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Original Research Article

Frequency of hypophosphatemia in critically ill children: risk factors and outcome

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ABSTRACT

Background: Phosphorus plays a vital role in maintaining metabolism and energy of body. The objective of this study was to determine the frequency, risk factors and outcome of hypophosphatemia (HP) in critically ill children admitted in pediatric intensive care unit.
Methods: This retrospective study included all critically-ill children having phosphate levels within 24 hours of admission from July 2019 to December 2020. Demographic, clinical and laboratory variables were collected. HP is defined as serum phosphorus level ≤4 mg/dl in this study. Descriptive statistics along with logistic regression analysis have been reported.
Results: Prevalence of HP was 53.7% (94/175). Median age was 2 year (0.5-15) and male were 58.5% (106). Serum magnesium level [2.2 (1.5-12.1) vs. 1.8 (1.2-4.0) mg/dl] and serum calcium level [8.7 (.18-10.7) 8.0 (1.8-14.0) mg/dl] were significantly low in the HP group as compared to the normo-phosphatemic group. There was no significant association of hypo-phosphataemia with admitting diagnosis, ICU therapies, and medications on univariate analysis. Hypo-phosphataemia at admission had no effect on mortality. On multivariate analysis, only male gender demonstrated independent association with HP (OR: 2.2; 95% CI 1.2-4.1; p<0.01).
Conclusions: HP is common in critically ill children and is significantly associated with male gender. Prospective, larger sample size studies are needed to study the prevalence and risk factors of HP at pediatric intensive care units.

Keywords: Hypophosphatemia, Critically ill children, Risk factors, Outcome

INTRODUCTION

Phosphorus is an important intracellular anion and is involved in many essential biological actions. Thus hypophosphatemia (HP) can result in dysfunction of many organs system mainly due to decreased production of adenosine triphosphate (ATP) and 2, 3-diphosphoglycerate (2, 3 DPG) as it is an energy currency of body.[1]

The incidence of HP is prevailing high in critically ill children admitted to general pediatric intensive care units, ranges from 20-80%.[2-5] There are many causes of HP in critically ill children including malnutrition, medications, surgery, enteral and parenteral glucose and sepsis. Clinically consequences of HP can present as ventilatory muscle weakness, arrhythmia, vasodilation, cardiac failure, rhabdomyolysis, psychosis, seizures, hemolysis and insulin resistance.[6] Studies have shown that phosphate supplementation can reverse many of these

adverse manifestations of HP and improve the outcome of critically ill patients.

Although electrolytes are routinely measured in patient admitted to intensive care unit and phosphorus is not usually the part of electrolyte panel because of less awareness regarding the incidence and complications of HP. The objective of this study was to determine the frequency of HP in critically ill children and to assess the associated risk factors and outcome compared with critically ill children who have normal serum phosphorus.

METHODS

This retrospective cross-sectional study enrolled children (age 0.5-15 years) of either gender admitted to a closed multidisciplinary-cardiothoracic pediatric intensive care unit (PICU) of Liaquat national hospital and medical college, Karachi, who had a serum phosphorus level done on admission between July1, 2019, and December 31, 2020. The study was approved by the institutional research ethics committee (0600-2021 LNH-ERC, dated: January 18, 2021). The patients with serum phosphorus level ≤4.0 mg/dl were considered as 'HP" (HP).[7] Severe HP is defined as serum phosphorus level ≤1 mg/dl. The serum phosphorus level was measured by Calorimetric method on Cobas c-501 analyser in our institutional laboratory. The sample size was calculated from WHO software for sample size calculation. The frequency of HP was reported 25% and absolute precision was 0.07 with 95% confidence interval, the estimated sample size was 147. After adding probable dropout of 20%, the final sample size was 175. We excluded all children admitted with known diagnosis of chronic kidney disease, rickets, and hypoparathyroidism. The following data were collected on a structured data collection sheet, including demographic data like age, gender, admitting diagnosis, pertinent medications administered, use of mechanical ventilation and inotropes and outcome (alive vs. expired).

Data was entered into SPSS V. 22 for analysis. Chi-square test for categorical variables and student-t test for continuous variables were applied. Predictors of HP and association of HP with mortality was evaluated by applying logistic regression analysis. Bivariate logistic regression analysis was run first and significant variables with a p<0.02 were entered into multivariable model. P value for independent predictors was set at <0.05.

RESULTS

A total of 175 children (22.7% of total admission) had serum phosphorus level performed within 24 h of admission in PICU during study period. Patients' characteristics are described in Table 1. The median age was 2.0 years (range 5 months-15 years) and 66.6% (109) patients were males. HP was detected in 53.7% (n=94) children. The median serum phosphorus level was 3.7 mg/dl (range 0.5-19.0) mg/dl. Six cases (3.4%) had severe HP in our COHORT. The patients admitted with acute respiratory illnesses in PICU had lower serum phosphorus level as compared to other categories of illnesses. However, it was not statistically significant (p<0.9). There was no significant difference between normophosphpotemic and HP groups with respect to use of mechanical ventilation. During the study period, furosemide, proton pump inhibitors, steroid, antiepileptic drugs were given 80.6% (n=144), 85% (n=146), 34.9% (n=61) and 48.6% (n=85) of children respectively. There was no significant association of any of these medications with HP in critically ill children. Serum calcium (p<0.03) and magnesium (p<0.002) were low in HP group, but serum potassium (p<0.71) was not affected by low serum phosphorus (Table 2). Being male child was only independent predictors of HP at multivariate logistic regression analysis (OR: 2.2; 95% CI 1.2-4.1; p<0.01) (Table 3). Overall mortality in study was 3.4% (n=6). There was no difference in mortality between 2 groups (p<0.85).

Table 1: Characteristics of critically ill children admitted in PICU (N=175).

Variables	All patients, n (%)	Control, n (%)	Cases, n (%)	P value
Age (years)	2 (0.5-20)	2 (0.5-14)	2 (0.5-20)	0.22
Gender				
Male	106 (60.6)	41 (50.6)	65 (69.1)	0.012
Female	69 (39.4)	40 (49.4)	29 (30.9)	
Cardiovascular disease (Yes)	18 (10.3)	9 (11.1)	9 (9.6)	0.74
Respiratory disease (Yes)	18 (10.3)	5 (6.2)	13 (13.8)	0.09
Neurological disease (Yes)	48 (27.4)	25 (30.9)	23 (24.5)	0.34
Mechanical ventilation (Yes)	51 (29.1)	24 (29.6)	27 (28.7)	0.89
Inotrope use (Yes)	69 (39.4)	32 (39.1)	37 (39.4)	0.98
Furosemide use (Yes)	141 (80.6)	65 (80.2)	76 (80.8)	0.92
Steroids use (Yes)	61 (34.9)	25 (30.9)	36 (38.3)	0.30
Anti-epileptic use (Yes)	85 (48.6)	42 (51.8)	43 (45.7)	0.42
PPI use (Yes)	146 (83.4)	63 (77.8)	83 (88.3)	0.06
Mortality (Yes)	06 (3.4)	3 (3.7)	3 (3.2)	0.85

PPI-Proton pump inhibitors.

Table 2: Laboratory parameters of critically ill children admitted in PICU, (n=175).

Variables	All patients, n (%)	Control, n (%)	Cases, n (%)	P value
Serum potassium (mEq/L)	3.6±0.98	3.7±1.1	3.6±0.9	0.71
Serum calcium (mg/dl)	8.6 (1.8-14.0)	8.7 (1.8-10.7)	8.0 (1.8-14.0)	0.03
Serum magnesium (mg/dl)	1.9 (1.2-12.1)	2.2 (1.5-12.1)	1.8 (1.2-4.0)	0.002
Serum phosphorus (mg/dl)	3.7 (0.5-19.0)	5.0 (4.0-19.0)	3.0 (0.5-3.9)	<0.001

Table 3: Risk factors of hypophosphatemia in critically ill children admitted in PICU, (n=175).

Factors	Un-adjusted model		Adjusted model*	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (Years)	1.01 (0.95-1.1)	0.65		
Gender (Male)	2.2 (1.2-4.1)	0.01	2.2 (1.2-4.1)	0.01
Cardiovascular disease (Yes)	0.85 (0.32-2.2)	0.74	-	-
Respiratory disease (Yes)	2.4 (0.83-7.2)	0.11	-	-
Neurological disease (Yes)	0.73 (0.37-1.4)	0.35	-	-
Mechanical ventilation (Yes)	0.96 (0.50-1.8)	0.89	-	-
Inotrope use (Yes)	1.0 (0.54-1.83)	0.98	-	-
Furosemide use (Yes)	1.0 (0.50-2.2)	0.92	-	-
Steroids use (Yes)	1.4 (0.74-2.6)	0.30	-	-
Anti-epileptic use (Yes)	0.78 (0.43-1.42)	0.42	-	-
PPI use (Yes)	2.2 (0.95-4.88)	0.07	-	-

DISCUSSION

We found HP on admission in critically ill children in more than half of the patients (53.5%). Data on prevalence of HP in critically ill children are limited, reported on small sample size and varies largely (20.0%-79.50%).[3,9,10] This wide range of prevalence is related to inconsistent cut-off values for defining HP for study purpose. There are many factors predisposing critically ill children for HP, including increased demand, low intake, exudative loss, redistribution from extracellular to intracellular compartment, and increased renal excretion.[3,6,11]

In our study, we found that children admitted with acute respiratory illnesses have had higher prevalence of HP as compared to other diagnostic categories. However, it was not statistically significant. El Shazley et al and Mohsen et al had shown a high association of HP with respiratory illnesses (60%).[2,8,12-15] The prevalence of HP in critically-ill children diagnosed with respiratory disorders was also reported by other studies. It might be attributed to the fact that hypophosphataemia was known to lead to muscle weakness and hypotonia.[4]

Many studies found association with use of mechanical ventilation and prolonged ventilation in HP group.[4,15] It is most likely related to deficiency of energy currency (ATP) which may lead to respiratory muscle weakness especially diaphragm and is associated with prolonged mechanical ventilation.[3,16] However, we didn't find any association between HP and use of mechanical ventilation like Santana e Meneses et al.[2]

Significant association of HP with other electrolyte abnormalities like calcium and magnesium in critically ill children were described in the few reports like our results.[17,18] In a study by El Beleidy et al found that HP was associated with hypokalemia (p=0.003) and hypomagnesaemia (p=0.004) in critically ill children.[18] In another study from PICU, deficiency of calcium (64%) and magnesium (46%) was observed along with HP on admission.[17] We found no association between HP and mortality and most of pediatric reports on HP in critically ill children have negative association with mortality.[19] However, most of adult ICU studies found positive association of HP with mortality.[20] We found a significant association of HP with male gender on multivariate analysis. However, few studies support this notion while others may support association with female gender.[22]

Limitations

We acknowledge the obvious limitations in this study like conducted in a single centre, retrospective in design and a small sample size. Another limitation is that we recorded the serum phosphorus only on admission in this cohort and missed the serial measurement of serum phosphorus to assess the effects of subsequent HP in critically ill children during the stay in PICU. We didn't evaluate other confounders like sepsis and malnutrition in this study. Despite high prevalence of HP in critically ill children, there is no consensus of definition of HP in pediatric age group. There is a strong need of consensus-based standard definition of HP with grading in severity in children and and further multi-centre large sample size

studies are required to verify our results and other published reports.

CONCLUSION

HP is a common electrolyte abnormality in critically ill children. Male gender only is independent predictor of HP in our study. Other electrolyte abnormalities are common in these children.

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