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Factors Involved in Predisposing Children with Critical Illness to Eventually Develop Hypophosphatemia at Zagazig University Hospitals

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Abstract

Background: Hypophosphatemia is a metabolic disorder that can have significant consequences and is frequently undiagnosed in critically ill children. While hypophosphatemia is typically characterized by nonspecific symptoms such as weariness and irritation, severe hypophosphatemia (less than 1.0 mg/dl) can result in much more severe complications including such decreased diaphragmatic contractility and cardiac arrhythmias.

Aim of the Study: Determine the prevalence of hypophosphatemia in critically ill children, as well as the clinical consequences and risk factors associated with the condition throughout patients' admission in the PICU.

Patients and Methods: A case-control study that was conducted over a period of one year, from July 2019 to June 2021, at PICU of Pediatrics Department, Zagazig University Hospitals.The study included 180 subjects that were classified into two groups, each of 90 subjects as follows; patients group, which included 90 cases, and the control group, which included 90 healthy infants and children.

Results: There was a statistically significant difference in weight, height percentile, ESR and CRP, hemoglobin level, TLC, PT, INR, alkaline phosphatase a serum, serum creatinine, PH, serum phosphorus level, presence of hypophosphatemia (20%), number of patients with hypophosphatemia, percent change in serum phosphorus, as well as percent change in serum phosphorus between the studied groups.

Conclusion: In our investigation, the obvious probable source of hypophosphatemia was prolonged TPN decision-making as well as sepsis. In the PICU, mild to moderate hypophosphatemia occurred. Hypophosphatemia was related with an increased length of stay in the PICU and poor outcomes.

Keyword: Hypophosphatemia; Critical Ill children; Risk factors.

1. Introduction

Hypophosphatemia is a metabolic disorder that can have catastrophic consequences and is frequently undiagnosed in critically unwell children [1]. Phosphate ions are necessary for bone mineralization and are involved in a variety of other biological processes, including signal transduction, nucleotide metabolism, adenosine triphosphate (ATP) synthesis, and enzyme control [2].

In the majority of cases, hypophosphatemia manifests as fatigue and irritability. However, severe hypophosphatemia (less than 1.0 mg/dl) can result in more serious complications including such decreased diaphragmatic contractility, cardiac arrhythmias, myocardial reduction, and severe congestive cardiac insufficiency during the postoperative period of cardiac surgery [3], leukocyte dysfunction, and nephropathy.

Possible risk factors for developing hypophosphatemia in critically ill children involve malnutrition, prolonged fasting, sepsis [5], catecholamine administration, antacid administration, B2 agonist administration, trauma, diuretic administration, as well as steroid therapy [6], as well as excessive parenteral glucose administration and respiratory alkalosis [7].

2. Patients and Methods:

2.1. Study design:

This study was a case-control study that was conducted over a period of one year, from, July 2019 to June 2021, at PICU of Pediatrics Department, Zagazig University Hospitals.

2.2. Study Subjects:

The study enrolled 180 people, who were divided into two groups of 90 each:

A. Patients group: included 90 cases who attended the PICU Pediatrics department faculty of Medicine Zagazig University.
B. Control group: included 90 healthy infants and children.

2.2.1. Inclusion criteria:

Both sexes are included, as is age greater than one month but less than 18 years, as is presentation with a serious illness and ICU hospitalization, as well as PICU admission lasting more than seven days.

2.2.2. Exclusion criteria

Individuals who were malnourished had chronic diseases such as renal, hepatic, as well as cardiac disease, diabetic ketoacidosis, acute renal failure, hemodynamic instability, patients who were not in their age group, oncology cases, and starved patients, as well as those who remained less than seven days and those who refused to be registered in this study.

2.2.3. Patients consent

Before patients or their parents were included in the trial, written informed consent was obtained following explaining and discussing the entire study design. Additionally, the study received approval from the local ethical committee.

2.3. Methodology:

All patients were subjected to the following:

a- Full history taking:

- Present history; for critical illness, history of using medication especially which has a significant effect on phosphorus level(catecholamines, antacids, steroids, and diuretics.
- Past history of previous admission, chronic illness, drug intake and operation.

- Family history: similar condition, consanguinity and socioeconomic state.

b- Full general examination:

- Includes weight for age and height for age, vital signs and appearance, activity

c- Complete local examination:

- Cardiovascular system, central nervous system, musculoskeletal system, respiratory system and abdominal examination.

d- Investigation:

- Routine laboratory investigations include:
- Liver function tests (serum albumin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase), kidney function tests (serum creatinine, blood urea nitrogen) and random blood sugar (RBS) **(Cobas 8000, Roche diagnostics)**.
- Complete blood count (CBC) measured by (**Sysmex XN 2000, SIEMENS).**
- C- reactive protein (CRP) **(Cobas 8000, Roche diagnostics)** and erythrocyte sedimentation rate.
- Bleeding profile (prothrombin time(PT), international normalized ratio(INR) measured by **(CA 1500 Sysmex)**.

Serum electrolytes and minerals level (potassium, sodium, calcium, phosphorus, and magnesium) **(Cobas 8000, Roche diagnostics)**. Patients were classified according to serum phosphorus level into normal phosphorus level 2.5-4.5 mg/dl, mild hypophosphatemia with serum phosphorus 2-2.5 mg/dl, moderate hypophosphatemia 1-2 mg/dl and sever hypophosphatemia <1 mg/dl)

2.3.1. Statistical Analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using the Chi-square test and Fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. Mann Whitney test (used with non-normally distributed data) was used to compare medians of two groups, and an independent sample t-test (used with normally distributed data) was used to compare the means of two groups. To compare medians of more than two groups over time, Kruskal Wallis test was used. To compare the change in parametric data within one group before and after, paired-sample t-test is used. To compare change in non-parametric data within one group before and after, Wilcoxon signed-rank test is used. Spearman rank correlation coefficient was used to assess the strength and direction of a linear relationship between two variables. The levelof statistical significance was set at 5% ($P<0.05$). A highly significant difference was present if $p\leq0.001$.

3. Results

Table (1): Distribution of the studied patients according to cause of admission:

Diagnosis	N = 90	%
Heart failure	14	15.5
Respiratory failure	54	60
Sepsis	20	22.3
Head trauma	2	2.2

Table 1 demonstrates that sixty percent (60%) of the patients had respiratory failure while about 22.3% had sepsis, also 15.5% had heart failure, finally 2.2% head trauma.

Table (2): Correlation between the studied groups regarding ABG findings, blood electrolyte and minerals on admission and after 7 days of hospital stay:

****p≤0.001 is statistically highly significant t Independent sample t test**

Table 2 displays that there was statistically non-significant difference between the studied groups regarding serum sodium, potassium or calcium on admission. In

Blood electrolytes	Groups				Test	
	Patient group		Control group		t	p
	Mean ± SD	Range	Mean ± SD	Range		
Sodium on admission (mmol/l)	140.17 ± 3.37	135 – 145	139.72 ± 3.23	135 – 145	0.904	0.367
Sodium after7 days (mmol/l)	139.16 ± 8.41	123 – 157				
p	0.221					
Potassium on admission (mmol/l)	4.28 ± 0.48	3.5 – 5	4.2 ± 0.44	3.5 – 5	1.148	0.253
Potassium after 7 days (mmol/l)	4.26 ± 0.55	3.3 – 5.4				
p	0.402					
Calcium on admission (mg/dl)	9.72 ± 0.98	8 – 11.5	9.85 ± 0.99	8.1 – 11.5	0.839	0.403
Calcium after 7 days (mg/dl)	9.63 ± 0.98	7.9 – 11.5				
p	<0.001**					
ABG	**Groups**				**Test**	
	Patient group		**Control group**		**t**	**p**
	Mean ± SD	**Range**	**Mean ± SD**	**Range**		
PH on admission	7.32 ± 0.043	7.25 – 7.4	7.401 ± 0.03	7.35 – 7.45	13.637	<0.001**
PH after 7 days	7.399 ± 0.031	7.35 – 7.45				
P (paired t)	<0.001**					
PCO2on admission (mmhg)	35 ± 4.37	30 – 42	39.14 ± 3.84	36 – 45	6.573	<0.001**
PCO2 after 7 days (mmhg)	34.967 ± 4.98	27 – 48				
P (paired t)	0.888					
PHCO3 on admission (mmol/l)	23.3 ± 4.6	18 - 23	25.5 ± 4.12	21 - 24	0.543	0.876
PHCO3 after 7 days (mmol/l)	21.3 ± 3.12	19- 24				
P (paired t)	0.321					

patients group, there was non-significant change in sodium or potassium; however, there was significant decrease in serum calcium after 7days.

There was statistically significant difference between the studied groups regarding PH on admission. While, there was statistically non-significant difference between them regarding PCO2 or PHCO3on admission. In patients group, there was non-significant change in PH, PCO2 or PHCO3over time.

Table (3): Correlation between percent change in serum phosphorus and the age, anthropometric measures and duration of PICU stay, duration of mechanical ventilation and CRP among patients group:

Parameters	Percent change in serum phosphorus	
	(r)	P
Age	0.106	0.322
Weight	0.016	0.884
length	0.031	0.772
duration of hospital stay	-0.015	0.891
Duration of MV days	0.038	0.721
CRP after 7 days	-0.256	0.345

r Spearman correlation coefficient p>0.05 is statistically non-significant

Table 3 shows that there was statistically non-significant correlation between percent change in serum phosphorus and either patient age, anthropometric measures or duration of MV days. While the correlation was negative with hospital stay duration and CRP after 7 days of admission but statistically non-significant too.

Table (4): Relation between hypophosphatemia and normal cases of patients group regarding drugs used in PICU:

Parameter	Hypophosphatemia N=18	Normo-phosphatemia N=72	Test X^2	P
Drugs:	N (%)	N (%)	FET	<0.001
Furosemide (n=20)	18 (90%)	2 (10%)		
Dopamine (n=18)	14 (77.8%)	4 (22.2%)	FET	<0.001
Steroids (n=28)	16 (88.8%)	12 (16.7%)	8.84	<0.001

**** P-value <0.001 is highly significant**

Table 4 demonstrates statistically significant relation between hypophosphatemia and drugs used for treatment in PICU, as most of patients received furosemide (90%), dopamine (77.8%) and steroid (88.8%).

4.Discussion

Hypophosphatemia is a metabolic disorder that can have catastrophicconsequences and is frequently undiagnosed in critically unwell children [1].

Phosphate is a precursor to a variety of intermediary molecules involved in critical physiological processes, including adenosine triphosphate, 2,3 diphosphoglycerate, and intracellular chemical messengers (e.g., cyclical adenosine monophosphate, cyclical guanosine monophosphate). Electrolyte imbalances typically occur in critically ill patients throughout their stay in the PICU. Phosphate imbalance is a common electrolyte condition. Such individuals are at a higher risk of morbidity. Hypophosphatemia is a metabolic abnormality that can have catastrophic consequences and is frequently undiagnosed in critically ill children (CIC) [9].

Hypophosphatemia is typically nonspecific and manifests as fatigue as well as irritability. However, severe hypophosphatemia (less than 1.0 mg/dl) can result in more severe complications such as decreased diaphragmatic contractility, cardiac arrhythmias, myocardial reduction, and severe congestive cardiac insufficiency during the postoperative period of cardiac surgery [8].

The purpose of this study was to determine the prevalence of hypophosphatemia in children admitted to our PICU, Pediatrics Department, Faculty of Medicine, Zagazig University, and to predict the risk and outcomes related with this disorder.

Hypophosphatemia was prevalent in severely unwell children in this case-control study. Hypophosphatemia was prevalent in critically ill children admitted to the PICU at a rate of 20%, as we detected 18 patients out of 90 CIC on admission. By conducting a seven-day follow-up on the patients' group. Chest issues (pneumonia, pneumothorax, pleural effusion, and pulmonary edoema) worsened by respiratory failure accounted for 60% (54 patients out of 90 CIC) of admissions, followed by sepsis at 22.3 percent (20 patients out of 90 CIC). 15.5 percent (14 patients out of 90 CIC) and finally, 2.2 percent for head trauma (2patients out of 90 CIC). According to Rady and Khalek Mohamed (2014) [10], 56% of patients with respiratory problems were hypophosphatemic. Similarly, Santana e Menses et al. (2009) [1] discovered that patients with respiratory disease were more likely than other subjects to have hypophosphatemia. Additionally, Fiaccadori et al. (1994) [11] discovered hypophosphatemia in 25% of adult patients hospitalized to the intensive care unit with chronic obstructive pulmonary illness. Kilic et al. (2012) [12] indicate that hypophosphatemia may have exacerbated their respiratory issues by causing muscle weakness and hypotonia.

CRP levels were statistically substantially higher in the patients' group than in the control group upon admission in the current investigation. Following seven days in the PICU, there has been no major change in CRP in the patients' group. The percent change in serum phosphorus and the CRP level on admission had a statistically non-significant negative correlation. This was consistent with the findings of Rady and Khalek Mohamed (2014) [10], who discovered a substantial correlation between CRP and positive cultures and hypophosphatemia. Additionally, Antachopoulos et al. (2002) [13] discovered a substantial negative connection between serum phosphate and CRP when researching acute viral illness in pediatrics, excluding severely sick children. Additionally, Barak et al. (1998) [14] report a correlation between infections and sepsis and hypophosphatemia.

On admission, there was no statistically significant difference in serum sodium, potassium, or calcium between both the study groups. There was no significant change in sodium or potassium levels in the patients' group; nonetheless, disturbances in phosphate homeostasis are frequently associated with aberrant calcium and bone mineralization. As a result, serum calcium levels in the patients' group were significantly lower after seven days than on admission (9.720.98 and 9.360.98) but remained within standard range. Additionally, the patients' group had a statistically significant drop in serum phosphorus upon admission compared to the control group (2.62 0.115 and 3.915 0.577). However, there was a substantial drop in phosphorus in the patients' group over time; also, there was no statistically significant difference in serum phosphorus levels on admission or after seven days between younger and older patients (less than three years).

Between the % change in serum phosphorus and serum potassium in the patients' group, there was a statistically significant negative association. There was no correlation between the percent change in serum phosphorus and the percent change in serum calcium or sodium. According to Rady and Khalek Mohamed (2014) [10], the mean serum phosphorus level was (3.5 mg/dl on day 1 and 3.7 mg/dl on day 7).The mean serum phosphorus level was significantly lower in children under three years of age than in those over three years of age. De Menezes et al. (2006) [8] discovered that 32 of 42 patients (76.2 percent) had hypophosphatemia, with a median level of 3.1 0.7 mg/dL. According to Shah et al. (2016) [9], the estimated phosphate levels at D1 and D3 were 3.7 (2.9, 4.4) mg/dl and 3.2 (2.5, 3.9) mg/dl, respectively.

On admission and then after seven days, the arterial blood gases (ABGs) for our patients' group were within normal limits: PH (7.32 0.043 and 7.399 0.031), Hco3 (25.34.6 and 24.33.12), and Pco2 (35 4.37 and 34.967 4.98). There was no significant change in Pco2, Hco3, or PH in the patients' group.

Our investigation discovered a substantial correlation between medicines that affect phosphorus levels, such as steroids, dopaminergic agents, and furosemides used in the PICU, and hypophosphatemia. By contrast, Rady and Khalek Mohamed (2014) [10] discovered no relationship between hypophosphatemia and any of the medicines known to reduce serum phosphorus levels as a side effect of their use (catecholamines, antacids, anticonvulsants, steroids, or diuretics). On the completely contrary, Santana e Meneses et al. (2009) [1] discovered that dopamine was associated with hypophosphatemia in 2009 PICU patients, which they attributed to increased urine phosphorus excretion. Additionally, Subramanian and Khardori (2000) [15] established a link between hypophosphatemia and diuretics or steroids.

5.Conclusion

Hypophosphatemia is frequent in children admitted to PICU. Our study highlights the importance of serum phosphorus level as predictive for the course of illness and outcome. The apparent acceptable cause of hypophosphatemia in our study is delayed TPN decision and sepsis. Mild to moderate hypophosphatemia developed in PICU.

Hypophosphatemia was associated with prolongation of duration of PICU stay and bad outcome.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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