Phosphorus abnormalities in a paediatric intensive care unit in North India

***Taruna Vijaywargiya[1], Satyajeet Maurya[2], Sitikant Mohapatra[1]**

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Abstract

Introduction: Critical illness triggers severe acute phase response which is associated with several metabolic derangements. Serum phosphorus level abnormalities are common among them and go unnoticed in sick children.

Objectives: To determine the prevalence of phosphorus abnormalities in sick children admitted to the paediatric intensive care unit (PICU) and its association with various clinical outcomes.

Method: We conducted a prospective, non-interventional study at a PICU in North India. During an 18-month period we investigated the incidence of phosphorus abnormalities in patients admitted to the PICU on admission and followed the course at day 3 and day 7 during their stay.

Results: The prevalence of phosphorus level abnormalities was 44.2% on admission to PICU; 34.9% patients had hypophosphataemia while 9.3% had hyperphosphataemia. Hypophosphataemia was significantly associated with severe malnutrition (p=0.041) while hyperphosphataemia was associated with organ failure (p=<0.001). Although the need for mechanical ventilation, duration of PICU stay and mortality were higher in hypophosphataemic patients and PRISM score was higher in hyperphosphataemic patients, these differences were not statistically significant. Changes in the baseline phosphorus levels after PICU stays of 3 days (p=0.346) and of 7 days (p=0.782) were not statistically significant.

Conclusions: Phosphorus abnormalities were highly prevalent in ill children admitted in the PICU. Hypophosphatemia was more common and was significantly associated with severe malnutrition while hyperphosphatemia was significantly associated with organ failure.

(Key words: Critically ill, Hypophosphataemia, Hyperphosphataemia, Children, Outcome, PICU)

Introduction

Phosphorus is an important part of energy metabolism, cellular signalling, nucleic acid metabolism, membrane integrity and bone mineralization[1]. Inorganic phosphorus is essential for the regeneration of high-energy phosphates such as adenosine triphosphate, 2,3-diphosphoglycerate and intracellular chemical messengers (e.g., cyclic adenosine monophosphate, cyclic guanosine monophosphate)[2]. The consequences of severe hypophosphataemia (less than 2.0 mg/dl) on various organ systems in critical care setting is attributed to deficiency in intermediate compounds, leading to severe muscle weakness, including respiratory and cardiac failure contributing towards high morbidity and mortality[3,4]. Therefore, it is crucial to maintain normal blood phosphorus levels. There have been a few studies in sick children to assess the prevalence and outcomes of hypophosphataemia[5-8] but hyperphosphatemia has not been studied much in sick children.

Objectives

To determine the prevalence of phosphorus abnormalities in sick children on admission to the Paediatric Intensive Care Unit (PICU) and its association with various clinical outcomes.

Method

A prospective cross-sectional study was conducted at the PICU, Vivekananda Polyclinic Institute of Medical Science, Lucknow India, on 129 patients aged 1 month to 16 years, who were hospitalized in PICU over 18-months between January 2019 and May 2020.

Inclusion and exclusion criteria: All children admitted to PICU, aged 1 month to 16 years, were included in study but patients with a history of chronic renal disorder, on renal replacement therapy, chronic diarrhoea, leukaemia, who left against medical advice and who did not give consent were excluded.

Complete history, clinical examination, anthropometry (weight, height, head circumference and mid upper arm circumference), demographic information, severity of illness using paediatric risk of mortality (PRISM) III[9] scores were noted on

[1]*Senior Consultant, Department of Paediatrics, Vivekananda Polyclinic Institute of Medical Sciences, Lucknow, India,* [2]*ADMO (IRHS), Subdivisional Railway Hospital, Gonda, India*
**Correspondence:* tarunavijay09@gmail.com
https://orcid.org/0009-0006-3452-7398

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admission. Organ failure was assessed according to paediatric organ dysfunction criteria, the diagnostic criteria for paediatric multi organ dysfunction syndrome (MODS).

Sepsis profile, blood gas analysis and blood chemistry were done on admission, including serum phosphorus levels by 'timed endpoint method'. Repeat serum phosphorus levels were assessed in samples taken on day 3 and day 7 in those who remained in the PICU. Grades of sepsis were classified according to the international consensus conference of sepsis[10].

Serum phosphorus was classified as normal, hypo or hyper according to reference ranges obtained from the Nelson textbook of paediatrics[11], viz. Phosphorus (Inorganic): 1-3 years: 3.8-6.5mg/dL; 4-11 years: 3.7-5.6mg/dL; 12-15 years: 2.9-5.4mg/dL.

Duration of mechanical ventilation if needed, total duration of PICU stay and outcome (discharged or died) were recorded.

Ethical issues: Approval to conduct study was obtained from the Institutional Ethics Committee of Vivekananda Polyclinic Institute of Medical Science, Lucknow, India (Thesis protocol code no. 24/2019) on 22.01.2019. Written informed consent was obtained from parents/guardians of study participants.

Statistical analysis: Statistical Package for Social Sciences version 21 was used. The values were represented in numbers and percentages, mean ± SD. Chi-square test, independent samples 't' test, analysis of variance (ANOVA) and Wilcoxon signed rank tests were used to compare the data. A 'p' value less than 0.05 was considered to be statistically significant. Linear correlation was evaluated using Pearson's correlation coefficient.

Results

Total 164 patients were admitted in PICU in the study period, of which 35 were excluded as per exclusion criteria. So, 129 patients were enrolled in study (Figure 1). Table 1 shows the baseline characteristics of the study population.

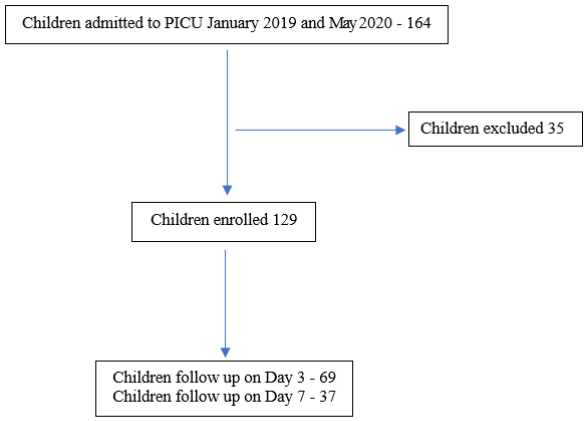

Figure 1: ***Study flow figure***

Table 1: ***Baseline characteristics of study population (n=129)***

Characteristic	Result
Age	
1 month to 5 years – n (%)	82 (63.6)
6 years to 12 years – n (%)	37 (28.7)
13 years to 16 years – n (%)	10 (07.8)
Gender	
Female – n (%)	43 (33.3)
Male – n (%)	86 (66.7)
Mean height ± SD (range) cm	95.52 ± 34.34 (46-165)
Mean weight ± SD (range) kg	15.87 ± 12.74 (1.65-61.2)
Mean head circumference ± SD (range) cm	45.85 ± 6.38 (30-59)
Severely malnourished – n (%)	10 (07.8)

Average Glasgow Coma Scale (GCS) score at admission was 11.22 ± 3.65 (ranged 3 to 15). There was organ failure in 17.1% cases, sepsis in 65.9% cases and 21.7% cases required mechanical ventilation. Duration of PICU stay ranged from 1 to 18 days (mean 4.34 ± 3.13 days). Of the 129 cases 108 (83.7%) patients were discharged while 21 (16.3%) expired. In our study population 74.4% presented with illness of more than 3 days duration, 33.3% presenting after 7 days of onset of illness.

A total 235 serum phosphate measurements were carried out 129, 69 and 37 on day 1, day 3 and day 7 respectively. Table 2 shows the phosphorus levels of the study population.

Table 2: ***Phosphorus levels of study population***

Day	Mean ± SD (mg/dl)	Range (mg/dl)
Admission to PICU	4.36 ± 1.56	1.5 - 11.4
Day 3	4.13 ± 1.59	1.5 – 12,0
Day 7	4.14 ± 1.9	2.1 – 13.0

Prevalence of hypophosphataemia on day 1, day 3 and day 7 was 34.9%, 42.0% and 51.4% respectively, while that of hyperphosphataemia on day 1, day 3 and day 7 was 9.3%, 5.8%, and 8.1% respectively (Table 3).

Table 3: ***Phosphorus concentrations in the study population***

Day	Total number of patients	Hypophosphataemia n (%)	Normophosphataemia n (%)	Hyperphosphataemia n (%)
Admission	129	45 (34.9)	72 (55.8)	12 (09.3)
Day 3	69	29 (42.0)	36 (52.2)	04 (05.8)
Day 7	37	19 (51.4)	15 (40.5)	03 (08.1)

Table 4 shows the association of baseline phosphorus levels with various parameters at admission. Proportion of severely malnourished patients was higher in phosphorus deficient (40% vs. 34.5%) and raised phosphorus (30% vs. 7.6%) while proportion of normal nutritional cases was higher among cases with normal phosphorus (58% vs. 30%). This was statistically significant (p=0.041). Proportion of cases with organ failure was significantly higher among hyperphosphataemia patients compared to hypophosphataemia and normophosphataemia (33.3% vs. 15.6% & 15.3%) (p<0.001) (Chi square test).

Although the duration of mechanical ventilation and mortality were greater in hypophosphataemic group, no significant association was observed between hypophosphataemia and prolonged ventilator support and mortality (Chi square test).

PRISM III score of cases with normal phosphorus levels was lower compared to those with deficient and raised levels (7.06 ± 5.76 vs. 8.60 ± 6.25 and 10.50 ± 6.35) but the difference was not statistically significant (ANOVA test). Though the mean duration of PICU stay was lower among cases with normal phosphorus levels compared with deficient and raised phosphorus (3.82±3.03 vs. 4.93±3.21 & 4.17±3.33days), this difference was not statistically significant (ANOVA test). Mortality rate was higher among cases with deficient phosphorus compared to raised phosphorus and normal phosphorus levels (22.2% vs. 16.7% and 12.5%) but was not statistically significant (Chi square test).

Table 4: ***Association of phosphorus with various parameters at admission***

Parameter	Total (n=129)	Hypophosphataemia (n=45)	Normophosphataemia (n=72)	Hyperphosphataemia (n=12)	p-value
Age group					
1 month to 1year - n (%)	50 (38.8)	15 (30.0)	29 (58.0)	06 (12.0)	
2 to 5 years - n (%)	32 (24.8)	14 (43.8)	15 (46.9)	03 (09.4)	0.088
6 to 12 years - n (%)	37 (28.7)	16 (43.2)	18 (48.6)	03 (08.1)	
13 to 16 years - n (%)	10 (07.8)	0 (0)	10 (100.0)	0 (0)	
Gender					
Female - n (%)	43 (33.3)	13 (30.2)	28 (65.1)	02 (04.7)	0.235
Male - n (%)	86 (66.7)	32 (37.2)	44 (51.2)	10 (11.6)	
Nutrition					
Normal nutrition - n (%)	119	41 (34.5)	69 (58.0)	09 (07.6)	**0.041**
Severe malnutrition - n (%)	10	04 (40.0)	03 (30.0)	03 (30.0)	
System abnormality					
Central nervous system - n (%)	48	21 (46.7)	25 (34.7)	02 (16.7)	
Respiratory - n (%)	38	10 (22.2)	24 (33.3)	04 (33.3)	0.298
Others - n (%)	43	14 (31.1)	23 (31.9)	06 (50.0)	
Duration of symptoms					
<3 days - n (%)	33	11 (33.3)	21 (63.6)	01 (03.0)	
3-7days - n (%)	53	19 (35.8)	29 (54.7)	05 (09.5)	0.562
>7 days - n (%)	43	15 (34.9)	22 (51.2)	06 (14.0)	
GCS score <12 - n (%)	77	27 (60.0)	43 (59.7)	07 (58.3)	0.995
Organ failure - n (%)	22 (17.1)	07 (15.6)	11 (15.3)	08 (33.3)	**<0.001**
Sepsis - n (%)	85 (65.9)	28 (62.2)	50 (69.4)	07 (58.3)	0.613
Mechanical ventilation - n (%)	28 (21.7)	12 (26.7%)	14 (19.4)	02 (16.7)	0.592
PICU stay (days) – Mean ± SD		4.93 ± 3.21	3.82 ± 3.03	4.17 ± 3.33	0.175
Mortality - *n (%)*	21 (16.3)	10 (22.2)	09 (12.5)	02 (16.7)	0.382
PRISM - Mean ± SD		8.60 ± 6.25	7.06 ± 5.76	10.50 ± 6.35	0.120

GCS: Glasgow coma scale, PICU: paediatric intensive care unit, PRISM: Paediatric Risk of Mortality

Table 5 shows the change in baseline phosphorus levels during PICU stay. The changes in baseline phosphorus levels after PICU stay of 72 hours and of 7 days were not statistically significant.

Table 5: ***Change in baseline phosphorus levels during paediatric intensive care unit stay***

Phosphorus level	**Total (n=69)**	**Below normal (n=27)**	**Normal (n=36)**	**Above normal (n=06)**	**p-value Wilcoxon signed rank test**
At 72 hours					
Below normal	29	20	09	0	
Normal	36	07	27	02	Z=0.943; p=0.346
Above normal	04	0	0	04	
Phosphorus level	**Total (n=37)**	**Below normal (n=18)**	**Normal (n=16)**	**Above normal (n=03)**	**p-value Wilcoxon signed rank test**
At 7 days					
Below normal	19	12	07	0	
Normal	15	06	09	0	Z=0.277; p=0.782
Above normal	03	0	0	03	

Discussion

In the present study, the incidence of phosphorus deficiency was 34.9% at admission. This finding is in line with studies by El Shazly AN, *et al*[5] and El Beleidy A, *et al*[6] who observed phosphorus deficiency in 42% and 47% cases at the time of admission in ICU children respectively. On the other hand, Shah SK, *et al*[7] found hypophosphataemia in 71.6% of critically ill children and found increased loss of phosphate through urine as the major cause of hypophosphatemia in critical illness, while Shahsavarinia K, *et al*[8] in a study on 83 critically ill children observed phosphorus deficiency only in 10.8% of the children at admission.

In our study, we did not find a significant association of phosphorus status with age or gender but found phosphate abnormality (both hyper and hypo) to be significantly associated with malnutrition (p=0.041). Significant association of low phosphorus levels with malnutrition was also seen in studies by Santana-e-Meneses JF, *et al*[12] and El Shazly *et al*[5]. In contrast, Shah SK, *et al*[7] and Kilic O, *et al*[13] did not find such association.

In the present study we found that hyperphosphataemia was significantly associated with organ failure (p<0.001) but did not show any significant association with sepsis, need for mechanical ventilation, prolonged PICU stay. There are a few studies of hyperphosphatemia and its outcome in adult patients[14], but we could not find studies in children. Hypophosphataemia did not show any significant association with sepsis, organ failure, need for mechanical ventilation, prolonged PICU stay and mortality which are similar to result of those of de Menezes FS, *et al*[15], Ruiz Magro P, *et al*[16] and Agrwal S, e*t al*[17]. On the other hand, Rady HI, *et al*[18] found a significant association of phosphorus levels with the need for mechanical ventilation, El Shazly *et al*[5] found a significant association of phosphorus levels with prolonged PICU stay but not with mortality, while Kilic O, *et al*[13] found a significant association of hypophosphataemia with the duration of mechanical ventilation and ICU stay.

Sepsis is considered as an important risk factor for hypophosphatemia[19]. In our study, although a greater proportion of septic patient were hypophosphataemic this was not statistically significant. Our study revealed hypophosphataemia in 42% of our patients at day 3 of admission and 51.4% of surviving/continuing patients on day 7 of admission. Shahsavarinia K, *et al*[8] found 26.5% between fourth to the sixth day, which increased to 34.9% between seventh to the tenth day of admission. A rise in prevalence of phosphorus deficiency has also been noted by El Shazly *et al*[5] from 42% of cases on day 1 to 62% of cases on day 7 and El Beleidy A, *et al*[6] from 56% on day 3 to 71% on day 10 of admission. Prevalence of hyperphosphatemia decreased from 9.3% at admission to 5.8% on day 3, but increased to 8.1% at day 7. The trend of change in phosphorus levels did not show a significant change over time.

In view of the disease-specific prevalence of these abnormalities, it is essential that instead of generalized studies in PICU patients, these abnormalities should be studied in context with specific critical illnesses separately. Further studies on larger sample size in specific patient populations are recommended.

Conclusions

In patients admitted to PICU, hypophosphataemia was present in 34.9% and hyperphosphataemia in 9.3%. Phosphorus abnormalities were not significantly associated with long PICU stay,

mechanical ventilation or sepsis. Hypophosphataemia was significantly associated with malnutrition while hyperphosphatemia was significantly associated with organ failure.

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