



Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes



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HIGHLIGHTS

- Hypophosphatemia was common in the first 7 days of pediatric intensive care unit hospitalization.
- Significant association between hypophosphatemia and duration of use of mechanical ventilation.
- Hypophosphatemia was associated with prolonged pediatric intensive care unit length of stay.
- Hypophosphatemia was associated with use of furosemide, dopamine, steroid and β_2 agonist.
- Good nutrition of critically ill children has an important role in improving their clinical condition.

ARTICLE INFO

Article history:

Received 10 May 2017
Received in revised form
30 July 2017
Accepted 30 July 2017

Keywords:

Hypophosphatemia
Critical illness
Malnutrition
Phosphorus

ABSTRACT

Background: Hypophosphatemia is one of the common disorders that develop in critically ill patients. It has potential complications and is often unrecognized in those patients.

Objective: Determining the incidence of hypophosphatemia in critically ill children, its association with clinical outcomes and the possible risk factors.

Methods: 50 patients were enrolled in the study. Levels of serum phosphate were measured on day 1 and day 7 of PICU (Pediatric intensive care unit) stay. The following variables were analyzed: age, gender, diagnosis on admission, malnutrition, phosphorus intake, clinical severity score on admission OFI (Organ Failure Index) and daily scores PELOD (Pediatric Logistic Organ Dysfunction), sepsis, use of dopamine, furosemide and steroids and assessment of nutrition by z scores.

Results: The incidence of hypophosphatemia on admission was 42%. On seventh day of admission incidence of hypophosphatemia was 62%. Malnutrition was present in 24% of patients, serum phosphorus level was significantly lower in malnourished than in well-nourished children (**p value = 0.018**). Hypophosphatemia was associated with prolonged PICU length of stay (**p < 0.001**) but was not associated with increased mortality (**p = 0.13**). Cases on parenteral nutrition and insufficient oral intake while on mechanical ventilator significantly showed hypophosphatemia (**p = 0.017**). Hypophosphatemia was associated with the use of furosemide, dopamine, steroids and β_2 agonist.

Conclusion: Hypophosphatemia was common in the first 7 days of PICU hospitalization and was associated with prolonged PICU stay, Significant association between hypophosphatemia and duration of use of mechanical ventilation, use of furosemide, dopamine, steroids and β_2 agonist.

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1. Introduction

Phosphate is a constituent of various intermediate compounds involved in key physiological processes such as adenosine triphosphate, 2,3-diphosphoglycerate and intracellular chemical messengers (e.g., cyclical adenosine monophosphate, cyclical

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guanosine monophosphate) [1,2]. Electrolyte disorders frequently develop in critically ill patients during the course of stay in PICU [3]. Phosphate disturbance is one of those frequently encountered electrolyte disorders. These are at increased risk of morbidity [4]. In general hospital populations, the prevalence of moderate hypophosphatemia ranges between 0.43% and 3.1% [5,6], and 45% of all hospital hypophosphatemia cases occur in the ICU population in this prospective study, hypophosphatemia was common in critically ill children that incidence of hypophosphatemia was 42% at admission. At seventh day incidence of hypophosphatemia was 62% and Potential risk factors in most patients with phosphate disturbance include malnutrition, which was present in 24% cases, sepsis was present in 34% of cases, drugs like catecholamine's 24% of cases, antacids 10% of cases, diuretics 36% of cases, steroid therapy 76% of cases [7].

Symptoms of hypophosphatemia tend to be nonspecific in the majority of cases and include fatigue and irritability. Lower level (less than 1.0 mg/dl) may lead to more hypophosphatemia serious problems such as reduced diaphragmatic contractility, cardiac arrhythmias, myocardial reduction and severe congestive cardiac insufficiency [8].

Phosphate disturbance has been reported to be associated with increased morbidity and mortality in critically ill patients such as respiratory failure, increase the duration of stay on mechanical ventilation, and increased PICU length of stay [9].

To date, the majority of studies have involved adults, but hypophosphatemia is generally underdiagnosed in children, where frequency and predisposing factors are not yet fully understood. Based on the premise that hypophosphatemia is a frequent, often undiagnosed disturbance in children, the aim of this study was to identify the incidence and risk factors for hypophosphatemia in critically ill children.

1.1. Aim of work

The aim of the study was to estimate the incidence of phosphate disturbance in critically ill children, study its clinical effects and risk factors in patients during their stay in PICU.

1.2. Patients and methods

The current cross sectional study was conducted at the Departments of Pediatrics and Clinical Pathology, Faculty of Medicine, Benha University Hospital, during the period from January 2016 to September 2016. After approval of the study protocol by the local research and ethical Committee of Faculty of Medicine, Benha University and after obtaining parents' written fully informed consent; 50 critically ill children were enrolled in the study. The study included all critically ill children from both sexes from 1 month and up to 18 years admitted to PICU in Benha university hospital. The cases included patients attending with pneumonia, central nervous system infection, acute heart failure, status asthmatics, and sepsis. Exclusion criteria: In our study, we excluded patients outside age group, PICU stay less than 7 days, patients refused to be involved in the study.

Blood specimens of serum phosphorus levels on admission and the second sample on seventh after admission were collected [5 ml whole blood collected in Red top tube (clot activator) from subjects], the specimens were centrifuged and the serum or plasma removed from the cells within 2 h of collection. Samples were frozen at -15°C to -20°C . Frozen samples were thawed only once. Analyze deterioration may occur in samples that are repeatedly frozen and thawed. DIALAB and EASYLYTE was used for samples analysis.

1.3. Clinical data collection

The study group was subjected to: Complete history taking including history of chronic illness, primary admission diagnosis and history of medications used especially that having significant effect on phosphate level. General examination and systemic review was done. Presence of infection or sepsis according to center for disease control and prevention [10]. Detecting severity of illness using (OFI) score and (PELOD) score [11].

Nutritional state classification, the weight-for-age (W/A) percentile is used as the anthropometric indicator for children younger than 2 years, whereas body mass index is used for children older than 2 years. By using percentiles developed for Egyptian children.

The target caloric requirements are calculated according to the recommended daily allowance and the route of administration based on age, sex and weight.

1.4. Laboratory analysis

Laboratory investigations including: CBC, CRP, ABG, random blood sugar, serum electrolytes, renal and liver function tests were done. Blood specimens of serum phosphorus levels on admission and the second sample on seventh day after admission.

Statistical analysis: Data were analyzed by (SPSS)

- **Description of quantitative** variables as mean, SD for normally distributed data and median value for abnormally distributed data.
- **Description of qualitative** variables as number & percentage.
- **Student t-test** was used to assess the statistical significance of the difference between two population means in study involving independent samples.
- **Chi-square test** was used to compare qualitative variable between independent groups samples.
- **Mann-Whitney U test** (Z value) for two independent samples of abnormal data distribution.
- **Level of significance**
 - Probability level (P-value) ≥ 0.05 = Non significant (NS).
 - P-value < 0.05 = Significant.
 - P-value < 0.001 = highly significant

Table 1
Demographic and clinical characteristics of study population.

Variable	No. (N = 50)	% (100.0)
Age (m)	Mean \pm SD (Median) Range	14.3 \pm 13.9 (9) 3–84
Sex	Male Female	26 24
Weight (kg)	Mean \pm SD Range	7.5 \pm 3.2 3–20
Length (cm)	Mean \pm SD Range	72.3 \pm 12.4 55–120
BMI (kg/m ²)	Mean \pm SD Range	13.8 \pm 2.4 7.1–19.6
Admission diagnosis		
Respiratory disorder	30	60%
Heart failure	7	14%
Sepsis	15	30%
Malnutrition	9	18%
Mechanical ventilated	18	36%
Acute encephalopathy	8	16%
Septic shock	3	6%
Trauma	1	2%

SD Standard deviation.

Table 2
Matching serum phosphorus levels on admission and on the 7th day among the studied group.

	Hypophosphatemia 7 TH Day		Normophosphatemia 7th Day		Total Count % within Ps
	Count	%	count	%	
Normophosphatemia on admission	18	62.1%	11	37.9%	29 100%
Hypophosphatemia on admission	1	4.8%	20	95.2%	21 100%
Total	19	38.0%	31	62.0%	50

Mc Nemar's test was used $P = 0.006$ (S).

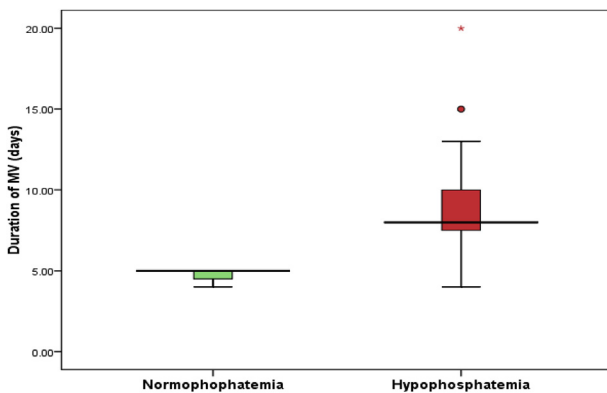
2. Results

In our study 50 critically ill children admitted to the PICU were included in the study. The baseline characteristics of the patients are shown in Table 1.

During the study period 42 patients of the studied group had been discharged and 8 patients died. On admission, incidence of hypophosphatemia was 42% (n 21) and incidence of normophosphatemia was 58% (n 19). While on seventh day of admission incidence of hypophosphatemia was 62% (n 31) and incidence of normophosphatemia was 38% (n 19) Table 2 Fig. 1.

On admission the majority of cases were suffering of respiratory problems as pneumonias, bronchiolitis, bronchial asthma, pneumothorax, pleural effusion and stridor. Thirty six percent (n = 18) of all cases were mechanically ventilated ($p = .02$). Fifteen patients of them were hypophosphatemic (n = 15 vs. n = 3) and spent more days being ventilated (8days vs. 5 days) ($P = 0.017$) Tables 3 and 4.

Box plot 1: for the median and range of duration of MV according to phosphorus level.



MV, mechanical ventilator.

Regarding PICU stay there was highly significant difference between normophosphatemic group and hypophosphatemic group ($P < 0.001$) Table 4.

Malnutrition was present in 24% (n = 12) of cases. There was significant association between malnutrition and hypophosphatemia ($p = 0.018$) Table 6.

Also there was a significant association between hypophosphatemia and the time to attain target caloric requirements by enteral route ($P = 0.005$). The median times to attain target caloric requirements by enteral route were 3/5 days in normo/hypophosphatemic groups respectively ($P = 0.005$) Table 5.

Seventeen cases (34%) were septic 10 of them had hypophosphatemia with no significant association ($P = 0.74$) Table 6.

Hypophosphatemia was associated with the use of furosemide

($P = .002$), steroids ($P = 0.005$), β_2 agonist ($P = .018$) and dopamine ($P = .018$) Table 6.

3. Discussion

In this prospective study, hypophosphatemia was common in critically ill children (prevalence 62%) during the first seventh days of PICU admission. It was independently associated with prolonged PICU length of stay. It was also associated with increased duration of stay on mechanical ventilator, but was not associated with increased mortality.

The prevalence of hypophosphatemia in this study was slightly higher than previous reports in critically ill children which showed the prevalence of 60% [12,13]. This observation may be due to increased frequency of serum phosphate measurement in our study. However, from all the reports, it is clear that there is higher prevalence of hypophosphatemia in PICU patients.

This study showed an independent association between hypophosphatemia and prolonged PICU length of stay ($P < 0.001$) the median time was 10 days in hypophosphatemic compared to 8 days in normophosphatemic group. Similar observation has been reported by Kilic et al. [13] ($P = 0.001$), Shah et al. [14] ($P = 0.005$) who reported that hypophosphatemia was associated with prolonged PICU length of stay > 6 d). Many children were admitted in PICU for respiratory support. It was shown that hypophosphatemia may impair diaphragmatic contractility during acute respiratory failure and may be one of the most important causes for difficult weaning from mechanical ventilator [15]. Hypophosphatemic patients spent more time on mechanical ventilator. In our study we found independent association between hypophosphatemia and prolonged mechanical ventilation as most patients was hypophosphatemic before the need for mechanical ventilation so hypophosphatemia lead to prolonged ventilator support.

Malnutrition is one of the risk factors for hypophosphatemia [16,17]; In our study there was a significant association between hypophosphatemia and malnutrition ($P = 0.018$). This agree with Souza de Meneses et al. [18] ($P = 0.04$) and in severe malnutrition ($P = 0.0182$). Santana e Meneses et al. [12] also reported significant association between malnutrition and hypophosphatemia ($p = 0.01$). In contrast Kilic et al. [13], ($p = 0.2$) and Shah et al. [14] ($p = 0.5$) reported that there was no significant association between malnutrition and hypophosphatemia.

In our study the time to attain target caloric requirements by enteral route demonstrated correlation with hypophosphatemia ($P = 0.005$) this agree with Kilic et al. [13], ($P = 0.006$).

Sepsis is considered as an important risk factor for hypophosphatemia [19–21]. Although, greater proportion of septic patient were hypophosphatemic but this observation did not reach statistical significance.

In our study there was a significant association between hypophosphatemia and furosemide use ($P = 0.002$). Santana e Meneses et al. [12] ($P = 0.09$) and Kilic et al. [13] ($P = 0.04$). Agreed with us

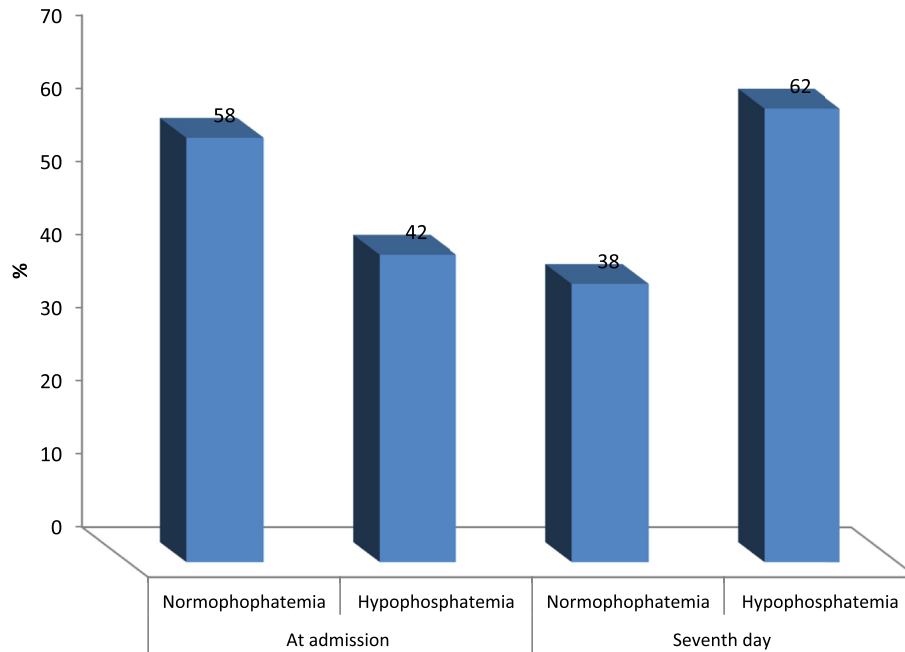


Fig. 1. Incidence of Hypophosphatemia among the studied sample.

this may result from the fact that Loop diuretics have effects on phosphate excretion, probably due to the fact that these drugs act on the loop of Henle where phosphate reabsorption is minimal. However, these drugs also exhibit a weak carbonic anhydrase activity, which can explain their weak phosphaturic effect [22]. In contrast Souza de Meneses et al. [18] reported that no significant association was found ($P = 0.7$).

In our study there was a significant association between hypophosphatemia and dopamine use ($P = 0.018$) This agree with Santana e Meneses et al. [12] ($P = 0.01$). This occur due to the movement of Pi from the extracellular to intracellular compartment

is common. It is related to the formation of Pi-containing intermediates of glycolytic metabolism [23]. In contrast Shah et al. [14] reported no significant association between dopamine use and hypophosphatemia ($P = 0.37$).

In our study there was a significant association between hypophosphatemia and steroids use ($P = 0.005$) this agree with Loudenot et al. [24] ($P = 0.001$) and Kilic et al. [13] ($p = 0.04$). In contrast with our study Souza de Meneses et al. [18] reported no association between steroid and hypophosphatemia ($p = 0.5$).

In our study there was a significant association between hypophosphatemia and β_2 agonist use ($P = 0.018$). This agrees with Kilic et al. [13] ($p = 0.026$).

The strength of the study is that it was a prospective study. Serum phosphate measurements were done at two time points to get an exact idea of serum phosphate level. In addition, the concept of the study might give some research ideas to the intensivists practicing in the resource limited settings, where total parenteral nutrition with phosphate is not available.

3.1. Conclusion

Hypophosphatemia is frequent in children admitted to PICU if they cannot be fed early by enteral route. More length of stay and ventilator support was associated with hypophosphatemia. Drugs

Table 3
Comparing serum phosphorus level according to use of mechanical ventilation.

		P		Total
		Normophosphatemia	Hypophosphatemia	
MV: No	Count	16	16	32
	% within P7s	84.2%	51.6%	64.0%
Yes	Count	3	15	18
	% within P7s	15.8%	48.4%	36.0%
Total	Count	19	31	50
	% within P7s	100.0%	100.0%	100.0%

$\chi^2 = 5.43$ $P = 0.02$ (S).
MV, mechanical ventilator. S, significant.

Table 4
Comparing duration of MV and PICU stay according to serum phosphorus level.

Variable	Normophosphatemia (N = 3)		Hypophosphatemia (N = 15)		MWU test	P value
	Median	Range	Median	Range		
Duration of MV (days)	5.0	4–5	8.0	4–19	2.39	0.017 (S)
Variable	Normophosphatemia (N = 19)		Hypophosphatemia (N = 31)		MWU test	P
	Median	Range	Median	Range		
Duration of PICU stay (days)	8.0	7–13	10.0	7–20	3.82	<0.001 (HS)

MV, mechanical ventilator. PICU, pediatric intensive care unit. HS, highly significant. MWU test, Mann Whitney U test.

Table 5
Time to attain target caloric requirement.

Variable	Normophosphatemia (N = 19)		Hypophosphatemia (N = 31)		MWU test	P value
	Median	Range	Median	Range		
Time to attain target caloric requirement (days)	3.0	0.25–9	5.0	0.5–12	2.98	0.005 (S)

MWU, Mann Whitney u test.

Table 6
Risk factor for hypophosphatemia.

Variable	N	Percentage of patients	Hypo-phosphatemia	Normo-phosphatemia	P value
Malnutrition	12	24	11	1	0.018
Drugs					
Furosemide	18	36	15	3	0.002
Dopamine	12	24	11	1	0.018
Steroid	38	76	28	10	0.005
β2 agonist	29	58	22	7	0.018
Ranitidine/omeprazole	5	10	4	1	0.31
Sepsis	17	34	10	7	0.74

like furosemide, dopamine, β2 agonist and steroids lead to hypophosphatemia.

3.2. Recommendation

Our recommendations are the following:

- 1-Early detection of hypophosphatemia in critically ill children is important to reduce duration of use mechanical ventilation and decrease time of pediatric intensive care unit stay.
- 2-Good nutrition of critically ill children has an important role in improving their clinical condition.
- 3-Further studies may be performed on a large sample size of children with critical illness to evaluate the magnitude of the problem.

Ethical approval

The study was approved by the research and ethical committees of the contributing hospital.

Funding

There was no funding.

Author contribution

Ahmed Nabih El Shazly: Substantial contributions to the conception and design of the work and acquisition of data.
Doaa Refaey Soliman: Drafting the work.

Conflicts of interest

There was no conflict of interest.

Guarantor

Ibrahim Abd El Naby Gad.

Consent

Written consent was taken from all patient.

Registration of research studies

Researchregistry 2501.

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