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Are We Aware that Hyperphosphatemia Affects Mortality and Morbidity as much as Hypophosphatemia in Pediatric Intensive Care Patients?

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Abstract

Objective

Hypophosphatemia was previously shown to affect the duration of admission, mechanical ventilator requirements, mortality and morbidity during pediatric intensive care. Different from previous studies, our study was planned with the aim of showing whether hyperphosphatemia affects morbidity and mortality in pediatric intensive care patients as much as hypophosphatemia.

Method

Patients' ages, genders, reason for admission, underlying diseases, phosphorus levels examined on admission and on the 1-4th and 5-10th-days, duration on mechanical ventilation, duration of admission, final status and PRISM and PELOD scores calculated in the first 24 hours of admission were recorded.

Results

Mortality was distinctly higher for those who were hypophosphatemic and hyperphosphatemic compared to those who were normophosphatemic. The highest mortality was identified in those who were hyperphosphatemic on the 5-10th-days. PELOD scores were only significantly different according to admission phosphorus levels (p:0.04).

Conclusion

In our study, we identified that hyperphosphatemia is a serious problem as hypophosphatemia for patients who admitted to the PICU. Patients identified to be hyperphosphatemic on admission had a significantly higher PELOD score. The significant difference of hyperphosphatemia in terms of PELOD score is one of the important points shown in our study. It should not be forgotten that like hypophosphatemia, hyperphosphatemia may cause serious problems in pediatric intensive care patients.

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Introduction

Phosphorus is an essential mineral generally found combined with oxygen in phosphate form in the body. Compounds containing phosphorus function in cell structures, cell metabolism, ensuring intercell regulation and maintaining the acid-base balance.

Though hypophosphatemia is commonly observed, diagnosis is rarely placed due to patients being generally asymptomatic. The incidence of hypophosphatemia among patients applying to the hospital for any reason is 1-5% but reaches 80% among those treated in intensive care units (1-3). The tendency toward hypophosphatemic increases in situations like malnutrition, refeeding syndrome, total parenteral nutrition, insufficient phosphorus intake, sepsis, burns, in the period after surgical operations, and with antiacid, diuretic or steroid use (4). Severe clinical findings are generally observed when serum phosphorus levels are below 1 mg/dl (5). It may cause problems related to the central nervous system (paresthesia, convulsions), respiratory system (acute respiratory failure, insufficient diaphragm spasm), muscle and skeletal system (osteomalacia, rhabdomyolysis), and hematologic system (hemolysis, platelet function disorder) (2). Hypophosphatemia in patients with mechanical ventilation may cause difficulty weaning from the mechanical ventilator, and lengthened duration on mechanical ventilation and in the intensive care unit (6). Finally, it negatively affects morbidity and mortality.

In clinical practice, the most common cause of hyperphosphatemia is renal failure. In mild or moderate renal failure, increasing parathormone levels and reducing tubular phosphorus reabsorption may prevent the development of hyperphosphatemia. In severe renal failure, this compensation mechanism cannot prevent the development of hyperphosphatemia. Hyperphosphatemia affects the nervous system and cardiovascular system most. Central nervous system findings occur with disrupted mental status, delirium, coma, convulsion, muscle cramps or tetany, and paresthesia, while hypotension and lengthened QT may be observed in the cardiovascular system.

This study, different from previous studies, was planned with the aim of showing whether hyperphosphatemia affects morbidity and mortality in pediatric intensive care patients as much as hypophosphatemia.

Patıents and Methods

This study was approved by Ankara Dr. Sami Ulus Maternity and Children's Training and Research Hospital Ethical Committee, and all parents signed the informed consent prior to enrollment.

Our study included patients admitted to the pediatric intensive care unit of an education and research hospital from 01/01/2008-31/12/2010. Data were collected from patient archive files and monitoring and treatment records of PICU patients.

The study included patients aged from 1 month to 18 years admitted to the PICU for at least 72 hours. Patients with chronic disease affecting phosphorus metabolism (primary hyperparathyroidism, X linked hypophosphatemia, rickets linked to vitamin D deficiency, chronic renal disease), with anorexia nervosa, with diabetic ketoacidosis coma, admitted for less than 72 hours, and re-admitted patients were excluded from the study.

Patient ages, gender, disease-causing admission (primary), underlying diseases (secondary), phosphorus levels on admission to PICU and on the 1-4th and 5-10th days if known, admission examination findings, clinical status (respiratory failure, heart failure, sepsis and septic shock) on the first day of PICU admission, weight on admission and age-adapted weight z-scores, laboratory findings (arterial blood gases, serum calcium, alkaline phosphatase, magnesium, potassium, total protein, albumin, creatine kinase (CK), CK-MB, lactate dehydrogenase, hemoglobin levels, white blood cell and platelet counts) on admission, day patients began feeding, day patients reached calculated target calories, days they reached calculated target protein intake, use of antacids, diuretics, steroids and inotrope, duration on mechanical ventilation (MV) in PICU, duration of PICU admission, final status, and PRISM (Pediatric Risk of Mortality) and PELOD (Pediatric Logistic Organ Dysfunction) scores calculated in the first 24 hours of admission were recorded (7,8). Reasons for admission to PICU were classified as respiratory system diseases, cardiovascular system diseases, central nervous system diseases, intoxication, sepsis and metabolic diseases.

Serum phosphorus levels examined on admission to PICU and on the 1-4th and 5-10th days if known were recorded in mg/dl form. Definition of hypophosphatemia and hyperphosphatemia were determined according to age based on normal serum phosphorus level limits (1 month-3 yrs: 3.8-6.5 mg/dl, 3–11 yrs:3.7-5.6 mg/dl, 11–15 yrs:2.9-5.4 mg/dl, 15–19 yrs:2.7- 4.7 mg/dl) (9). Patients were divided into two groups based on days feeding was begun as the first three days and after the first three days. Those beginning nutrition in the first three days formed the early nutrition group, while those beginning nutrition after the 3rd day formed the late nutrition group. Times to reach target calorie and target protein intake were examined in 2 groups as early (0-5 days) and late (after 5 days).

Statistical Assessment

Statistical analyses were performed with the SPSS for Windows Version 15.0 program. Numerical variables are shown as mean±standard deviation (SD) or median (min-max) values.

Qualitative variables are given as number and percentage. For differences between groups in terms of numerical variables, one-way analysis of variance was used for those abiding by parametric test assumptions and with the Kruskal Wallis test used for those not abiding by parametric test assumptions. The chi-square test was used to determine whether there were differences in terms of qualitative variables. Correlations between numerical variables were examined with the Pearson correlation coefficient. Whether variation in mean serum phosphorus levels was significant or not was examined with the repeated measures variance analysis. The McNemar test was used to investigate whether the variation in patient numbers when grouped according to serum phosphorus levels were significant or not. The significance level was taken as $p<0.05$.

Results

Patient information from files of 277 patients admitted to the PICU from 01/01/2008-31/12/2010 that could be accessed was evaluated. Of these, 103 were admitted for less than 3 days, 7 patients had repeated admission, 20 patients had insufficient data, 8 patients had chronic renal disease and 23 patients had diabetic ketoacidosis and were removed from the study. Thus, the study included 117 patients. When admission diagnoses are investigated, more than half (52.1%, 61/117 patients) were observed to be respiratory system diseases and intoxication.

Mean age was 5.13 years (1 month-18 years) with 61 females (52.1%) and 56 males (47.9%) out of 117 patients. Of patients, 51.3% (60) were under the age of 2. With the aim of assessing malnutrition, the weight z-score calculation was performed according to age for 114 patients with data accessible. Of patients, 64% (73/114) were within -2 SD and normal limits, while 36% (44/114) were malnourished below -2 SD. The distribution of phosphorus level groups according to calculated weight z-scores based on admission weights found no significant difference in phosphorus level group distribution when examined for those who were malnourished on admission.

Time of beginning feeding information was reached for 107 of 117 patients. Of patients, 93/107 (86.9%) began feeding in the early period and 14/107 (13.1%) began in the late period. When group distributions according to phosphorus levels are examined in terms of beginning nutrition, there was a statistically significant difference between the early nutrition group and the 1-4th day patient rates (p:0.003) with no difference for the group beginning nutrition late (p:0.135). This difference appeared to be primarily due to patients with hyperphosphatemic status.

The phosphorus levels of all 117 patients were examined on admission to PICU and from 1-4th days, while the levels of 56 patients were examined from 5-10th days. The mean phosphorus levels of patients were 4.97±1.61 mg/dl on admission, 4.57±1.11 mg/dl on 1-4th days and 4.65±1.41 mg/dl on the 5-10th days. When the variation in mean phosphorus levels are compared according to repeated phosphorus measurements, there was a significant difference between admission and 1-4th day mean phosphorus levels with no statistically significant differences between admission and 5-10th day and between 1-4th and 5-10th day mean phosphorus levels.

Data about the antiacid, diuretic, steroid or catecholamine use were reached for 86 patients. Of patients, 40.6% (35/86) used antiacids, 47.6% (41/86) used diuretics, 24.4% (21/86) used steroids and 58.1% (50/86) used catecholamine. There was no significant difference between patients using antiacid, diuretics or steroid treatment in terms of admission, 1-4th day and 5-10th day mean phosphorus levels or patient rates according to phosphorus levels. Patients receiving catecholamine treatment had a significant difference in patient rates according to 5-10th day phosphorus levels (p:0.025). Patients receiving catecholamine treatment had higher rates in the hypophosphatemic group based on 5-10th day values.

Of patients, 37.6% (44/117) used a mechanical ventilator. There was a significant difference in patients requiring mechanical ventilator according to admission phosphorus levels (**table 1**) (p:0.023). Those with hypophosphatemic and hyperphosphatemic admission phosphorus levels required more mechanical ventilation than those who were normophosphatemic; however, there was no statistically significant difference between duration on mechanical ventilator based on admission, 1-4th day and 5-10th day phosphorus levels.

Table 1. Distribution of serum phosphorus levels according to mechanical ventilation requirements of PICU patients

Serum Phosphorus Levels On Admission		Hypophosphatemia N (%)	Normophosphatemia N (%)	Hyperphosphatemia N (%)
Mechanical Ventilator Requirements ***p:0.023**	Needs mechanical ventilator (N:43)	10(23.2)	20(46.5)	13(30.3)
	No need of mechanical ventilator (N:73)	10(13.6)	53(72.6)	10(13.8)

Mean admission duration of patients was significantly different according to phosphorus levels examined on the 1-4th days (p:0.024). Those who were hypophosphatemic on the 1-4th day had longer mean admission durations (**table 2**); however, there was no significant difference in mean admission durations according to admission and 5-10th day phosphorus levels.

There was a statistically significant difference for mortality according to admission, 1-4th day and 5-10th day phosphorus levels. Mortality was distinctly higher for those who were hypophosphatemic and hyperphosphatemic compared to those who were normophosphatemic. The highest mortality (75%) was identified in patients who were hyperphosphatemic on the 5-10th days (**table 3**).

PRISM and PELOD scores were calculated to assess the seriousness of the patient's clinical status. Mean PRISM score was 10.7±13.2 (min-max:0-75, median:5) and mean PELOD score was 9.9±14 (min-max:0-50, median:3). When PRISM and PELOD scores calculated in the first 24 hours were compared according to admission phosphorus levels, only PELOD scores were significantly different according to admission phosphorus levels (p:0.04). Patients who were hypophosphatemic and hyperphosphatemic had higher PELOD scores compared to those who were normophosphatemic (**table 4**).

When patient admission phosphorus levels are compared according to the presence of heart, respiratory failure and sepsis in the clinical tableau on admission, there was a significant difference identified for the presence of sepsis and cardiac failure with admission phosphorus levels with no difference identified for respiratory failure. The presence of sepsis and cardiac failure was higher in those who were hyperphosphatemic (**table 5**).

Table 2. Distribution of serum phosphorus levels according to mean admission duration to the PICU

Serum Phosphorus Levels	Admission N (%)			1-4th day N (%)			5-10th day N (%)		
	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
Mean Admission Duration (day,mean±SD)	11,05± 7,22	9,75± 19,86	14,56± 18,13	12,24± 11,56	10,55± 19,21	10,66± 22,38	15,25± 10,96	18,72± 24,96	22,25± 31,85
p	0.08			0.024			0.5		

Table 3. Distribution of serum phosphorus levels according to final status of PICU patients

Serum Phosphorus Levels		Admission N (%)			1-4th day N (%)			5-10th day N (%)		
		Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
Final Status	Died N:18	4(22,2)	7(38,9)	7(38,9)	5(27,8)	9(50)	4(22,2)	4(30,8)	6(46,2)	3(23,1)
	Alive N:98	16(16,3)	67(68,4)	15(15,3)	20(20,4)	73(74,5)	5(5,1)	4(9,5)	37(88,1)	1(2,4)
P		0.04			0.05			0.007		

Table 4. Distribution of serum phosphorus levels according to PELOD scores of PICU patients

Serum Phosphorus Levels	Admission N (%)			1-4th day N (%)			5-10th day N (%)		
	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph	Hypo phosph	Normo phosph	Hyper phosph
PELOD scores (mean±SD)	11,5± 16	7,6± 12,1	7,6± 12,1	10,9± 15,1	9,1± 13,2	14,6± 15,9	17,3± 18,2	8,2± 10,4	18,1± 14,3
p	0.04			0,22			0,4		

Table 5. Distribution of serum phosphorus levels according to presence of sepsis, cardiac and respiratory failure in PICU patients

Serum Phosphorus Levels on admission		Hypophosphatemia N (%)	Normophosphatemia N (%)	Hyperphosphatemia N (%)	p
Clinical Status	Sepsis N:30	5(16.7)	13(43.3)	12(40)	**0,02**
	Respiratory Failure N:62	14(22.6)	37(59.7)	11(17.7)	0,26
	Cardiac Failure N: 33	7(21.2)	13(39.4)	13(39.4)	**0,01**

Discussion

Variations in phosphorus levels, especially hypophosphatemia, do not have clear or specific symptoms and findings reflecting the clinical tableau making it difficult to monitor the clinical importance of phosphorus. Literature scans observed very few studies about phosphorus levels in pediatric intensive care units, with assessments only of single phosphorus level measured during admission or assessment of a classification of whether patients are hypophosphatemic are not (1,10,11). This study was performed in pediatric patients and has the feature of multipurpose assessment in terms of progression and hypo-normo-hyperphosphatemic formation with admission and repeated measurements during monitoring. When PRISM and PELOD scores are examined, they appear to be a heterogeneous group.

According to repeated phosphorus measurements of patients, phosphorus levels fell on the 1-4th day and increased again on the 5-10th days. When mean phosphorus levels are compared, a statistically significant difference was only found between admission (4.97±1,61 mg/dl) and 1-4th day (4.57±1,11 mg/dl) (p:0.034).

A study published by Menezes in 2009 prospectively observed 82 children under the age of 7, and reported no significant difference in mean phosphorus values in 3 measurements repeated within the first 10 days (12). During measurements during the admission duration, with any value, 26.4% of our patients were hypophosphatemic and 22.2% were hyperphosphatemic. The study published by Menezes in 2006 identified that 76% of patients were hypophosphatemic. The reason for this rate is higher than our study is that in Menezes' study a single phosphorus value was examined on the 3rd day and the age groups were different. Additionally, children assessed in this study had distinctly higher rates of malnutrition (83% <-2SD) compared to our study group (36%), which may have affected results as it is a significant risk factor for hypophosphatemia. Menezes reported they found a significant correlation between malnutrition and hypophosphatemia in this study (13). The prospective study by Menezes in 2009 found a positive correlation between weight z-scores of patients on admission and phosphorus levels and showed that mean phosphorus levels of malnourished patients were significantly low (12). In our study, malnourished patients with weight z-score (<-2SD) had higher hypophosphatemia on admission compared to those who were not malnourished (31.1% compared to 12.3%). Additionally, this difference was not statistically significant (p:0.09).

The use of antiacid, steroids and diuretics which can affect phosphorus levels in patients did not affect mean admission, 1-4th day and 5-10th-day phosphorus levels (p:0.73,0.38,0.49, respectively). The 2006 study by Menezes did not show a significant correlation between steroid and diuretic use with hypophosphatemia, which appears to comply with our study results (13). The 2009 Menezes study showed a correlation between diuretic use above 2 mg/kg and any dose of dopamine with hypophosphatemia (12). In our study, patients receiving catecholamine support appeared to have significantly high hypophosphatemia rates in the 5-10th day values (p:0.025).

Phosphorus levels may be associated with hunger and time beginning feeding. It is known that with the increased anabolic activity at cellular levels with the beginning of the feeding and ATP synthesis and the intake of phosphorus into cells, especially in malnourished patients, may cause falls in phosphorus levels leading to serious outcomes (12,14). The majority of our patients began early feeding in the first three days. When early feeding patients are compared with admission, the 1-4th day hyperphosphatemic group clearly reduced and the hypophosphatemic group increased and this was statistically significant (p:0.003).

In our study when the difference in phosphorus levels are compared with scores showing the severity of clinical disease and organ dysfunction status of patients, mean PELOD scores were observed to differ according to admission phosphorus levels (p:0.04). The PELOD scores of patients who were hyperphosphatemic on admission were higher. A retrospective study in Turkey by Kılıç *et al*. in 2008 reported being hypophosphatemic did not cause a significant difference in terms of PELOD scores. However, this study only assessed patients as being hypophosphatemic or not (15). The significant difference in PELOD score with hyperphosphatemia is one of the important points shown in our study.

Patients with sepsis and cardiac failure on admission were found to have significantly high rates of hyperphosphatemia (p:0.02 and 0.01). Patients with respiratory failure did not show different patient rates according to serum phosphorus levels (p:0.26). Hyperphosphatemia may have developed due to organ dysfunction that may accompany sepsis and cardiac failure. However, though the mechanism is not clear, studies of septic adults and animal studies reported hyperphosphatemia development linked to sepsis-associated multiple organ failure and increased parathormone (16-18).

Of our patients, 37.6% received MV support and hypophosphatemic and hyperphosphatemic patients according to admission values had significantly high rates of MV requirements. However, the duration on mechanical ventilator did not differ according to phosphorus levels. The 2009 study by Menezes reported 13 of 16 patients requiring mechanical ventilation were hypophosphatemic (12). However, patients in this study were only classified as hypophosphatemic and normophosphatemic. The significantly higher rates of mechanical ventilation requirements in hyperphosphatemic patients is associated with more pronounced accompanying organ dysfunctions.

The mean admission duration of patients in our study was 10.9±17.9 days, with durations significantly longer for patients who were hypophosphatemic on 1-4th day values. Hypophosphatemia developing in patients admitted to the PICU lengthens the duration of stay. In our study group, 15.4% of 117 patients died. Mortality was significantly high in patients who were hyperphosphatemic and hypophosphatemic on admission, 1-4th day and 5-10th day values (p: 0.04,0.05,0.007). The highest mortality (75%) occurred among patients who were hyperphosphatemic on the 5-10th days. Though hypophosphatemia did not reach serious levels in patients admitted to the PICU, it increased MV requirements, morbidity and mortality.

In our study, like hypophosphatemia, hyperphosphatemia was identified to be a severe problem for patients admitted to the PICU. Patients identified to have hyperphosphatemia on admission had a higher PELOD score. Additionally, the hyperphosphatemic rates in patients with sepsis and cardiac failure were significantly high. Especially the higher mortality in patients who were hyperphosphatemic on the 5-10th day may be linked to this.

Just like hypophosphatemia, it should not be forgotten that hyperphosphatemia may cause severe problems in pediatric intensive care patients.

Disclosure

The authors have nothing to disclose

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