABLE 2 The electrolyte characteristics among the subgroups during the first week of life.

	SGA infants ($n = 41$)	AGA infants ($n = 129$)	p value
Phosphate (mmol/L)	0.97 ± 0.07	1.44 ± 0.04	<0.001
95% CI for mean	0.82 – 1.12	1.37 – 1.52	<0.001
No hypophosphatemia, no. (%)	4 (10%)	64 (50%)	<0.001
Hypophosphatemia, no. (%)	18 (44%)	46 (36%)	0.343
Severe hypophosphatemia, no. (%)	19 (46%)	19 (14%)	<0.001
Potassium (mmol/L)	3.0 ± 0.1	3.6 ± 0.1	<0.001
95% CI for mean	2.8 – 3.2	3.5 – 3.7	<0.001
No hypokalemia, no. (%)	6 (14%)	61 (47%)	<0.001
Hypokalemia, no. (%)	13 (32%)	52 (40%)	0.323
Severe hypokalemia, no. (%)	22 (54%)	16 (13%)	<0.001

Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age.

4 | DISCUSSION

Our analysis showcases that preterm SGA infants who were administered HPPN presented with significantly lower serum levels of phosphate and potassium when compared to AGA infants. We hypothesize that early electrolyte disturbances resemble metabolic changes in RFS which occurs after the introduction of PN in malnourished patients.[2] RFS is characterized by electrolyte changes and cardiorespiratory symptoms resulting from the rapid conversion of catabolism to anabolic state.[9] High intake of amino acids induces production and secretion of endogenous insulin and promotes tissue anabolism. Insulin induces intracellular redistribution of phosphate and potassium (principal electrolytes for cellular growth and production of

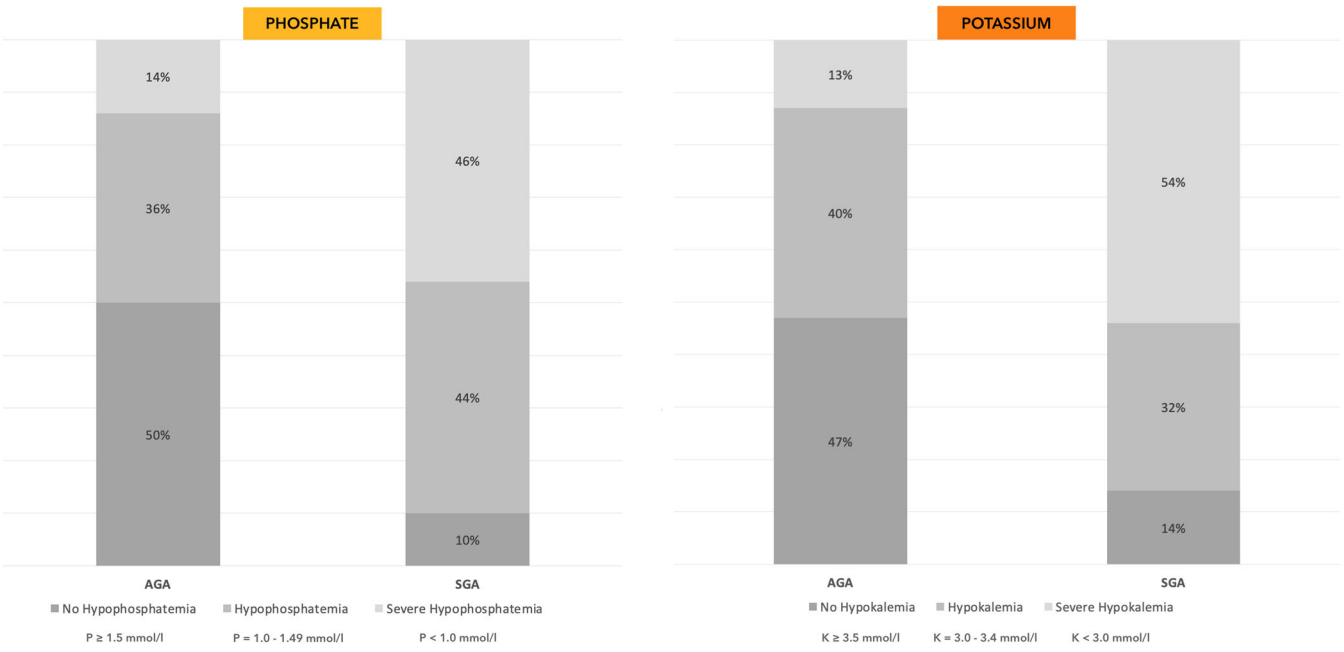

FIGURE 2 Relative occurrence of electrolyte disturbances among the subgroups–appropriate for gestational age (AGA) and small for gestational age (SGA) newborns.

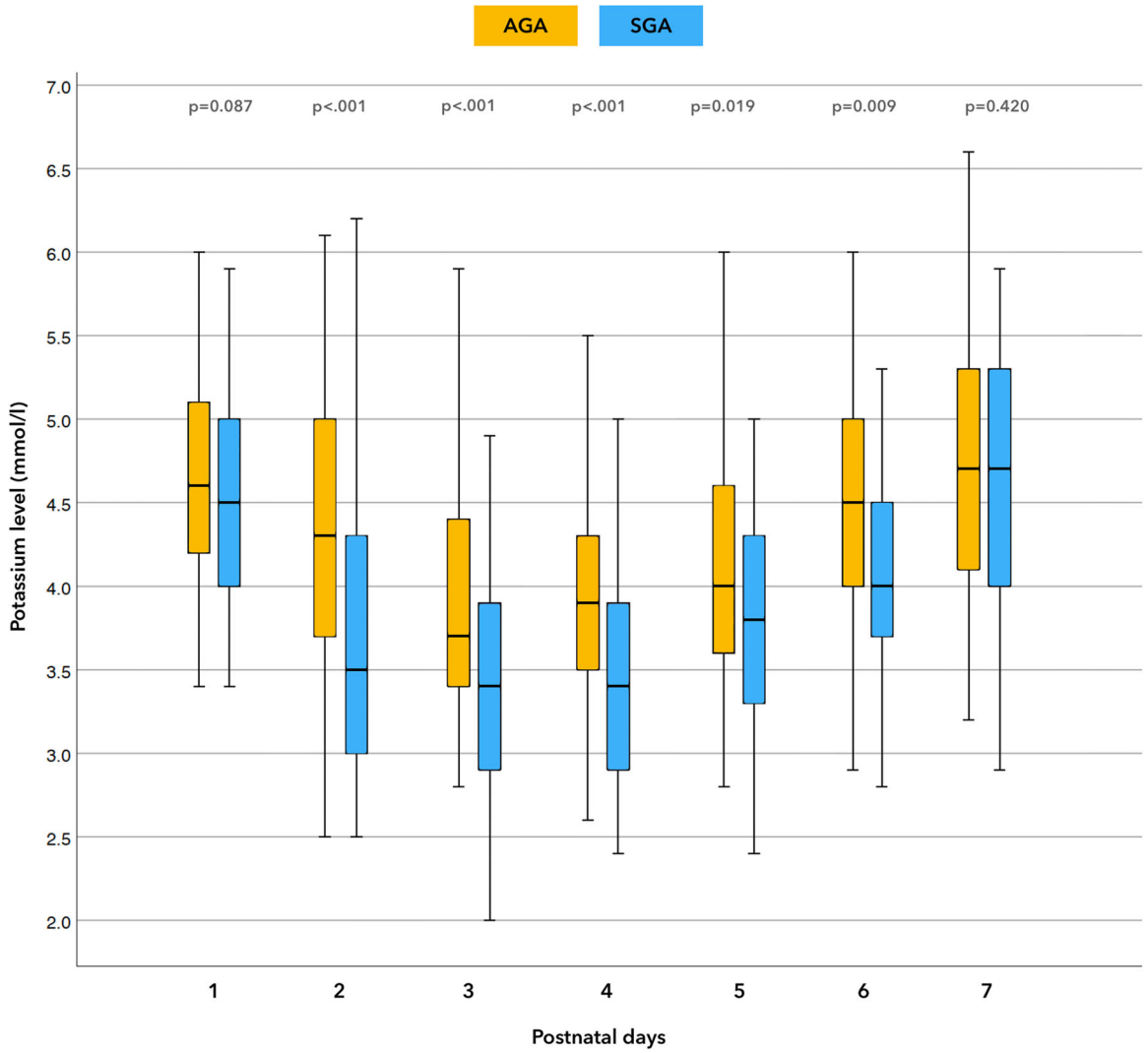

FIGURE 3 Development of potassium levels among appropriate for gestational age (AGA) and small for gestational age (SGA) preterm newborns during the first week of life.

adenosine tri-phosphate), which leads to the lowering of their concentration in blood serum.[2,9] It is estimated that approximately 0.33 mmol of phosphate are used per gram of retained amino acids.[8,11] In adult patients, RFS typically appears 2–5 days after the initiation of feeding.[11]

Moreover, potassium and phosphorus are antenatally actively transferred through the placenta and the majority of phosphorus accretion happens during the third trimester.[14] This transfer may be limited in placental insufficiency that is largely responsible for SGA status and perhaps plays a more critical role in electrolyte deficiencies than gestational age according to our results.[11] Consequently, preterm SGA infants receiving HPPN are endangered by both relative and absolute electrolyte deficiencies.[15] Therefore, the baseline electrolyte values in cord blood and/or immediately after birth could provide us with a more dynamic picture of metabolic changes in these high-risk preterm infants.[16]

The ESPGHAN recommends to routinely check phosphate levels in preterm SGA infants receiving PN during the early postnatal period.[4,17] Other authors are more specific and emphasize that the phosphate levels should be measured by the third day of life and should be retaken more often during the first week of life (every 2–3 days).[2] The severe hypophosphatemia was very common in our study (46% among SGA infants) and could be caused by the fact that large proportion of our patients did not have serial phosphate measurements. Our study revealed that repeated measurement of phosphate within first days after birth is essential to prevent the development of serious hypophosphatemia in SGA infants. The measurement of phosphate in the cord blood should be also considered.[16] Reasonable approach to reduce the risk of hypophosphatemia is optimizing phosphate parenteral supplementation.[4,9]

Potassium balance poses another challenging issue as we found severe hypokalemia in 54% of

SGA infants. This finding supports the ESPGHAN guidelines that recommend to monitor potassium closely in the preterm SGA infants.[18] Interestingly, potassium (1–2 mmol/kg/day) may be recommended from the first day of life when giving HPPN with sufficient energy supply to prevent severe hypokalemia in VLBW infants.[19] In conjunction with regular evaluation of renal function (satisfactory urine output) and serum potassium (risk of nonoliguric hyperkalemia), this approach might be beneficial for preterm SGA infants.[17,19]

Hypophosphatemia and hypokalemia represent symptoms of RFS which is mainly associated with cardiorespiratory complications.[20] Severe hypophosphatemia and hypokalemia can lead to phagocyte dysfunction, hypovolemia and muscle hypotonia.[9,15] These factors may contribute to more frequent usage of inotropic drugs and invasive ventilation in VLBW infants.[9,15] In contrast, there were no major differences in neonatal morbidity and mortality among the subgroups. Significantly higher gestational age in SGA infants can explain this finding. Furthermore, it may be difficult to assess the impact of metabolic changes in VLBW infants where apnea of prematurity, decreased muscle tone and hemodynamic instability are quite common during the first week of life.[5] Despite study limitations (retrospective analysis, variable time of electrolyte assay), we believe that neonatologists should be aware about mentioned electrolyte disbalances and their potential impact on neonatal outcome.[15]

In conclusion, our study revealed that repeated measurement of phosphate and potassium is needed when HPPN strategy is utilized. We should be careful especially in preterm SGA infants where significant hypophosphatemia and hypokalemia might have serious clinical consequences.[18] Close monitoring of these electrolytes is warranted and the common practice of limiting intake of specific electrolytes (potassium) during the first days after birth should be reconsidered.[19] Consequently, administered PN can be then optimized with sufficient intake of phosphate and potassium to prevent severe electrolyte deficiencies.[18] Another option that is used in older children and adult patients with RFS is to implement gradual increase of nutrition to prevent severe electrolyte deficiencies, however, there is insufficient body of evidence for this approach in preterm newborns.

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CONFLICT OF INTEREST STATEMENT

Peter Korček was involved in the development of NeoDiet software.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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