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Research Article

Severe Hypophosphatemia: Its Prevalence and Predictors Associated with In-hospital Mortality

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Abstract

Background: It has been unclear about prevalence and in-hospital mortality of severe hypophosphatemia among hospitalized medical patients. Predictors for in-hospital mortality have not yet been determined in terms those may include serum nadir phosphate level, or baseline disease as a cause of hypophosphatemia.

Methods: A retrospective cohort study was conducted for all adult patients with severe hypophosphatemia (<1.5 mg/dL) at a Japanese community teaching hospital from January 2009 to December 2014. Prevalence of severe hypophosphatemia was determined and in-hospital mortality was compared between patients with severe hypophosphatemia and all hospitalized adult patients during the same study period. Predictors for in-hospital mortality were analyzed among patients with severe hypophosphatemia based on multivariable logistic regression model adjusted for demographics, causes of hypophosphatemia, nadir phosphate level, and presence of hemolysis.

Results: From a total of 482,812 admitted adult patients, 97 patients (0.02%) had severe hypophosphatemia. The common causes of severe hypophosphatemia were malnutrition, infection, or malignancy. In-hospital mortality among those with severe hypophosphatemia was 21.6% and it was significantly greater than that (0.26%) of all hospitalized adult patients (P<0.001). Concomitant malignancy was associated with increased in-hospital mortality with odds ratio of 10.98 (95% CI, 1.56-77.1). Mortality was not related to lower nadir level of serum phosphate.

Conclusion: Although severe hypophosphatemia was uncommon in hospitalized patients, in-hospital mortality among patients with severe hypophosphatemia was high (about 20%). However, this in-hospital mortality was associated with baseline malignant disease but not with the magnitude of serum nadir phosphate level.

Keywords: Hypophosphatemia, Mortality, Malignant disease

Introduction

Phosphorus is an important electrolyte、which conducts five main functions in a human body [1]. First, phosphorus can be found in cells as a component of adenosine trisphosphate, the main player in energy storage, muscle contraction and neuro-transmission. Second, phosphate constitutes 2, 3- diphosphoglycerate (2, 3-DPG), which modulates oxygen release out of hemoglobin. Third, phosphate is essential component in lipid-bilayer of cell membrane, nucleic acids and nucleoproteins. Forth, phosphate works as a buffer in urine and plasma. Fifth, phosphorus is used as co-factor for important modulating enzymes of glycolysis.

Imbalances of phosphate concentration can have serious clinical effects because of its importance in human physiological functions described above. Hypophosphatemia is reported up to 5% of hospitalized patients and up to 30-50% if patients are septic, alcoholic or hospitalized intensive care unit. There are three primary mechanisms by which hypophosphatemia can occur: inadequate intestinal phosphate absorption, rapid redistribution of phosphate from the extracellular fluid into cells, and increased renal urinary loss. In hospitalized patients, redistribution is the leading cause of hypophosphatemia, including antecedent starvation or malnutrition, diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), and respiratory alkalosis [2,3].

Patients with hypophosphatemia are often asymptomatic unless plasma phosphate

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< 1 mg/dL. If present, patients have pathological effects including rhabdomyolysis, neurological deficits, respiratory failure, impaired myocardial contractility, arrhythmia, delirium, seizure, and failure of weaning from ventilation or hemolytic anemia [4-23]. Severe hypophosphatemia may be associated with increased mortality as about 20% in hospitalized patients [24].

Nonetheless, predictors for in-hospital mortality have not yet been determined among patients with severe hypophosphatemia. It has also been unclear about the associations between mortality and nadir level of serum phosphate, its hemolytic complication or baseline causative diseases of hypophosphatemia. Additionally, few studies have described about prevalence and in-hospital mortality of severe hypophosphatemia among hospitalized medical patients in an acute care hospital in Japan. Thus, in the current study, we aimed to investigate causes for severe hypophosphatemia in all patients admitted at a community teaching hospital in Japan and determined predictive factors associated with in-hospital mortality in these patients.

Methods

Study subjects

The current study was conducted on inpatients consecutively admitted to the Mito Kyodo General Hospital, a 401-bed university-affiliated community teaching hospital, in a 6-year study period from January 2009 to December 2014. The hospital provides primary and secondary care without pediatrics and obstetrics to a population of approximately 480,000 in Mito City, Ibaraki, Japan. The hospital also has six critical care units. The institutional review board of the hospital approved the study. Patients with severe hypophosphatemia (<1.5 mg/dL) after admission during this period were included, based on the hospital database of electronic medical records. We also included patients treated in critical care units, but we did not include outpatients. We excluded data of the same patients who were admitted twice or more and we used initial data from such patients. We also excluded patients who received care in pediatrics or obstetrics.

Data collection

We collected data of age, gender, in-hospital mortality, baseline disease of hypophosphatemia, serum nadir phosphate level, hematocrit, serum concentrations of total protein, albumin, blood urea nitrogen, creatinine, sodium, potassium, chloride, calcium, magnesium, lactate dehydrogenase, alkaline phosphatase, indirect bilirubin. Hemolysis was defined as a condition with elevated serum LDH and indirect bilirubin. Malnutrition was defined as a condition with lower serum albumin level less than 3.0 mg/dL or those with the description of malnutrition on the charts. We also determined the number of total inpatients and mortality during the same period.

Statistical analysis

We determined significant risk factors associated with mortality among patients with severe hypophosphatemia using multivariable adjusted logistic regression model. Potential risk factors included data of baseline diseases. Two-sided P values less than .05 were considered statistically significant. All statistical analyses were conducted by STATA (version 13, College Station, TX, USA).

Results

During the study period, in a total of 482,812 admitted patients, 97 patients had severe hypophosphatemia with prevalence of 0.02%, with a mean age of 62 years (range, 15-98) and 49 (48%) were men.22 patients out of these 97 patients (23%) needed intensive care. Table 1 shows the clinical characteristics of patients with severe hypophosphatemia.

Among these 97 patients with severe hypophosphatemia, 25 patients (26%) had infection, 18 (19%) had malnutrition, 18 (19%) had DKA or HHS, and 11(18%) had malignant disease. No one had hemolysis. Figure 1 shows the baseline diseases of severe hypophosphatemia among inpatients.

During the study period, overall in-hospital mortality was 1252 / 482,812 (0.26%). Among 97 patients with severe hypophosphatemia, 21 patients (21.6%) died during the hospitalization. Table 2 shows that increased in-hospital mortality was associated with age with odds ratio of 1.06 (95% CI, 1.01-1.11) and concomitant malignant disease with odds ratio of 11 (95% CI, 1.56-77.2). Lower nadir level of serum phosphate or presence of hemolysis was not associated with mortality (P=0.41).

Characteristic		Patients with severe hypophosphatemia	
Age, mean (years)		64.23	(SD, 20.7)
Male gender		49	(48%)
Laboratory data	Total protein (mg/dl)	1.56	(SD, 1.05)
	Serum albumin (mg/dl)	2.61	(SD, 0.80)
	Blood urea nitrogen (mg/dl)	20.8	(SD, 14.5)
	Serum creatinine (mg/dl)	0.95	(SD, 0.85)
	Serum sodium (mEq/l)	140	(SD, 7.51)
	Serum potassium (mEq/l)	3.49	(SD, 0.66)
	Serum calcium (mEq/l)	8.05	(SD, 1.08)
	Serum magnesium (mEq/l)	1.83	(SD, 0.45)
	Serum phosphate (mEq/l)	1.12	(SD, 0.26)
	Alkaline phosphatase (IU/l)	317	(SD, 5.0)
	Lactate dehydrogenase (IU/l)	4.2	(SD, 191)
	Hematocrit (%)	32.0	(SD, 6.52)

Table 1: Clinical characteristics of patients with severe hypophosphatemia (n=97)

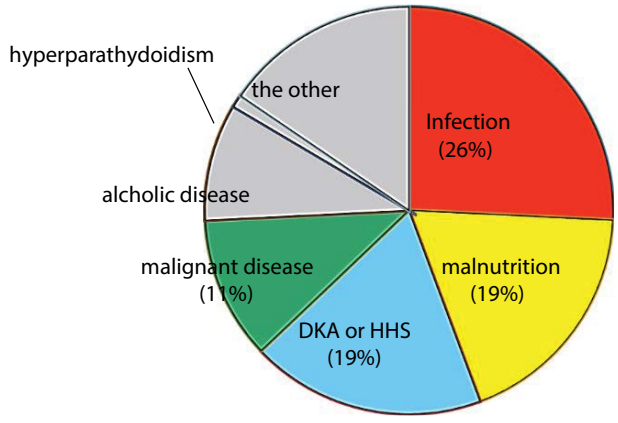

Figure 1: Factors associated with in-hospital mortality among patients with severe hypophosphatemia (n=97)

	OR	95% CI of OR	SE	p-value
Age	1.06	1.00 1.11	0.03	0.04
Male gender	1.44	0.44 4.70	0.87	0.55
Malignancy	11.0	1.56 77.1	11.0	0.02
Infection	0.24	0.04 1.47	0.22	0.12
Alcoholic disease	2.12	0.20 23.0	2.58	0.12
DKA or HHS	0.34	0.03 4.47	0.45	0.41
The other	0.31	0.03 3.31	0.37	0.33

Table 2: Factors associated with in-hospital mortality among patients with severe hypophosphatemia (n=94)

Discussion

In our study, the mortality of patients with severe hypophosphatemia was high. Older age and malignant disease was associated with in-hospital mortality. However, nadir level of serum phosphate was not associated with in-hospital mortality. These results suggest that what directly affects mortality in such patients is not the level of hypophosphatemia itself but the graveness of baseline diseases causing hypophosphatemia. Hypophosphatemia can be considered to reflect a result from seriousness of baseline diseases and not to lead to mortality in itself.

The reason why nadir level of serum phosphate was not associated with in-hospital mortality may be explain the fact that it's unclear whether serum phosphate level is parallel with intracellular its level, which reflects the amount of ATP or 2, 3-DPG. Firstly, only one percent phosphate is found in blood. On the other hand, 85 % is stored as hydroxyapatite crystals in bone, 14% consists of soft tissue, lipid-bilayer of cell, nucleic acid carrying genetic information, ATP, and so on. Secondly, main cause of hypophosphatemia is redistribution of the phosphorus, which leads increase of intracellular phosphorus. ATP or 2, 3-DPG concentration inside cells would remain unaffected [25,26].

Our study showed infection, malnutrition, DKA, HHS or malignant disease as leading baseline diseases for severe hypophosphatemia. As previous studies suggested, there were no patients with hemolysis in our patients with severe hypophosphatemia. Hemolytic anemia has been reported in patients with rapid fall of the level of serum phosphate or very severe hypophosphatemia [4,21-23,27]. This result reflects the fact that no one has exclusively severe hypophosphatemia in our study.

In our survey, chronic alcoholism was not identified as one of leading causes for severe hypophosphatemia. This might reflect relatively smaller amount of ethanol drinking in Japanese people than those of overseas. In addition, the prevalence of alcohol dependence might have lower among Japanese people [28].

The current study has several limitations. First, this survey may not be representative of all hospitals in Japan. There are about 900,000 beds in Japan. Our study was conducted in acute care hospital with 401 beds but without obstetric, pediatric, or cardiovascular surgery wards. Secondly, our study design was retrospective and some patients with severe hypophosphatemia might have been missed. Third, subjects of our study were limited to those with severe hypophosphatemia (<1.5 mg/dL). If subjects would include all patients with hypophosphatemia (<2.5 mg/dL), proportion of baseline disease and factor related with mortality might have been changed. Patients with primary hypoparathyroidism with hypophosphatemia might have been identified, in which serum phosphorus concentration are seldom less than 2.0 mg/dL [27].

In conclusion, although severe hypophosphatemia was uncommon in hospitalized patients, in-hospital mortality among patients with severe hypophosphatemia was high. In-hospital mortality of patients with severe hypophosphatemia was associated with baseline malignant disease but not with the magnitude of serum nadir phosphate level. Hemolysis is not identified among our patients. Further prospective study will be needed whether replacement therapy with phosphate improve the prognosis of patients with hypophosphatemia.

Disclosure

Nothing to report.

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