Hypophosphatemia in Severe Traumatic Brain Injury*

Hipofosfatemia no Traumatismo Cranioencefálico Grave

Rayne Borges Torres[1], Renato Giuseppe Giovanni Terzi[2], Antônio Luís Eiras Falcão[3], Nelci Fenalti Höehr[4], Venâncio Pereira Dantas Filho[5]

SUMMARY

BACKGROUND AND OBJECTIVES: *The aim of this study was to identify the incidence of hypophosphatemia in severe traumatic brain injury (TBI), as well as to investigate the causes and its clinical significance.*

METHODS: *Fifty-nine serum phosphate determination were done in 14 severe TBI in adults*

RESULTS: *Seven patients developed hypophosphatemia (< 2 mg/dL). Univariate analysis exhibited association of low phosphate levels with higher pH (p = 0.0129), severe systemic inflammatory response syndrome (SIRS) (p = 0.0008) and positive water balance (p = 0.0001). Multivariate analysis highlighted only the association of hypophosphatemia with severe SIRS (p = 0.0001) and lower urine output (p = 0.0126). It was estimated that risk of death increased 3.24 times when serum phosphate fell by one mg/dl. Severity of SIRS was a determinant factor of death (p = 0.005).*

CONCLUSIONS: *Hypophosphatemia is common in TBI and it appears to be associated to SIRS. Alkalosis and volume expansion were contributing factors. Hypophosphatemia in TBI is a marker of severity and death.*

Key Words: *Head injury; hypophosphatemia; risk of death; SIRS; systemic inflammatory response syndrome; traumatic brain injury; TBI*

Phosphate is the most abundant intracellular anion and plays a crucial role in the regulation of vital functions. It is responsible for cellular membrane integrity, for it plays a part in enzyme regulation, for formation of adenosine triphosphate (ATP), for oxygen delivery to the tissues and for cellular immunity. It functions as a primary urinary buffer and it is an important element of bone structure[1].

Hypophosphatemia directly affect the rate of red cell glicolysis, leading to depression of ATP levels and of 2,3–diphosphoglicerate (2,3–DPG). Affinity of oxygen for hemoglobin is modulated by 2,3 –DPG. The clinical complications caused by hypophosphatemia are attributed to reduction of cellular energy stores (reduction of ATP) and to tissue hypoxia (low levels of 2,3-DPG) (1) and include: muscle weakness, frequently associated to respiratory muscles[2], cardiac dysfunction, including cardiac hypocontractility and ventricular tachycardia[3], dysfunction of the central nervous system[1], changes in hematological[4] and immune systems[5]. All these changes may aggravate the clinical state of seriously sick patients, eventually leading to death.

Reduction of serum phosphate may occur due to a decreased intestinal absorption, to an increased urinary excretion or, more commonly, to an internal redistribution[1,6,7].

Despite the fact that of hypophosphatemia is a known disturbance that may be present in traumatic brain injury (TBI)[8-11], the possible causes and clinical implications in these patients were studied little[10]. The objective of the present study was to identify the incidence of hypophosphatemia in patients with severe TBI, as well as the possible causes and its clinical importance.

METHODS

The study included 14 adults with severe TBI admitted to the Intensive Care Unit of the University Hospital of Campinas. The study was approved by the Hospital Research Ethics Committee and informed consent was obtained from the patient's legal representatives. Age, gender, Glasgow Coma Scale (GCS) score on admission[12], the cause of the head trauma, the evaluation of the computerized tomography by the Marshall classification (13) and the presence or absence of associated lesions are displayed on table 1. All patients exhibiting focal lesion as well as those with gunshot injuries underwent surgery. All patients were intubated and on mechanical ventilation. Intracranial pressure was continuously monitored as well as respiratory mechanics, capnography and pulse oximetry. A microsensor catheter in the brain parenchyma (Codman) was used to monitor intracranial pressure. Respiratory variables, capnography and oximetry were continuously recorded with a respiratory profile monitor (CO_2SMOPlus Dixtal). Jugular bulb blood hemoglobin saturation was continuously monitored with a 4-French fiberoptic oxymetric catheter (Baxter-Edwards) and/or in an intermittent way by hemo-oximetry of a blood sample collected from the same catheter, or from a 16G catheter. A central venous catheter

1. Physical Therapist and Master of Science. Intensive Care Unit - CAISM – Centro de Atenção Integral à Saúde da Mulher – UNICAMP.
2. Full Professor of Surgery - Faculdade de Ciências Médicas - UNICAMP
3. Assistant Physician – UTI - Hospital das Clínicas - UNICAMP
4. Assistant Professor - Clinical Pathology Department - Faculdade de Ciências Médicas - UNICAMP
5. Assistant Professor – Bioetrhics and Neurosurgery - Faculdade de Ciências Médicas and Hospital das Clínicas da UNICAMP
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Correspondence to: Rayne Borges Torres, M.D. - Rua Hermantino Coelho, 195/113 - Bloco: Plaza - Mansões Santo Antônio - 13087-500 Campinas – SP, Brazil - E-mail: raynebt@yahoo.com.br

Table 1 – Characteristics of the Patients with Severe TBI						
	Gender	Age	GCS	TA	Associated lesion (s)	CT
1	M	26	7	MT	No	DIII
2	F	19	8	GW	No	-
3	M	33	7	BE	No	DII
4	M	25	3	FA	No	Focal
5	F	19	6	GW	No	-
6	M	19	7	GW	No	-
7	F	30	6	RO	Pneumothorax	Focal
8	M	28	6	RO	Fracture of humerus and liver lesion	DIII
9	M	49	6	AU	Hemothorax	DIII
10	M	28	5	FA	No	Focal
11	M	23	6	AU	Fracture of femur	DIII
12	M	19	8	AU	No	DIV
13	M	15	8	AU	Pulmonary contusion	DIII
14	M	25	8	RO	Fracture of humerus	DIV

M: male; F: female; GCS: Glasgow coma scale; TA: Accident type; MT: motorcycle; GW: Gunshot wound; BE: beating; FA: fall; RO: running over; AU: automobile; CT: computerized tomography by the Marshall classification; DII, DIII, DIV and focal: II, III and IV diffuse and focal lesion, respectively.

(superior vena cava) and a urinary bladder catheter were also positioned. The correct location of the venous catheters was confirmed by radiography.

PROTOCOL OF TREATMENT

Basal hydration of 30 mL/kg/day was complemented in accordance to recorded water loss. Enteral nutrition was started between 24 and 48 hours after injury. Electrolyte replacement was performed according to the basal needs, added by correction of eventual losses.

The patients were positioned supine to approximately 30 degrees elevation with the head in a neutral position. It was attempted to keep the cerebral perfusion pressure (CPP) always above 70 mmHg, with volume replacement and/or administered norepinephrine. Sedation was started with fentanyl associated to midazolam (0.5 mg of fentanyl and 75 mg of midazolam in 250 mL of 5% glucose, dripping started at 10 to 20 microdrops/min, or in sufficient dose to sedate, according to the individual response of each patient).

Mechanical ventilation was optimized to keep cerebral oxygen extraction between 24% to 42% whenever intracranial pressure was above 20 cmH_2O[14,15]; if intracranial pressure remained elevated IV mannitol 20% was given in bolus (0.5 a 1 g/kg/dose) or sedation was substituted by thionembutal (initial dose between 0.5 to 2 mg/kg/hour up to a maximum of 4 mg/kg/hour). If after these isolated or combined alternative procedures, intracranial pressure remained elevated, a new brain computerized tomography was performed and the need for a surgical decompression was evaluated. No patient needed decompressive surgery.

The use of mannitol, furosemide and vasoactive drugs was recorded. Daily water balance and urine output was also registered.

The systemic inflammatory response syndrome (SIRS) is a common occurrence in patients with TBI. Diagnosis was made based on consensus criteria suggested by SCCM/ESICM/ ACCP/ATS/SIS[16]. The number of analyzed patients is small, therefore SIRS was categorized in two degrees according to severity: degree 1, represents the group that developed SIRS or sepsis but did not need nor-epinephrine or it was below 0.1 µg/mL/kg (in these patients nor-epinephrine was used to keep the CPP rather than to treat the hypotension induced by SIRS); degree 2, represents the group that developed circulatory or septic shock and that needed over 0.1 µg/mL/kg nor-epinephrine.

LABORATORY DATA

Arterial and venous blood gases as well as hemo-oximetry of the jugular bulb were performed daily and analyzed by the ABL 700® (Radiometer) equipment. The calculation of the partial pressure of the oxygen that saturates 50% of the hemoglobin (P50) corrected to standard condition (temperature 37 ºC, pH 7.4 and $PaCO_2$ 40 mmHg) was obtained directly from venous blood gases. The concentration of 2,3-diphosphoglicerate per hematocrit (2,3-DPG/Hct) was measured by spectrophotometry, using 665® Catalog reagents (Sigma Diagnostic). The first measurement was collected from the arterial blood in the first 12 hours of hospital admission. The remainders were performed daily, always in the morning. Serum phosphate was measured in an auto-analyzer with "Roche Diagnostics" reagents.

Collection of data was performed for six days after admission to the Intensive Care Unit. The normal range of phosphate for our hospital laboratory is 2.5 to 4.5 mg/dL. Values below 2 mg/dL were considered as hypophosphatemia and values below 1 mg/dL were considered as severe hypophosphatemia.

STATISTICAL ANALYSIS

The Mann-Whitney nonparametric test was used to compare variable such as age, GCS and APACHE II between groups. To compare and correlate the variable that had more than one measurement in each patient the GEE analyses –

generalized estimating equations, an extension of generalized linear models was used[17]. This analysis takes into consideration measurements obtained in the same patient at different times (longitudinal measurements) and analyses the simultaneous change on several variables in the same patient and in the patients' group. The continuous variables as well as the categorical variables used in this analysis were classified by pre-determined cut values.

RESULTS

Fifty nine measurements of serum phosphate were performed in 14 patients during the six days of study (Table 2). It was observed that seven out of fourteen patients developed hypophosphatemia and in three of them the hypophosphatemia was severe.

ANALYSIS OF THE FACTORS ASSOCIATED WITH HYPOPHOSPHATEMIA

The following variables were analyzed as possibly related to hypophosphatemia: the mean daily pH, the severity of SIRS, the water balance, of urine output, the amount of mannitol infused in 24 hours, the use or not of dopamine and the transfusion of blood. Seven patients developed degree 1 SIRS and seven, degree 2 SIRS. Seven patients were transfused.

Univariate analysis showed that only the pH, severity of SIRS and water balance correlated with hypophosphatemia. Serum phosphate was lower with higher pH, more severe SIRS and more positive water balance. Low urine output exhibited a trend to be associated with hypophosphatemia (Table 2).

The pH, the severity of SIRS, the water balances and urine output were included in the multivariate analysis. Finally serum phosphate exhibited significant association with severity of SIRS and low urine output (Table 2).

Table 2 – Variables Observed in Severe TBI Associated to Hypophosphatemia

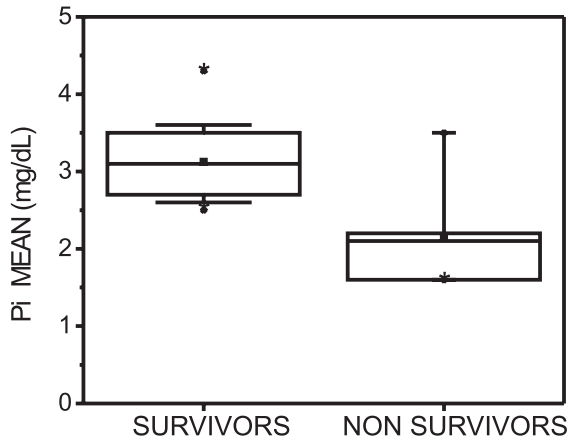
	Variables	Z	P	
Univariate analysis	pH	-2.49	0.013	*
	Severity of SIRS	-3.34	0.0008	*
	Water balance	0.87	0.38	NS
	Diuresis	1.79	0.07	NS
	Mannitol	0.98	0.33	NS
	Dopamine	-3.80	0.0001	*
	Blood transfusion	0.76	0.44	NS
Multivariate analysis	pH	0.07	0.95	NS
	Severity of SIRS	-4.32	0.0001	*
	Water balance	2.30	0.022	*
	urine output	0.00	0.997	NS

* Significant difference ($p < 0.05$)
NS: Non significant difference

ANALYSIS OF DEATH RISK FACTORS

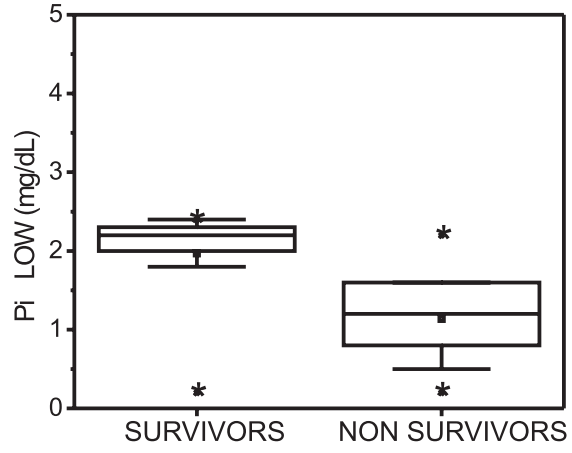
Six patients died in the acute phase within 10 days after admission. Five of them developed hypophosphatemia and in three of them the hypophosphatemia was considered severe (< 1 mg/dL). In those who survived, two developed hypophosphatemia but in none serum phosphate values were below 1 mg/dL. Using each patient's phosphate mean (PiM) and lowest value (PiL) to compare survivors from non-survivors, phosphate levels were lower in the group that did not survive ($p < 0.05$) (Figure 1). The GEE analysis revealed a significant difference between both groups and it was estimated that for each decrease in one phosphate unit (1 mg/dL), the risk of death increased 3.24 times. There was no significant difference between the groups as far as age, GCS and APACHE II (Table 3).

Figure 1 - Mean Serum Phosphorus (PiM) exhibited Significant Difference between Survivors and non-Survivors.



(*) Outlier; (□) Mean

Figure 2 - Lowest Serum Phosphorus (Pi LOW) also exhibited Significant Difference between Survivors and non Survivors.



(*) Outlier; (□) Mean

Table 3 – Comparison of Age and GCS and APACHE II in TBI Survivors and non-Survivors

	Age		GCS		AP II		AP II %	
Survivors	23.4	6.8	6.8	1.8	17.5	5.6	21.8	12.6
Non survivors	28.5	11	6.2	0.8	19.7	4	24.6	11.9

GCS: Glasgow Coma Scale, APII: APACHE II punctuation and AP %: risk of death at APACHE II. Mann Whitney nonparametric test

To analyze associated risk factors of death the following variables were analyzed: the concentration of DPG/Hct, the amount of mannitol in 24 hours, mean pH, mean base excess, severity of SIRS and transfusion. Severity of SIRS was a determinant factor of death, considering that all six patients who died developed degree 2 SIRS but only one survivor was classified as degree 2 SIRS. Other factors did not exhibit correlation with death (the amount of mannitol, mean pH and mean base excess).

OTHER RESULTS

When the phosphate was below 2 mg/dL there was a significant positive correlation between serum phosphate and the concentration of 2,3-DPG/Hct ($Z = -2.70$, $p = 0.007$). There was a significant correlation between the concentration of 2,3-DPG/Hct and the P50st ($Z = 5.56$, $p = 0.0001$).

DISCUSSION

Data from the present study reveals that hypophosphatemia is a common finding in the acute phase of severe TBI. Seven out of 14 patients presented an important fall in the serum phosphate. The development of hypophosphatemia in severe TBI had been previously reported[8-11], but the causes and the clinical implications were superficially approached. Pas'ko et al.[10] observed that in severe TBI, hypophosphatemia had relation to hypocapnia, to the absence of phosphate in parenteral nutrition and to major losses of phosphate in the urine and in the gastric aspirate. It is important to enhance that they did not investigate the concurrence of SIRS.

There are evidences that hyperventilation may lead to phosphate reduction[18-22]. Nevertheless, a marked hypophosphatemia has been seen only when hyperventilation is associated to intravenous glucose administration[18-20]. Severity of hypophosphatemia has been associated with longer[22] and more intense[21] hyperventilation. In the present work, patients with severe head injury were submitted to optimized ventilation[14,15], sometimes being submitted to hyperventilation for short periods of time in order to control intracranial hypertension. Glucose solution was administered daily. These associated factors may have contributed to the development of hypophosphatemia. Hypophosphatemia induced by hyperventilation has been attributed to the migration of blood phosphate ion to the interior of the cell, leading to an increased intracellular glycolytic activity in response to the intracellular pH increase. The glucose infusion leads to increase in blood insulin levels promoting increased migration of the phosphate ion into the cell[18].

Volume expansion has been previously reported as predisposing factor in the development of hypophosphatemia[7,23]. Our data confirms this observation, because hypophosphatemia correlated with positive water balance. The use of loop diuretics lead to an increase of renal excretion of phosphate, possibly leading to a moderate hypophosphatemia[6,24]. The effect of osmotic diuretics, such as mannitol is debatable[25,26]. In the present investigation no correlation was observed between the amount of mannitol and serum phosphate.

Severity of SIRS, correlated with hypophosphatemia in both univaried and multivariate analysis, suggesting that this is a major factor associated with hypophosphatemia in these TBI patients. SIRS is frequently present in the initial phase of severe TBI, and it may be aggravated or develop at a later stage, associated with systemic infection (sepsis). The correlation between sepsis and hypophosphatemia had already been described by Barak et al.[27], where a major prevalence of hypophosphatemia in patients with sepsis was identified (80%) in comparison with the presence of infection without sepsis (65%) and with the incidence in normal people (15%). They also observed a correlation between hypophosphatemia and elevated inflammatory cytokines levels during the initial phase of sepsis, mainly when cultures were positive. In previous studies, hypophosphatemia in trauma was associated to early stress – liberation of catecholamine[23], which in turn may be associated to development of SIRS.

In the present work we observed that the development of hypophosphatemia is, in itself, a marker of risk of death. The risk of death increased 3.24 times for each unit (1 mg/dL) decrease in serum phosphate. In surgical patients or in Intensive Care Units, hypophosphatemia seems to be associated with increased mortality and complications (among them, sepsis)[24,28-30]. Its correction seems to improve prognosis, as shown in the study by Pas'ko et al. performed in severe TBI decreasing mortality by 14.6%[10]. Zazzo et al.[24] and Bollaert et al.[31] demonstrated beneficial effects on cardiac performance after the correction of hypophosphatemia in septic patients. However, Riou et al[32] observed that correction of hypophosphatemia is not associated with any hemodynamic change in brain dead patients. Hypophosphatemia was not treated by the attending physician and only three patients progressed to brain death. Hypophosphatemia was a risk of death marker in severe SIRS (degree 2) (equivalent to circulatory shock or septic shock) or, in organ dysfunction. The reduction of urine output exhibited correlation with hypophosphatemia in the multivariate analysis, probably because of renal dysfunction associated to severe SIRS.

Complications caused by hypophosphatemia are attributed to the reduction of ATP and 2,3-DPG[1]. The 2,3-DPG has an important function in oxygen transport. The increase in concentration of the 2,3-DPG in the blood reduces oxygen affinity by the hemoglobin and therefore increases P50st. In the present study serum phosphate below 2 mg/dL correlated with reduced 2,3-DPG. The expected correlation between the P50st and the 2,3-DPG was also observed.

It is concluded that hypophosphatemia is a common occurrence in severe TBI, most likely associated to SIRS. Aggravating factors are alkalosis and volume expansion. Hypophosphatemia is a marker of severity and of risk of death in TBI.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O objetivo deste estudo foi identificar a incidência de hipofosfatemia no traumatismo cranioencefálico (TCE) grave, bem como identificar as causas e a sua significância clínica.

MÉTODO: Cinqüenta e nove medidas do fosfato sérico foram realizadas em 14 adultos com TCE.

RESULTADOS: Sete pacientes desenvolveram hipofosfatemia (< 2 mg/dL). Na análise univariada, quanto mais

baixo o fosfato, mais alto estava o pH (p = 0,0129), mais grave a síndrome da resposta inflamatória sistêmica (SIRS) (p = 0,0008) e mais positivo o balanço hídrico (p = 0,0001). Na análise multivariada houve associação apenas da hipofosfatemia com a gravidade da SIRS (p = 0,0001) e o baixo débito urinário (p = 0,0126). Estimou-se que, o decréscimo em uma unidade de fosfato (mg/dL) aumenta o risco de óbito em 3,24 vezes. A gravidade da SIRS foi fator determinante de óbito (p = 0,005).

CONCLUSÕES: A hipofosfatemia é comum no TCE grave, parece estar associado à SIRS, tendo como fatores agravantes, a alcalose e a expansão volêmica. A hipofosfatemia é um indicador de gravidade e de risco de óbito no TCE grave.

Unitermos: hipofosfatemia, risco de óbito, síndrome da resposta inflamatória sistêmica, TCE; Traumatismo craniano

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