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Hypophosphatemia in Critically ill Children: Insight from a Case Control Study

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ABSTRACT

Hypophosphatemia is a common yet under-recognized electrolyte abnormality in critically ill children. Early detection and treatment of hypophosphatemia can help avoid complications and enhance outcomes in critically ill children. **Objectives:** To determine the frequency of hypophosphatemia at the time of Pediatric Intensive Care Unit (PICU) admission and throughout the PICU stay, and to evaluate the need for serial phosphate level monitoring. **Methods:** This case-control study was carried out in the PICU at Ziauddin University Hospital, North Campus, from March to September 2019. Data were collected from 136 (68 cases and 68 controls) patients. At enrollment, each participant underwent a thorough clinical examination. Baseline laboratory investigations were performed according to institutional PICU protocols. **Results:** On Day 1, 61.7% of cases had hypophosphatemia, rising to 80% by Day 3. Serum phosphate levels were significantly lower in cases than controls at both admission (3.42 ± 1.20 vs. 4.71 ± 0.70 mg/dL) and Day 3 (3.08 ± 0.74 vs. 4.62 ± 0.70 mg/dL), both p<0.001. Cases had a significantly longer duration of illness before admission (10.02 ± 11.99 vs. 5.37 ± 4.74 days; p=0.004) and PICU stay (4.35 ± 2.44 vs. 3.49 ± 1.41 days; p=0.01). **Conclusion:** It was concluded that hypophosphatemia is common among critically ill children and often develops after admission. A single phosphate measurement at admission is insufficient for detecting all cases. Therefore, a series of phosphate measurements during the PICU stay is recommended.

INTRODUCTION

Phosphorus in all its forms is a fundamental element of the tissues and is required for many fundamental functions. It is involved in various physiological processes, including cell signalling, energy metabolism, and is a vital component of cell membranes and bones [1]. Most of the phosphorus is found intracellularly or inside the bones, while less than 1% is in plasma. There is an age-related as well as diurnal variability in the phosphorus concentration. A high concentration of phosphorus in childhood is required to promote growth. Regarding diurnal variation, there is a peak in phosphorus levels during sleep [2, 3]. Hypophosphatemia may present with a range of clinical symptoms, including irritability, altered mental status, seizures, coma, and neuromuscular dysfunction such as rhabdomyolysis. It may also be associated with hemolysis, abnormal liver enzyme levels, and bone marrow suppression affecting erythrocytes, platelets, and white blood cells [2, 3]. Severe hypophosphatemia can impair cardiac muscle performance, weaken respiratory muscles, and potentially lead to multi-organ dysfunction [4]. Despite the routine measurements of serum calcium, sodium, and potassium in critically ill children, phosphorus is not routinely monitored, particularly in asymptomatic cases of hypophosphatemia [5]. Hypophosphatemia has been documented as a contributing risk factor for decreased cardiac output, trouble in weaning off from the ventilator, respiratory failure, cardiac arrhythmias and increased death rate in septic patients [6-9]. Early diagnosis and aggressive treatment of hypophosphatemia may altogether diminish the risk of arrhythmias and improve prognosis [10]. Studies showed that hypophosphatemia occurred in most of the patients (56%) during their PICU

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stay [11]. One study found that 60.2% of the patients developed hypophosphatemia from the time of admission to the seventh day [12]. Another study found that the prevalence of low phosphorus levels was 44.4% on Day 1, rising to 63.9% on Day 3, and then gradually declining to 56.9% on Day 7 and 42.8% on Day 10 [13]. Hypophosphatemia was found to be prevalent with infections and an increased number of starvation days in children and associated with poor outcomes in children admitted to the PICU [8]. One study found infections (dengue fever, enteric fever) as the most common risk factor for hypophosphatemia in 38.2% of patients, followed by respiratory diseases (pneumonias, bronchiolitis, bronchial asthma, pleural effusion, interstitial lung diseases) in 26.4%, followed by sepsis in 5.9%, central nervous system (CNS) infection in 5.9%, and poisoning in 5.9% of patients [14]. Hypophosphatemia is a common yet under-recognized electrolyte abnormality in critically ill children. Early detection and treatment of hypophosphatemia can help avoid complications and enhance outcomes in critically ill children.

This study aimed to report the frequency of hypophosphatemia in critically ill children both at the time of admission and during PICU stay. Also, to demonstrate that a single phosphate level measurement at admission is insufficient, as many children who had normal levels on Day 1 developed hypophosphatemia by Day 3. It also aims to recommend routine serial monitoring of serum phosphate levels in PICU settings.

METHODS

This case-control study was conducted in the Intensive Care Unit of the Pediatric Department, Ziauddin University Hospital, North campus, from March to September 2019. Study approval was obtained from the ethical review committee of Ziauddin University Hospital via reference code 0410818LKPED, and written informed consent was obtained from all participants before their inclusion in the study. The sample size was calculated using the Open Epi sample size calculator (version X.X; www.openepi.com) for unmatched case-control studies. This study is based on assumptions on data reported by Meneses *et al.* [15], which showed a prevalence of acute respiratory disease of 66.0% in children with hypophosphatemia (exposed group) and 40.6% in those with normal phosphatemia (unexposed group). Assuming a two-sided confidence level of 95%, a power of 80%, an exposure ratio of 1:1, and using these proportions, the corresponding odds ratio was approximately 2.86. Based on these parameters, the required sample size was calculated to be 136 participants in total (68 per group). Children aged 1 month to 16 years admitted to the PICU were included in the study if they had a minimum PICU stay of 48 hours and at least two serum phosphate level readings available during admission. Children were classified as cases if they had low serum phosphate levels and as controls if they had normal serum phosphate levels. Patients were excluded if they had known chronic kidney disease or parathyroid disorders, known genetic or metabolic phosphate disorders, were receiving phosphate supplementation before admission, or had incomplete records or were discharged within 48 hours. Children were defined as cases if they had hypophosphatemia, defined as serum phosphorus levels less than 3.8 mg/dL in children younger than 2 years, and less than 3.5 mg/dL in those older, measured at the time of admission or day 3. Children were defined as controls if they had normophosphatemia, defined as serum phosphorus levels equal to or above 3.8 mg/dL in children younger than 2 years, and equal to or above 3.5 mg/dL in those older, measured at the time of admission or day 3. At enrollment, each participant underwent a thorough initial evaluation that included a detailed clinical history, physical examination, and vital signs assessment. Baseline laboratory investigations were performed according to institutional PICU protocols. Complete blood count (CBC) was performed using an automated hematology analyser (Sysmex XN-1000, Sysmex Corporation, Japan). Arterial blood gas (ABG) analysis was conducted using a blood gas analyser (ABL800 FLEX, Radiometer Medical, Denmark). C-reactive protein (CRP), serum electrolytes, serum creatinine, blood urea nitrogen (BUN), serum aminotransferases, alkaline phosphatase, magnesium, calcium, and phosphorus were measured using an automated chemistry analyzer (Cobas c501, Roche Diagnostics, Germany). Vitamin D levels and parathyroid hormone (PTH) were assessed using chemiluminescence immunoassay kits on a Cobas e411 analyser (Roche Diagnostics, Germany). All tests were performed according to the respective manufacturers' protocols. Specimens for bacterial culture were collected as needed: two aseptic blood samples in aerobic/anaerobic bottles, one urine sample (clean-catch or catheter) in a sterile container, and one tracheal aspirate via suction into a sterile tube. All specimens were processed using standard microbial organism detection protocols in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. Serum phosphorus levels were measured at two points on admission and on the third day of hospitalization and analyzed in the institutional clinical laboratory. Serum phosphorus levels less than 3.8 mg/dL in children younger than 2 years, and less than 3.5 mg/dL in those older, were used to define hypophosphatemia. Infection was diagnosed based on clinical signs of infection, increased white blood cell count and positive bacterial culture. Respiratory disease was diagnosed on clinical signs and

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abnormal radiological findings such as pulmonary infiltrates or consolidation. Sepsis was diagnosed on ≥2 SIRS criteria with confirmed infection. SIRS criteria were confirmed by monitoring body temperature, heart rate, respiratory rate, and white blood cell (WBC) count. Body temperature was measured using a digital thermometer, heart rate and respiratory rate were monitored clinically, and WBC count was measured through CBC. Diabetic ketoacidosis was diagnosed on elevated blood glucose >200mg/dL, decreased venous pH<7.3 or bicarbonate < 18 mmol/L, and ketonuria or ketonemia. Blood glucose, bicarbonate, and serum ketones were measured using an automated chemistry analyser (Cobas c501, Roche Diagnostics, Germany). Venous blood gas analysis for pH and bicarbonate levels was performed using a blood gas analyzer (ABL800 FLEX, Radiometer Medical, Denmark). In all hypophosphatemic patients, a spot urinary sample was obtained to calculate the fractional excretion of phosphorus ($FePO_4$), aiding in determining renal phosphate handling. Children identified with hypophosphatemia were treated with intravenous phosphate supplementation in the form of potassium phosphate. The dose and rate of administration were determined by the PICU team based on individual patient parameters. Electrolyte levels were closely monitored during treatment to ensure safety and therapeutic efficacy. Parathyroid hormone (PTH) levels were also measured in selected hypophosphatemic patients when clinically indicated, to assess potential secondary causes. Strict adherence to inclusion and exclusion criteria, data collection in a pre-designed structured proforma was maintained throughout the study to minimize bias and control for potential confounding variables. Data quality was assured by double-checking records, following standardized sample collection procedures, and performing all tests from a single laboratory. The primary dependent variable was serum phosphate level, which was utilized to define the critically ill patients into cases (hypophosphatemia) and controls (normophosphatemia). Independent variables included demographic characteristics (age and gender), clinical variables (duration of illness before admission and diagnosis on admission), and clinical outcomes (use of mechanical ventilation and duration of PICU stay). Data analysis was conducted using SPSS software, version 21.0. Continuous variables were summarized using either mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution. Categorical variables were expressed as frequencies and percentages. To compare continuous variables, independent t-tests were utilized, while the Chi-square test was applied for categorical variables. A p-value less than 0.05 was regarded as statistically significant.

RESULTS

A total of 136 children were admitted to the ICU with critical illness, classified either into the case group (68 children with hypophosphatemia) or the control group (68 children with normal phosphate levels). In the study population, the age distribution showed that 52.9% of cases were below 2 years of age compared to 44.1% in controls, while 47.1% of cases and 55.9% of controls were aged 2 years or above. However, the difference was not statistically significant (p=0.3). Gender distribution was nearly equal across both groups, with no significant difference observed (p=0.6) (Table 1).

Table 1: Age and Gender Distribution in Case and Control Groups

Variables	Category	Case (n=68)	Control (n = 68)	Chi-square Value	p-value
Age (Years)	2	36 (52.9%)	30 (44.1%)	1.06	0.3
	≥2	32 (47.1%)	38 (55.9%)		
Gender	Male	34 (50.0%)	37 (54.4%)	0.265	0.6
	Female	34 (50.0%)	31 (45.6%)		

Among the 68 children classified as cases, hypophosphatemia was present in 61.7% cases on Day 1 and increased to 80% by Day 3, showing a progressive decline in phosphate levels in the case group. Thus, the overall frequency of hypophosphatemia among cases during PICU stay was 100% by design, with a significant proportion developing it after admission. Serum phosphate levels were significantly lower in cases than controls at both admission (p<0.001) and Day 3 (p<0.001). The mean duration of illness before hospital admission was significantly longer in the case group (10.02 ± 11.99 days) compared to the control group (5.37 ± 4.74 days), with a statistically significant difference (p=0.004) (Table 2).

Table 2: Phosphate Findings and Duration of illness Before Admission in Case and Control Groups

Variables		Case (n=68)	Control (n=68)	p-Value
Phosphate Findings	Day 1 New Cases	42 (61.7%)	26 (38.3%)	-
	Day 3 Total Cases	55 (80%)	-	-
	Serum Phosphate at Admission	3.42 ± 1.20 (0.95–6.81)	4.71 ± 0.70 (3.54–6.27)	<0.001
	Serum Phosphate Day 3	3.08 ± 0.74 (1.18–4.87)	4.62 ± 0.70 (3.59–6.7)	<0.001
	FE Phosphate at Admission	17.84 ± 12.11 (0.53–65.75)	-	-
	FE Phosphate Day 3	17.87 ± 14.84 (1.71–66.76)	-	-
Duration of illness Before Admission		10.02 ± 11.99 (1–90)	5.37 ± 4.74 (1–30)	0.004

The average length of PICU stay was significantly longer in the case group compared to the control group (4.35 versus 3.49 days; p=0.01), indicating a notable association between hypophosphatemia and prolonged critical care. However, the duration of mechanical ventilation did not differ significantly between groups (3.38 versus 3.40 days;

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p=0.9), suggesting that hypophosphatemia did not affect ventilation duration (Table 3).

Table 3: PICU Stay and Mechanical Ventilation in Case and Control Groups

Variables	Case (n=68)	Control (n = 68)	p-Value
Length of PICU Stay	4.35 ± 2.44 (2–20)	3.49 ± 1.41 (2–10)	0.01
Mechanical Ventilation (n=20 and 10)	3.38 ± 1.69 (1.5–9)	3.40 ± 2.41 (1–9)	0.9

The primary diagnoses were similar between both groups, with infections and respiratory conditions being the most common in both. Among cases, 44.1% had infections and 41.1% had respiratory conditions, while in controls, respiratory disease was slightly more prevalent at 52.9%, and infections were seen in 39.7%. Infection was present in 57.4% of the case group compared to 42.6% of the control group, suggesting a higher occurrence among patients who developed hypophosphatemia (p=0.08) (Table 4).

Table 4: Diagnosis at Admission in Case and Control Groups

Diagnosis	Case, n (%)	Control, n (%)
Infection	30 (44.1%)	27 (39.7%)
Respiratory Disease	28 (41.1%)	36 (52.9%)
Sepsis	5 (7.4%)	3 (4.4%)
Diabetic Ketoacidosis	5 (7.4%)	2 (2.9%)
Chi-square Value	–	–
P-value	2.944%	0.4%
Infection		
Yes	39 (57.4%)	29 (42.6%)
No	29 (42.6%)	39 (57.4%)
Chi-square Value	-	-
p-value	2.941%	0.08%

DISCUSSION

The findings of this study revealed a significant association between hypophosphatemia and adverse clinical parameters in critically ill children. Hypophosphatemia was present in 61.7% of cases on Day 1 and increased to 80% by Day 3, showing a progressive decline in phosphate levels in the case group. Serum phosphate levels were also significantly lower in cases than controls at both admission (p<0.001) and Day 3 (p<0.001). Our study findings are similar to the findings of previous studies that also find a high frequency of hypophosphatemia in children. A study by El Shazly *et al.* reports that hypophosphatemia was present in 42% of critically ill children on day 1 and increased to 62% on day 7 [16]. A study by Springer *et al.* reports that hypophosphatemia ranged from 27.2% to 37.5% critically ill children within three days of admission [17]. Another study by Shah *et al.* reports that hypophosphatemia was reported in 71.6% critically ill children within 10 days of admission [18]. Another study by Lusteau *et al.* found that hypophosphatemia was diagnosed in 41% critically ill children at PICU admission and then increased to 46% during the stay [19]. All similar studies report that hypophosphatemia mostly worsens after PICU admission in critically ill children, primarily due to increased renal phosphate excretion. However, our study reports stable fractional excretion of phosphate on Day 1 and Day 3 (17.84 versus 17.87), indicating that factors of critical illness are responsible for hypophosphatemia. Another significant finding of this study was the longer length of PICU stay (4.35 versus 3.49 days; p=0.01) in the case group compared to the control group, indicating a significant association between hypophosphatemia and prolonged critical care. Our study findings are similar to the findings of previous studies that also find a longer length of PICU stay in critically ill children with hypophosphatemia. A study by El Shazly *et al.* reports the 8-day PICU stay in normophosphatemia children and 10-day PICU stay in hypophosphatemia children (p<0.001) [16]. Another study by Shah *et al.* also reports that hypophosphatemia was associated with prolonged PICU stay of > six days in critically ill children [18]. Another study by Shah *et al.* reports the 4-day PICU stay in Normophosphatemia children and 7-day PICU stay in Hypophosphatemia children (p=0.001) [20]. All similar studies report that hypophosphatemia is significantly associated with longer length of PICU stay because hypophosphatemia worsens clinical status and delays the recovery of critically ill children. Another non-significant finding of this study was the similar duration of mechanical ventilation (3.38 versus 3.40 days; p=0.0) in the case group compared to the control group, indicating a non-significant association between hypophosphatemia and duration of mechanical ventilation. In contrast to our study findings, Lusteau *et al.* report the significant association of mechanical ventilation with hypophosphatemia. Duration of mechanical ventilation was significantly higher with hypophosphatemia than normophosphatemia (109 versus 67 hours; p=0.007) [19]. The difference was observed in the duration of mechanical ventilation due to different factors such as sample size, patient age, and their underlying diagnosis, which can change the phosphate-related respiratory compromise. No statistically significant differences in the distribution of initial diagnosis and infections between groups were evident (p=0.4 and 0.08, respectively), although a greater prevalence of infections and respiratory pathologies was apparent in the hypophosphatemic group. All in all, these data add weight to the importance of routine serum phosphate measurement in critically ill children, especially those with prolonged episodes of illness or infections. Early identification and correction of hypophosphatemia is likely to reduce the time in PICU and enhance overall patient care [21, 22].

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CONCLUSIONS

It was concluded that hypophosphatemia is a common metabolic disturbance among critically ill children, which often worsens from the day of admission to day three of PICU stay. These findings of our study highlight that a single serum phosphate measurement at admission is insufficient for detecting all cases of hypophosphatemia. Therefore, a series of phosphate measurements during the PICU stay is recommended. This underscores the clinical value of routine serial phosphate monitoring rather than relying solely on admission values. Based on this evidence, it is recommended that pediatric intensive care protocols incorporate regular phosphate assessments to facilitate early detection and timely correction, potentially reducing PICU stay and improving outcomes.

Authors Contribution

Conceptualization: LK
Methodology: LK, MI, FZ[1]
Formal analysis: MI
Writing review and editing: LK, MI, FZ[1], FZ[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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