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HYPOPHOSPHATEMIA FOLLOWING SEVERE TRAUMATIC BRAIN INJURY IS ASSOCIATED WITH INCREASED RISK OF MORTALITY
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HYPOPHOSPHATEMIA FOLLOWING SEVERE TRAUMATIC BRAIN INJURY IS ASSOCIATED WITH INCREASED RISK OF MORTALITY

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ABSTRACT

Background: **Electrolyte dysfunctions following traumatic brain injury have been associated with poor outcomes. The aim of this study was to determine the incidence of serum phosphate ion abnormalities and their association with specific clinical, radiological and acid-based parameters.**

Methods: **This was a prospective cross-sectional study of 95 patients with severe head injury hospital admitted between November 2019 and February 2020. Data collected included patient demographics, injury mechanisms, pre-hospital interventions, clinical examination findings, CT Scan head findings, serum electrolyte findings (at admission and 48 hours later), arterial blood gas, and outcome (30 days). The data collected was entered in the Social Sciences Statistical Package for analysis.**

Results: **Hypophosphatemia was reported in 40 (42.1%) and 29 (48.3%) of cases, while hyperphosphatemia was reported in 5 (5.3%) and 5 (8.3%) of cases at admission and 48 hours post-admission. Low phosphate levels were significantly correlated with pre-hospital use of intravenous fluids (P=0.041), mannitol use (p=0.048), lower diastolic pressure (p=0.043), tachypnoea (p=0.044), hypoxemia (p=0.011) and respiratory alkalosis (p<0.001). Hypophosphatemia was associated with a high risk of death; odds ratio 4.12(P=0.031) at admission and odds ratio 7.5 (P=0.098) 48hrs post-admission.**

Conclusion: **Hypophosphatemia is the predominant serum phosphate ion abnormality seen in severe traumatic brain injury and is associated with significant high risk of mortality.**

INTRODUCTION

Severe traumatic brain injury, defined as Glasgow Coma Scale ≤ 8, is a major cause of death and disability worldwide and is associated with enormous direct and indirect costs to the public (1–3). Traumatic Brain Injury (TBI) is more common in developing nations , especially in Kenya due to the increasing number of road accidents (4,5). In our set-up, most hospital-based studies have shown that severe head injury is associated with a mortality rate of > 50% and poor functional outcomes (6–8). These bad outcomes may be associated with secondary brain insults caused by inflammatory and biochemical cascades of primary brain injury (9). Secondary brain insults include hypoxia, electrolyte dysfunction, ischaemia and cerebral edema (2,10,11).

Phosphate is a major intracellular anion and is involved in many physiological functions such as acid-base buffering, cell signaling, energy transfer, DNA and RNA storage and translation of information, and muscle tone maintenance (12,13). Hypophosphatemia leads to muscle weakness, cardiac dysfunction, including hypocontractility, ventricular tachycardia and cardiac arrest, impaired mental status, and seizures (12,14). Weakness of the respiratory muscles leads to difficulty weaning off the ventilator and increased incidence of respiratory infections, thus prolonging ICU stay (15–17). There is however a paucity of data on phosphate ion abnormalities in severe traumatic brain injury. The objective of this study was to determine the incidence of serum phosphate ion abnormalities in severe TBI patients and their association with specific clinical, radiological and acid-based parameters.

MATERIALS AND METHODS

Study design and site: An analytical cross-sectional study conducted over 4 months (1st November 2019 to 28th February 2020). The study site was the Kenyatta National Hospital Accident and Emergency Unit and Intensive Care Unit (ICU). Kenyatta National Hospital is located in Nairobi, Kenya, and is the largest hospital and the country's leading neurotrauma referral center. The hospital serves patients from various regions and socioeconomic backgrounds.

Study population: Ninety-five patients presenting with severe head injury defined by Glasgow Coma Scale (GCS) ≤ 8 and whose next of kin had given informed consent were recruited into the study. Patients with known pre-existing chronic illness were excluded from the study. The mean age was 31.3±12.5 years.

Study variables: Data collected included patient demographics, mechanisms of injury, prehospital interventions, clinical examination findings, Computer Tomography (CT) Scan head findings, serum phosphate levels (at admission and 48hrs later), arterial blood gas, and outcome (30 days). The Injury Severity Score (ISS) was used to quantify the severity of injury to the patient (61–63). The serum phosphate tests were done using Biolis 50i Superior Chemistry Analyser (Tokyo Boeki Medisys – Japan). Daily internal quality control checks were done to ensure that the results were valid. In addition, external quality control checks were done through the Randox

International Quality Assessment Scheme (RIQAS). The reference range for serum phosphate from our laboratory is 0.90-1.62mmol/L.

Statistical analysis: Data gathered was entered into Statistical Package for Social Sciences (SPSS) version 20.0 for analysis. Metric data are shown as means and standard deviation, nominal data as frequency and valid percent. Variables were tested for normal distribution using the Kolmogorov-Smirnov test in addition to histograms. If the assumption of normality was violated, Mann-Whitney U and Kruskal-Wallis tests were performed to test for differences between groups, instead of student's t-test and ANOVA (Analysis of Variance) tests respectively. Admission and 48hrs post admission variables were compared using the paired t-test. Categorical data was analysed by Pearson's Chi-square test. Correlation between the serum phosphate and the study variables (clinical, radiologic and acid base) was determined using Pearson's correlation coefficient (r). Odds ratio were calculated for each electrolyte abnormality to determine its associated risk of mortality (30-day mortality). A p-value of <0.05 was considered as significant.

Ethical considerations: The study was conducted in compliance with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (P723/08/2019). Written informed consent was obtained from the next of kin of the patients as the patients could not consent in view of their low GCS.

RESULTS

Incidence of phosphate ion abnormalities

The mean serum phosphate ion levels were 1.03±0.39 mmol / l (n=95) and 1.17±0.53 mmol / l (n=60) at admission and 48 hours after admission. Hypophosphatemia was the predominant abnormality reported in 40 (42.1%) and 29 (48.3%) of admission and 48 hours post-admission cases, respectively (Figure 1). Hyperphosphatemia was reported in 5 (5.3 per cent) cases at admission and in 5 (8.3 per cent) cases 48 hours after admission. Paired T test showed no statistically significant differences between admission and post-admission serum phosphate ion levels (p=0.568).

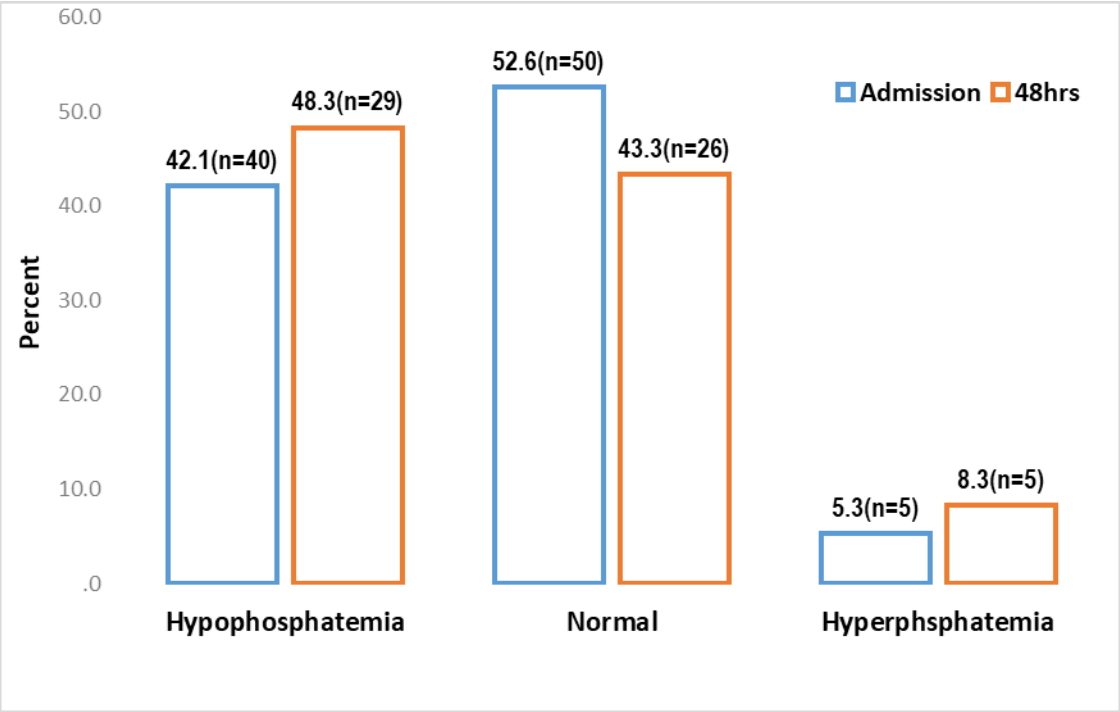

Figure 1: Serum phosphate levels at admission and 48hrs later

Association between serum phosphate and clinical parameters

Use of IV fluids and mannitol, diastolic blood pressure, respiratory rate and oxygen saturation were significantly correlated with the admission serum phosphate levels (Table 1). In contrast, post-admission phosphate ion levels were significantly correlated with GCS score. There were no statistically significant differences between the clinical parameters and the three groups of serum phosphate levels (Table 2).

Table 1

Correlations between serum phosphate and specific clinical parameters

	Phosphate levels at Admission (n=95)		**Phosphate levels after 48hrs (n=60)**	
	Correlation coefficient	**P value**	**Correlation coefficient**	**P value**
Age	-0.208	0.409	0.022	0.938
Time from injury to presentation (hrs)	-0.187	0.442	0.230	0.409
Pre-hospital use of IV fluids	-0.473*	0.041	0.198	0.479
Pre-hospital use of Mannitol	-0.442	0.048	0.271	0.328
Systolic BP	-0.146	0.552	0.044	0.878
Diastolic BP	-0.469*	0.043	-0.192	0.492
Heart rate	0.273	0.259	0.021	0.940
Respiratory rate	0.493*	0.044	-0.253	0.383
Temperature	0.357	0.175	0.014	0.967
Saturation O2	-0.615*	0.011	0.049	0.885
Pupil examination	-0.342	0.152	-0.177	0.527
Total GCS Score	0.102	0.676	0.547*	0.035
ISS Score	0.006	0.981	0.030	0.916

Table 2

Comparison between serum phosphate ion levels and clinical parameters

		Hypophosphatemia	**Normal**	**Hyperphosphatemia**	**p-value**
Age	Admission	37.5±14.5	29.6±14.7	35.0±0.1	0.543
	48hrs post admission	34.6±14.9	28.3±7.9	35.5±13.5	0.690
Time from injury to presentation (hrs)	Admission	28.4±29.7	19.7±34.6	17.0±0.1	0.838
	48hrs post admission	18.8±15.7	9.5±7.7	47.2±17.7	0.358
Pre-hospital use of IV fluids	Admission	56.5%	30.0%	25%	0.115
	48hrs post admission	42.9%	30%	35%	0.804
Pre-hospital use of Mannitol	Admission	60.5%	50%	12.5%	0.142
	48hrs post admission	28.6%	25.0%	-	0.559
Systolic BP	Admission	116.0±2.1	137.6±19.1	134.8±32.7	0.133
	48hrs post admission	126.0±21.8	134.0±9.6	129.0±20.0	0.802
Diastolic BP	Admission	64.5±18.5	82.4±16.1	89.0±0.1	0.094
	48hrs post admission	76.9±15.2	90.5±9.3	83.5±18.0	0.251
Heart rate	Admission	81.4±20.1	85.8±19.1	101.0±5.3	0.627
	48hrs post admission	81.1±13.4	99.0±29.1	82.0±17.5	0.337
Respiratory rate	Admission	24.0±0.1	20.9±3.8	19.1±2.0	0.096
	48hrs post admission	21.7±2.3	21.0±4.8	20.0±2.3	0.726
Saturation O2	Admission	90.0±0.1	92.9±1.9	96.0±3.6	0.112
	48hrs post admission	92.4±6.9	96.5±2.1	94.5±0.7	0.694
Total GCS Score	Admission	7.1±1.0	6.8±1.4	7.8±0.1	0.617
	48hrs post admission	6.4±1.8	6.8±1.3	7.8±0.1	0.245
ISS Score	Admission	19.5±3.2	22.4±12.1	18.0±0.1	0.769
	48hrs post admission	19.7±3.4	27.8±19.5	22.0±8.4	0.517

Association between serum phosphate & radiologic parameters

None of the radiological parameters revealed statistically significant differences between the three groups (Table 3) nor showed significant correlations with serum phosphate ion levels (Table 4).

Table 3

Comparison between serum phosphate and radiologic parameters

		Hypophosphatemia	**Normal**	**Hyperphosphatemia**	**p-value**
Compressed/absent Basal cisterns	*Admission*	85%	70%	92.5%	0.208
	48hrs post admission	87.5%	85%	75%	0.312
Midline shift (mm)	*Admission*	11.0±4.2	10.4±9.1	15.0±0.01	0.842
	48hrs post admission	8.8±6.3	8.8±4.8	5.0±7.1	0.728
Presence of epidural Hematoma	*Admission*	37.5%	30%	50%	0.427
	48hrs post admission	14.3%	5%	5%	0.600
Presence of subdural hematoma	*Admission*	12.5%	40%	60%	0.164
	48hrs post admission	28.6%	50%	50%	0.746
Presence of Traumatic SAH	*Admission*	50%	40%	65%	0.554
	48hrs post admission	65%	25%	50%	0.144
Contusion hemorrhages	*Admission*	37.5%	60%		0.440
	48hrs post admission	57.1%	75%	50%	0.794
SDH Thickness (mm)	*Admission*	5.0±0.01	8.3±2.9	15.0±0.01	0.238
	48hrs post admission	10.0±0.01	10.0±7.1	10.0±0.01	0.998
Rotterdam CT Score	*Admission*	3.9±0.8	3.4±1.2	5.0±0.01	0.297
	48hrs post admission	4.6±1.0	4.0±0.8	3.5±1.3	0.279

Table 4

Correlations between serum phosphate and radiologic parameters

		Phosphate at admission (n=95)	Phosphate 48hrs post-admission (n=60)
Midline shift (mm)	*Pearson Correlation*	-0.326	0.117
	Sig. (2-tailed)	0.475	0.783
Epidural Hematoma	*Pearson Correlation*	0.249	-0.006
	Sig. (2-tailed)	0.193	0.970
Subdural hematoma	*Pearson Correlation*	-0.351	-0.179
	Sig. (2-tailed)	0.263	0.579
Traumatic SAH	*Pearson Correlation*	0.173	-0.245
	Sig. (2-tailed)	0.591	0.443
Contusion hemorrhages	*Pearson Correlation*	-0.308	0.149
	Sig. (2-tailed)	0.331	0.644
EDH volume (mls)	*Pearson Correlation*	0.249	-0.006
	Sig. (2-tailed)	0.193	0.970
SDH Thickness (mm)	*Pearson Correlation*	0.701	-0.163
	Sig. (2-tailed)	0.506	0.793
Rotterdam CT Score	*Pearson Correlation*	-0.152	-0.415
	Sig. (2-tailed)	0.637	0.180

Association between serum phosphate & acid-base parameters

Up to 30 out of 40(75%) of patients with hypophosphatemia at admission either had respiratory alkalosis or compensated respiratory alkalosis ($p<0.001$). Hypophosphatemia at admission was associated with statistically significant higher pH and lower pCO2 compared to hyperphosphatemia (Table 5). Admission pH and pCO_2 revealed significant correlations with the serum phosphate ion levels (Table 6).

Table 5

Comparison between serum phosphate ion levels and acid-base parameters

		Hypophosphatemia	Normal	Hyperphosphatemia	p-value
pH	Admission	7.46±0.11	7.33±0.13	7.18±0.01	0.041*
	48hrs post admission	7.43±0.07	7.44±0.07	7.41±0.08	0.784
pCO_2	Admission	4.25±0.53	4.79±0.35	7.34±0.01	0.046*
	48hrs post admission	4.80±0.93	5.14±0.79	4.92±0.85	0.830
HCO_3	Admission	20.70±3.29	19.22±2.94	20.10±0.02	0.610
	48hrs post admission	23.36±3.07	25.30±1.96	23.30±2.87	0.502
Base deficit	Admission	-3.04±4.91	-5.26±4.53	-8.70±0.01	0.420
	48hrs post admission	-0.49±3.27	1.13±2.43	-0.65±2.19	0.611

Table 6

Correlations between serum phosphate ion and acid-base parameters

	Phosphate at admission (n=95)		**Phosphate 48hrs post-admission (n=60)**	
	Correlation coefficient	p-value	Correlation coefficient	p-value
pH	-0.416	0.046	-0.260	0.350
pCO_2	0.447	0.045	0.134	0.633
HCO_3	-0.218	0.371	-0.032	0.909
Base deficit	-0.357	0.134	-0.109	0.699

Association between serum phosphate & 30-day mortality

The risk of mortality was higher in hypophosphatemia occurring 48hrs post admission OR 7.5(95% CI: 1.08-90.24, p=0.098) compared to hypophosphatemia at admission (OR 4.12(95% CI: 1.14-14.83, p=0.031). The odds of mortality for those with hyperphosphatemia was OR 3(95% CI 0.09-90.97, p=0.53) and OR 3(95% CI 0.15-59.89, p=0.47) at admission and 48hrs post admission respectively.

DISCUSSION

Hypophosphatemia was the predominant abnormality, noted in 42.1% and 48.3% of the cases at admission and 48hrs post-admission respectively. Our results are consistent with findings from previous studies that reported an incidence of hypophosphatemia of 28.5-56 percent among TBI patients (18–21). The occurrence of hypophosphatemia seems to be more among the severe head injury patients. A prospective study of 145 patients in Thailand with traumatic brain injury revealed hypophosphatemia in 72(49.6%) patients (18). Of these, 56(77.8%) had severe head injury while 14(19.4%) and 2(2.8%) had moderate and mild TBI respectively. Even among critically ill trauma patients in the intensive care units, those with traumatic brain injury have significantly lower phosphate levels (16).

There are three main mechanisms of hypophosphatemia: increased renal excretion, decreased intestinal absorption, and shifts from the extracellular to intracellular compartments (14). The intracellular influx of phosphate is the most common cause of hypophosphatemia in critically ill patients and may be caused by respiratory alkalosis, hyperglycemia, refeeding syndrome, and high catecholamine levels (12,14). All these conditions are common in severe traumatic brain injury (15,16). Renal loss of phosphate is accentuated by metabolic acidosis and drugs such as diuretics, glucocorticoids, and aminoglycosides (14,22). Polyuresis is common in patients with head injury and may result from the syndrome of inappropriate antidiuretic hormone secretion, cerebral salt loss, and use of hyperosmolar therapies such as mannitol (15,16,21). Hypophosphatemia may also be dilution due to rapid volume expansion (21). Indeed, hypophosphatemia was associated with respiratory alkalosis in the current study, and serum admission levels of phosphate showed significant

negative correlations with prehospital use of mannitol or intravenous fluids.

Phosphate is involved in many physiologic functions such as acid-base buffering, cell signalling, energy transfer, and information storage and translation in DNA and RNA, and maintenance of muscle tone (12,13). Hypophosphatemia leads to muscle weakness, cardiac dysfunction including hypocontractility, ventricular tachycardia, and cardiac arrest, altered mental status, and seizures (12,14). In the current study, hypophosphatemia was associated with significantly lower diastolic blood pressure and Glasgow Coma Score. The weakness of the respiratory muscles leads to difficulty in weaning from the ventilator as well as increased respiratory infections (20,23). In the present study, low levels of phosphate were associated with reduced oxygen saturation, increased respiratory rate and respiratory alkalosis. Respiratory and cardiovascular complications of hypophosphatemia are associated with a 2- to 4-fold increase in mortality in critically ill patients (12). The odds of death in the current study was 4.12 (p=0.031) at admission and 7.5(p=0.198) at 48hrs post-admission.

Hyperphosphatemia was reported in 8.3% of the cases 48hrs after admission. This concurs with findings from previous studies that reported an incidence rate of 6%-9.8% (19,23). Hyperphosphatemia may be caused by renal insufficiency, excessive phosphorus intake, acidosis, hemolysis, rhabdomyolysis, and hypothyroidism (19,23). Hyperphosphatemia results in acute renal failure and calcification of organs such as the heart and the lungs (17,24). Phosphate chelates with calcium and may lower the biologically active ionized calcium fraction leading to clinical features of hypocalcemia (24). It is an independent risk factor for mortality among critically ill patients, an odds ratio of 3.29, $p<0.001$ (25). No study has however reported the risk of mortality for head injury patients with hyperphosphatemia. In the current study, hyperphosphatemia was associated with a 3-fold increase in mortality compared to normophosphatemic patients.

CONCLUSION

Hypophosphatemia is the predominant serum phosphate ion abnormality seen in severe traumatic brain injury and is associated with significant high risk of mortality.

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