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Original

Hypophosphatemia associated risk factors in pediatric intensive care patients

Emine Sibel Şan[1], Seher Erdoğan[2], Mehmet Boşnak[2], Murat Şan[1]

[1]Department of Pediatrics, [2]Division of Pediatric Critical Care, Gaziantep University Faculty of Medicine, Gaziantep, Turkey. E-mail: seher70@gmail.com

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The aim of this work is to determine the prevalence and risk factors of hypophosphatemia in pediatric patients admitted to intensive care unit. The study was performed prospectively in patients admitted to the Pediatric Intensive Care Unit between June 2014 and December 2014. Fifty-seven patients were included in the study. The mean age of the study population was 24 months (2-192 months); 25 patients (43.9%) were male and 32 were female (56.1%). The mean body weight z-score was -1.47 ± 2.23, and 23 (40.4%) patients had malnutrition. On admission 16 (28.1%) patients had hypophosphatemia. There were no statistically significant differences between the hypophosphatemic patient group and normophosphatemic patient groups in terms of demographic and clinical characteristics. There were also no significant differences between the two groups in terms of risk factors. Potassium and creatinine levels were significantly lower in the hypophosphatemic group, compared to the normophosphatemic group. According to a multivariate logistic regression analysis, risk factors for hypophosphatemia were low potassium level (OR: 16.76; 95% CI: 2.09 - 134.72; p: 0.008), malignant solid tumors (OR: 52.40; 95% CI: 2.04 – 1,344.32; p: 0.017, p: 0.036). and female gender (OR: 6.18; 95% CI: 1.12 - 34.00; p: 0.036). Prospective studies with larger sample size should be conducted to study the prevalence and risk factors of hypophosphatemia at pediatric intensive care unit.

Key words: hypophosphatemia, intensive care unit, total parenteral nutrition.

Hypophosphatemia is one of the most common problems in intensive care units. Phosphorus levels of 1-2.5 mg/dl are called moderate hypophosphatemia, and <1 mg/dl as severe hypophosphatemia. The prevalence of moderate hypophosphatemia in patients hospitalized for various reasons was reported between 2.8 and 3.1%, while this ratio varies between 8.8% and 80% in patients admitted to intensive care unit (ICU)[1,2]. Malnutrition, refeeding, total parenteral nutrition poor in phosphorus, sepsis, burns, respiratory alkalosis, post-operative period, and the use of antacid therapy, diuretics, mannitol and corticosteroids are the major risk factors for hypophosphatemia[3].

Phosphate is involved in the synthesis of the body's most important energy source, adenosine triphosphate (ATP). It also acts as a cofactor for diphosphoglycerate synthesis, phospholipid construction in cell membrane, the enzyme system, and bone mineralization[4].

In most cases hypophosphatemia produces nonspecific symptoms such as weakness and irritability. The major clinical manifestations include acute respiratory failure, arrhythmias, hypertension, and generalized weakness and mental status changes. By tissue hypoxia it causes functional alterations in erythrocytes and leukocytes, hemolytic anemia, platelet dysfunction, and thrombocytopenia[5,6].

The aim of this study is to determine the prevalence and the risk factors of hypophosphatemia in pediatric cases admitted to the intensive care unit.

Material and Methods

The study included patients admitted to the Pediatric ICU (PICU) of Gaziantep University

Faculty of Medicine between June 2014 and December 2014. It was approved by Gaziantep University Ethics Committee and conducted in a prospective fashion.

The study subjects were between 1 month and 18 years old and received medical care at the intensive care unit for at least 3 days. Because hypophosphatemia is likely to occur in cases with primary hyperparathyroidism, X-linked hypophosphatemia, rickets, chronic renal failure, anorexia nervosa, and prematurity, patients with these conditions were excluded, as were those who had previously stayed at the PICU and who received continuous renal replacement therapy (CRRT). Patients' ages, gender, primary systemic disorders, indication of PICU admission, daily phosphorus levels on admission and during follow-up at PICU, organ failure on admission to PICU, or surgical status, risk factors for hypophosphatemia (using aluminum containing antacids, steroids, vasopressors, diuretics, or insulin; developing respiratory alkalosis or metabolic acidosis; receiving intermittent hemodialysis, peritoneal dialysis, or IV glucose infusion; and undergoing nasogastric decompression), diet, support for mechanical ventilation (MV), length of stay at PICU and MV, length of hospital stay, Pediatric Risk of Mortality Score III at 24 hours (PRISM III-24), Pediatric Logistic Organ Dysfunction Score (PELOD) and Pediatric Multiple Organ Dysfunction Score (P-MODS) on day 7; weight on admission to the PICU were recorded.

The clinical diagnosis of respiratory failure was defined as the need for the use of the accessory respiratory muscles, decreased muscle tone, respiratory wheezing-groaning, coughing, loss of gag reflex, PaO_2<50 mmHg, $PaCO_2$> 50 mm Hg, presence of respiratory acidosis (pH <7.35)[7].

Sepsis was diagnosed on the basis of suspected infection coupled with the existence of signs and symptoms of inflammation [leukocyte count > 12,000 / mm^3 or < 4,000 / mm^3, neutrophil percentage > 10%, plasma C-reactive protein (CRP) >2 SD higher than normal value, plasma procalcitonin level > 2 SD higher than normal value], hyperthermia (rectal temperature > 38.5° C) or hypothermia (rectal temperature <35.0° C), tachycardia, and the presence of at least one evidence showing impaired organ function, such as altered mental status, hypoxemia, increased serum lactate level, or jerky pulses[7].

Heart failure diagnosis was based on tachycardia, gallop rhythm, poor amplitude pulse, cold-pale-damp skin, tachypnea, dyspnea, stasis crackles, cyanosis, hepatomegaly, saturation in jugular veins, cardiomegaly, or the presence of left ventricular dysfunction in echocardiography[8].

Central nervous system failure diagnosis was made on the basis of a Glasgow coma score less than 11 and/or a drop by more than 3 points, an acute change in consciousness, and convulsions[7].

Hematological failure was diagnosed by a platelet count of less than 80 000/mm^3, or an International Normalized Ratio (INR) greater than 2[7].

Renal failure diagnosis was based on a serum creatinine level two times above the upper limit determined by age, oliguria (24-hour urine output <1 ml/kg/hour), and anuria (absence of urine output for at least 4 hours)[7].

Hepatic failure was diagnosed on the basis of a total bilirubin level greater than 4 mg/dl or an ALT level greater than 2 times of the upper limit[7].

Weight z-score by age was calculated separately for Turkish girls and boys, by the formula using the median and standard deviation values of tables "(patients weight - average weight that matches the patient's age) / weight standard deviation by age"[9].

PRISM, PELOD, and PMODS scores were calculated using computer-aided calculators online websites designed for this purpose (http://www.sfar.org/scores/pelod.php, http://www.sfar.org/scores/pmods.php, http://www.sfar.org/scores/prism.php).

Hypophosphatemia was diagnosed on the basis of a phosphorus level that is lower than the normal serum phosphorus level by age (1 month - 3 years: 3.8 to 6.5 mg/dl; 3-11 years: 3.7 to 5.6 mg/dl; 11-15 years: 2.9 to 5.4 mg/dl; 15-19 years: 2.7 to 4.7 mg/dl).

Patients with hypophosphatemia were treated by a six-hour infusion of 0.08 mmol/kg (2.5 mg/kg) or 0.16 mmol/kg (5 mg/kg) potassium phosphate solution, depending on the severity of hypophosphatemia. Phosphorus level was measured every six hours until it

was normalized; infusion dose was repeated as necessary. Nutritional regimens of the groups with or without hypophosphatemia were not different. Patients who had hypophosphatemia at PICU admission were grouped as Group 1 and those who had normophosphatemia as Group 2.

Statistical analysis

Data analysis was performed with the Statistical Package for Social Sciences (SPSS 11.5; SPSS Inc, Chicago, III.) software package. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normal distribution of continuous variables. Descriptive statistics were expressed as mean ± standard deviation or median for continuous and discrete numeric variables (minimum-maximum) and as number of cases and (%) for the categorical variables. The significance of difference between the mean values of the variables was analyzed with Student's t test and Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square or Fisher's exact test. Factors that differentiate hypophosphatemic patients from normophosphatemic patients were determined by multiple variable forward stepwise elimination logistic regression analysis. At univariate statistical analysis, variables with a p level of <0.25 were included in the multivariate logistic regression model as candidate risk factors. The odds ratio and 95% confidence interval of each variable were calculated. Statistical significance was set at $p < 0.05$.

Results

A total of 109 patients were screened, and 57 patients were enrolled in the study. Fifty-two patients were excluded from the study; of

Table I. Main Clinical Characteristics of the Patients.

Variable	Total (n: 57)	Hypophosphatemia (n: 16)	Normal phosphate (n: 41)	p
Age, month	24 (2-192)	26.5 (2-129)	24 (2-192)	0.873
Gender				0.231
Male, n (%)	25 (43.9%)	5 (31.2%)	20 (48.8%)	
Female, n (%)	32 (56.1%)	11 (68.8%)	21 (51.2%)	
BMI z-score	-1.47 ± 2.23	-1.92 ± 2.34	-1.29 ± 2.19	0.347
Malnutrition, n (%)	23 (40.4%)	5 (31.3%)	18 (43.9%)	0.382
Respiratory failure, n (%)	42 (73.2%)	12 (75%)	30 (73.2%)	1.000
Sepsis, n (%)	23 (40.4%)	7 (43.8%)	16 (39%)	0.744
Cardiac failure, n (%)	17 (29.8%)	6 (37.5%)	11 (26.8)	0.523
Hematologic failure, n (%)	13 (22.8%)	6 (37.5%)	7 (17.1%)	0.158
Postoperative, n (%)	10 (17.5%)	2 (12.5%)	8 (19.5%)	0.708
Renal injury, n (%)	10 (17.5%)	3 (18.8%)	7 (17.1%)	1.000
Acute encephalopathy, n (%)	9 (15.8%)	2 (12.5%)	7 (17.1%)	1.000
Hepatic failure, n (%)	7 (12.3%)	2 (12.5%)	5 (12.2%)	1.000
PRISM-III	13.35	14.2 ± 9.0	13.8 ± 7.8	0.859
PELOD	9.41	11 (0-23)	10 (0-32)	0.300
P-MODS	5.31	5.1 ± 3.1	5.2 ± 3.2	0.930
Mechanical ventilation, n (%)	38 (66.7%)	9 (56.3%)	29 (70.7%)	0.297
Mechanical ventilation, days	8 (1-360)	8 (3-22)	8 (1-360)	0.813
PICU LOS, days	7 (2-360)	7.5 (3-22)	7 (2-360)	0.872
Hospital LOS, days	14 (2-360)	11.5 (6-103)	14 (2-360)	0.619
Mortality, n (%)	30 (52.6%)	9 (56.3%)	21 (51.2%)	0.733
Serum potassium, mEq/L	4.3±1.1	3.8±0.9	4.6±1.3	0.031
Creatinine, mg/dl	0.4±0.9	0.3±0.10	0.5±0.15	0.029

PRISM-III: pediatric risk of mortality score; PELOD: pediatric logistic organ dysfunction score; P-MODS: pediatric multiple organ dysfunction score; PICU: pediatric intensive care unit, LOS: length of stay

these 16 had previously been hospitalized at the PICU, 12 had chronic renal insufficiency, 14 stayed less than three days at PICU, 8 had a history of premature birth, and two were receiving CRRT.

The average age of the patients was 24 months (2-192 months); 25 patients (43.9%) were male and 32 were female (56.1%). Average body weight z-score was -1.47 ± 2.23. Twenty-three patients (40.4%) had malnutrition. The most common indication for PICU admission was respiratory failure, followed by heart failure and renal failure (Table I).

Sixteen (28.1%) patients had hypophosphatemia on admission. Thirty-eight patients (66.7%) were supported by mechanical ventilation. The average duration of mechanical ventilation was 8 (1-360) days. Thirty-six patients were fed with total parenteral nutrition (TPN) while 11 patients received enteral nutrition and 10 patients received parenteral + enteral nutrition. The average duration of stay at intensive care unit was 7 days (2-360) and the average length of hospital stay was 14 days (2-360 days). Thirty patients died during follow-up (52.6%).

There were no statistically significant differences ($p>0.05$) between Group 1 and Group 2 in terms of demographic and clinical characteristics. There were no significant differences between the two groups with respect to risk factors either (Table II). On admission potassium and creatinine levels were significantly lower in Group 1 compared to Group 2 (p: 0.031 and p: 0.029, respectively). There were no significant differences for MV support, MV duration, PRISM, PELOD and P-MODS scores, diet, length of stay at ICU and length of stay at hospital, and mortality.

Five patients (4 girls, 1 boy) had both hypopotassemia and hypophosphatemia; all of these patients were in the prepubertal period. Of the 23 patients with malnutrition, five had hypophosphatemia and 2 had hypopotassemia; no patient in this group had both hypopotassemia and hypophosphatemia.

According to the multivariate logistic regression analysis, predictors of hypophosphatemic group versus normophosphatemic group on admission were low potassium, having malignant solid tumors, and female gender (Table III).

Discussion

The prevalence of hypophosphatemia in the general hospital population is 1-5%, whereas it can reach to 80% in patients admitted to intensive care units. Conditions like malnutrition, refeeding syndrome, total parenteral nutrition, inadequate intake of phosphorus, sepsis, burns, post-surgery, and the use of antacids, diuretics, and steroids may increase the tendency for hypophosphatemia[10-12].

A number of studies have been conducted on phosphorus levels in patients hospitalized at intensive care units. Gaasbeek et al.[13] reported a hypophosphatemia prevalence of 28-34% at the intensive care setting while Hoffman et al.[14] and Giovanni et al.[15] reported rates of 45% and 64%, respectively. In our study, the corresponding figure was 28.1%. Zazzo et al.[16] found a hypophosphatemia prevalence of 40.8% at surgical intensive care unit. They identified

Table II. Comparison of Risk Factors for Hypophosphatemia

Risk Factors	Hypophosphatemia (n:16)	Normal phosphate (n:41)	p
Vasopressor therapy, n (%)	11 (68.8%)	25 (61%)	0.585
Diuretics therapy, n (%)	9 (56.3%)	20 (48.8%)	0.612
Insulin therapy, n (%)	8 (50%)	11 (26.8)	0.095
Steroid therapy, n (%)	8 (50%)	11 (26.8)	0.095
Glucose Infusion, n (%)	-	1 (2.4%)	1.000
Peritoneal dialysis, n (%)	-	1 (2.4%)	1.000
Metabolic acidosis, n (%)	11 (68.8%)	21 (51.2%)	0.231
Respiratory alkalosis, n (%)	2 (12.5%)	8 (19.5%)	0.708
Antacid therapy, n (%)	2 (12.5%)	8 (19.5%)	0.708
TPN, n (%)	12 (75%)	24 (58.5%)	0.247
Parenteral + enteral, n (%)	4 (25%)	6 (14.6%)	0.260

TPN: total parenteral nutrition

Table III. Independent Variables for Hypophosphatemia

Independent Variables	Odds ratio	95% CI	p- value
Female gender	6.18	1.12 - 34.00	0.036
Presence of malignant solid tumors	52.40	2.04 – 1,344.32	0.017
Hypopotassemia in hospitalization	16.76	2.09 - 134.72	0.008

CI: confidence interval

sepsis and the use of total parenteral nutrition and diuretics as risk factors, and found a higher mortality rate in the hypophosphatemic group compared to normophosphatemic group.

In patients with malnutrition body phosphorus stores are depleted, and decreased consumption of phosphorus is known to be responsible for the development of hypophosphatemia. A study conducted to determine hypophosphatemia frequency and risk factors by de Meneses et al[17] at PICU, it was reported that 76% of patients had hypophosphatemia, with the risk being higher in patients with malnutrition. They also reported that they did not identify any relationship between hypophosphatemia and mortality, the length of stay in intensive care unit, and the duration of mechanical ventilation. Similarly, we also found no relation between hypophosphatemia and mortality or duration mechanical ventilator support.

Meneses et al.[18] prospectively evaluated 82 patients hospitalized at PICU. They reported that during a 10-day follow-up, 61% of patients developed hypophosphatemia, with serum phosphorus levels being lower in patients with malnutrition than patients without; acute respiratory distress and dopamine use were the significant risk factors for the development of hypophosphatemia. In our study, we observed no significant difference between patients with and without malnutrition with regard to serum phosphorus levels. Similarly, there was no correlation between dopamine use, respiratory failure, and hypophosphatemia.

In a study conducted in 2012, Kılıc et al.[19] found a hypophosphatemia prevalence of 60.2% at PICU. They also noted that there is a significant relationship between hypophosphatemia, sepsis and the use of furosemide, steroids and H_2 blockers; they also reported that hypophosphatemic patients had a longer duration of mechanical ventilator support and intensive care unit stay

Endocrinological and metabolic changes that occur in the presence of SIRS and sepsis contribute to the development of interleukin production and increased catabolism, leading to hypophosphatemia. In a prospective study of 238 patients, the prevalence of hypophosphatemia varied by the clinical diagnosis, with hypophosphatemia rate being reported 45% in pneumonia, 35.7% in bacterial upper respiratory tract infections, 18% with urinary tract infections, and 4.4% in viral infections. The highest prevalence was noted among patients with pneumonia, and with higher CRP levels. It was reported that there was a significant negative correlation between CRP and serum phosphorus levels; with hypophosphatemia developing during the rising period of CRP, and being restored before CRP returns to normal[20]. Shen et al.[21] studied 26 patients with sepsis and severe hypophosphatemia (serum phosphorus level <1 mg/dl) and 29 patients with sepsis but without severe hypophosphatemia (serum phosphorus level> 1 mg/dl). The authors showed that 80.8% of patients with sepsis and severe hypophosphatemia and 34.5% of patients with sepsis but without severe hypophosphatemia died. They concluded that severe hypophosphatemia was among risk factors for death in patients with sepsis. The relationship between serum phosphorus levels and CRP was not investigated. In our study, seven of 23 patients hospitalized with sepsis (30.4%) were hypophosphatemic. No mortality increase due to hypophosphatemia was observed.

Thompson et al.[22] studied adult intensive care unit patients and showed that hypophosphatemia was more frequent among patients receiving

TPN; such patients may still have developed hypophosphatemia even after phosphorus support was provided. They stressed the need for supporting the phosphorus level in patients becoming hyperglycemic while receiving TPN, receiving insulin therapy, having chronic weight loss, and taking antacid and diuretic therapy.

Chermesh et al[23] compared patients with severe and moderate hypophosphatemia and found that patients with severe hypophosphatemia stayed longer at intensive care unit compared to the ones with moderate hypophosphatemia; they also reported that the mortality rate was significantly higher in the former. Camp et al.[24] found no association between mortality and severe hypophosphatemia. Similarly, Suzuki et al.[25] reported that hypophosphatemia neither extended the length of intensive care unit stay, nor it was a risk factor for mortality.

Hoffmann et al.[14] reported that severe hypophosphatemia was associated with mortality, and hypophosphatemia was more common in neoplastic patients compared to septic patients. In our study, having malignant solid tumors, low potassium levels, and female gender were found as independent determinants for hypophosphatemia.

Several studies have shown that hypophosphatemia had a negative effect on diaphragmatic function and that it complicated weaning process[26-28]. Our results did not support these reports.

Patients with refeeding syndrome are also at risk for hypopotassemia. In our study, serum potassium levels on admission were significantly lower in the hypophosphatemic patients compared to normophosphatemic patients ($p = 0.031$). When adjustment was made for potential risk factors, the presence of hypopotassemia increased the prevalence of hypophosphatemia by 16.76 folds. Serum potassium levels should be closely monitored and intravenous potassium supplementation should be provided whenever necessary during follow-up or hospitalization of hypophosphatemic patients.

Limitations of our study are cross sectional design, clinical heterogeneity and small size of study population.

Hypophosphatemia is common in the pediatric intensive care unit; female gender, hypopotassemia and malignant solid tumors were risk factors. Prospective studies with larger sample size should be conducted to study the prevalence and risk factors of hypophosphatemia in pediatric intensive care units.

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