Identification of risk factors for iatrogenic hypophosphatemia: A retrospective case-control study

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Running title: Risk factors for hypophosphatemia

Zhidong Qi MD[1†], Sibo Yang MSc[2†], Jingdong Qu MD[1], Ming Li MD[1], Rui Huang MD[1], Qiuyuan Han MS[1], Guiying Hou PhD[1], Huaiquan Wang PhD[1]

[1]Department of Critical Care, The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China
[2]Department of Pediatrics, The 1st Affiliated Hospital of Harbin Medical University, Harbin, China
[†]Both authors contributed equally to this manuscript

Authors' email addresses and contributions:
ZQ: qizhidongyisheng@163.com
Conception and design; data collection; statistical analysis; analysis and interpretation; writing the article; critical revision; final approval

SY: yangsiboky@163.com
Contribution: Conception and design; statistical analysis; analysis and interpretation; writing the article; critical revision; final approval

JQ: kuailedexiaodaifu@126.com
Contribution: Data collection; analysis and interpretation; writing the article; final approval.
ML: limingprivate@163.com
Contribution: Data collection; analysis and interpretation; writing the article; final approval.

RH: exatop@yeah.net
Contribution: Data collection; analysis and interpretation; writing the article; final approval.

QH: icujiaoyanshi@163.com
Contribution: Data collection; analysis and interpretation; writing the article; final approval.

GH: hgying001@163.com
Contribution: Data collection; analysis and interpretation; writing the article; final approval.

HW: haiquanwang2827@sina.com
Contribution: Conception and design; data collection; statistical analysis; analysis and interpretation; writing the article; critical revision; final approval.

Corresponding Author: Dr Huaiquan Wang, Department of Critical Care, The 2nd Affiliated Hospital of Harbin Medical University, No. 246 Xuefu Road, Harbin 150000, China. Tel: +86-13009802827. Email: haiquanwang2827@sina.com

ABSTRACT

Background and Objectives: To investigate the iatrogenic risk factors for hypophosphatemia in intensive care unit (ICU) patients. **Methods and Study Design:** A total of 120 patients were enrolled and further divided into 4 groups, namely normal, mild, moderate or severe, according to the degree of hypophosphatemia. A number of related factors were analyzed and compared among the 4 groups, including the treatment method and outcomes. Univariate and multivariate regression analyses were employed to identify and confirm the risk factors associated with the occurrence of hypophosphatemia. **Results:** The results revealed that the acute physiology and chronic health evaluation II (APACHEII), Sequential Organ Failure Assessment (SOFA), modified NUTrition Risk in Critically ill (NUTRIC) scores as well as the length of patient stays in ICUs exhibited a gradually increasing trend of aggravation of hypophosphatemia. Univariate regression analysis identified the use of dehydrating drugs to be closely associated with the occurrence of hypophosphatemia, which was further confirmed by a multivariate regression analysis. **Conclusions:** The use of dehydrating drugs led to hypophosphatemia; therefore blood phosphorus concentrations should be closely monitored during treatment of ICU patients.

Key Words: hypophosphatemia, phosphorous metabolism disorders, iatrogenic disease, intensive care unit, phosphorus, refeeding syndrome

INTRODUCTION

The inorganic salt of phosphorus is essential for normal functioning of the human body, but its content in the body is only about 700 g, making up about 1% of the body weight, with its concentration in blood being 0.8~1.6 mmol/L. Physiologically, phosphorus mainly exists in bones and teeth in the form of hydroxyapatite, is absorbed in the small intestine and excreted by the kidney in the form of soluble phosphate in urine, and may also be found in the feces and sweat at lesser concentrations.

Even though phosphorus is widely present in food, patients often develop hypophosphatemia as a result of disease and fasting. Studies have shown that the incidence of hypophosphatemia is about 50% in hospitalized patients, including 24% for those with the early stages of hypophosphatemia. Comparatively, about 10% to 80% of intensive care unit (ICU) patients develop hypophosphatemia.[1] Hypophosphatemia can pathogenetically reduce energy production in the body and affect the functions of the respiratory muscles, along with a decrease in active substances on alveolar surfaces; patients undergo decreased alveolar

surface tension and developed atelectasis. It can also affect the 2, 3-diphosphate glycerol in red blood cells to make the oxygen dissociation curve shifts to the left, and oxygen dissociation from hemoglobin more difficult, thereby further aggravating hypoxia in these patients.

Hypophosphatemia may also be associated with the pathogenesis of many severe diseases possibly due to reduced phosphate uptake because of a poor diet and fasting, while severe infection, diuretics and glucocorticoids enhance the loss of phosphate and further reduce blood phosphate concentrations.[2] Since ICU patients are critically ill and often suffer from severe water and electrolyte metabolism disorders, the incidence of hypophosphatemia is higher than that of patients in general wards,[3] and hypophosphatemia is associated with the poor prognosis of critically ill patients.[4] It was has also been found that close monitoring of blood phosphate concentrations, early detection of hypophosphatemia and timely supplementation of phosphate preparations can significantly improve patient prognosis.[5]

Apart from patients' existing diseases, refeeding syndrome (RFS) is considered to be a major factor that contributes to the development of hypophosphatemia. RFS presents as a series of symptoms caused by re-intake of nutrients after long-term starvation or malnutrition, with an electrolyte metabolism disorder characterized by hypophosphatemia. The mechanism of RFS is related to insulin secretion, electrolyte transfer and enhanced anabolism,[6] and its aggravation has been linked to fasting, parenteral nutrition, intravenous glucose or insulin administration and the use of catecholamines or diuretics. However, it is not clear which iatrogenic factors are the key factors leading to hypophosphatemia in patients. Therefore, this study retrospectively analyzed the risk factors for patients with hypophosphatemia in the ICU, with the aim of addressing these questions.

MATERIALS AND METHODS

Inclusion and exclusion criteria

A total of 120 patients from the Intensive Care Department of the Second Affiliated Hospital of Harbin Medical University from December 1, 2018 to December 31, 2019 were selected and further divided into groups according to the blood concentration of phosphate on admission to ICU, with 30 cases in each group. The medical records of all the patients were retrospectively reviewed to extract relevant data for further analysis. This study adhered to the Declaration of Helsinki, and approval was obtained from the Ethics Committees of the Second Affiliated Hospital of Harbin Medical University (approval number: KY2019-184).

The study Inclusion criteria were: (1) a length of ICU stay ≥48 h; (2) age between 18 and 75 years; (3) three or more blood phosphate concentrations measurements were carried out in the ICU. Exclusion criteria were: (1) patients with hyperphosphatemia; (2) patients with a history of either primary or secondary hyperthyroid or parathyroidism; (3) patients suffering from bone malignant tumor; (4) patients having autoimmune diseases; (5) pregnant and lactating women; and (6) clinical data that were incomplete or unavailable.

Diagnostic and grading criteria for hypophosphatemia

After ICU admission, patients with blood phosphate concentrations <0.8 mmol/L for 2 consecutive days were diagnosed as having hypophosphatemia. Then the patients were further stratified according to their concentration of blood phosphate thus: a concentration between 0.6-0.8 mmol/L as mild hypophosphatemia; a concentration between 0.3-0.6 mmol/L as moderate hypophosphatemia and a concentration <0.3 mmol/L as severe hypophosphatemia. The diagnostic criterion for hyperphosphatemia was a blood phosphate concentration >1.60 mmol/L.

Experimental grouping and indicators

According to the blood phosphate concentration, 120 patients were divided into normal, mild, moderate and severe hypophosphatemia groups, with 30 patients in each group. All the test results were provided by the biochemical laboratory in our hospital. Observation indicators included gender, age, acute physiology and chronic health evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and modified NUTrition Risk in Critically ill (NUTRIC) scores, total hospitalization days, hospitalization days in the ICU, number of cases with hypoproteinemia or elevated creatinine, total insulin given, number of cases who received enteral nutritional suspension or total parenteral nutrition, total energy provided, energy from enteral nutritional suspension, energy from total parenteral nutrition, days without nutritional support, number of cases with blood purification, time of blood purification, number of cases administered dehydrating drugs, amount of total furosemide used, amount of total mannitol used and the number of cases given catecholamines, including total epinephrine, noradrenaline and dopamine.

Statistical analysis

The normally distributed data were represented by mean ± SD, and analyzed using a t-test with a significance level of α=0.05. Non-normally distributed data are presented as median

and interquartile spacing [M(QR)], and a Kruskal-Wallis H test used for comparison between groups where appropriate. Categorical variables are presented as frequencies as well as percentages, and compared between groups using a χ^2 test or the exact probability method. Univariate and multivariate logistic regression models were used to analyze the risk factors for hypophosphatemia. All data were processed by statistical software SPSS ver. 22.0. A *p*-value <0.05 was considered to be significant.

RESULTS

Demographic information

A total of 120 patients with an average age of 55±13 years were included and divided into 4 groups according to severity of hypophosphatemia, namely normal, mild, moderate and severe. Of the patients, 75% were male and 15.8% had diabetes. The case numbers of hypoproteinemia, elevated creatinine concentrations or diabetes were similar across the 4 groups. Interestingly, ICU stays in all 4 groups trended up with severity (no significant difference between groups), while total hospital stays trended down slightly with severity (no significant including APACHEII, SOFA and Modified NUTRIC scores).

Treatment and outcomes

The medical treatments received by the 4 groups in the ICU are summarized in Table 2. On the one hand, since the incidence of stress hyperglycemia was very high in critically ill patients, insulin was commonly used to treat hyperglycemia. On the other hand, the use of insulin increased significantly with an increasing severity of hypophosphatemia, suggesting insulin use contributed to the development of hypophosphatemia. The duration without nutritional support was 1.99±1.57 days, and there were no significant differences between enteral or parenteral nutrition supplementation or the total energy administered. Total norepinephrine given to the 3 hypophosphatemia groups was significantly lower than that given to the normal group. ICU patients often receive dehydrating medications to reduce their intracranial pressure or pulmonary edema. As the severity of hypophosphatemia increased, so did the proportion of patients receiving dehydrating drugs.

Logistic regression analysis

In order to analyze the relationship between relevant factors and the occurrence of hypophosphatemia, univariate logistic regression and multivariate logistic regression were performed sequentially. The results are shown in Table 3 and Table 4, which shows that the

use of dehydrating drugs was significantly corelated to the occurrence of hypophosphatemia, while other factors were not found to contribute to hypophosphatemia.

DISCUSSION

The results of the present study showed that APACHEII, SOFA as well as modified NUTRIC scores were gradually increased and the length of ICU stay was prolonged with the aggravation of hypophosphatemia. Univariate analysis along with multivariate regression revealed that the use of dehydrating drugs lead to an increased incidence of hypophosphatemia. It has been reported that hypophosphatemia is an independent factor affecting the mortality of patients.[7] A study involving 1,555 patients found that the APACHEII score increased gradually in the hypophosphatemia group, with the duration of mechanical ventilation and ICU stays in the hypophosphatemia group significantly longer than in the normal group. ICU mortality in the hypophosphatemia group was significantly higher than for the normal group (32.6% vs 13.1%). Taken together, hypophosphatemia was associated with a critical condition, mechanical ventilation duration, a prolonged stay in the ICU and mortality of these patients. Therefore, blood phosphate concentration monitoring certainly carries important diagnostic value in judging the prognosis of severely ill patients.[8]

Another significant finding of the present study was the identification of the use of dehydrating drugs as a risk factor for the occurrence of hypophosphatemia. In ICU patients, dehydrating drugs are commonly prescribed to reduce volume load, intracranial pressure or pulmonary edema. The main excretion route of phosphate from the human body is through the kidneys in the form of soluble phosphate excreted in the urine, so the use of dehydrating drugs may lead to hypophosphatemia. The dehydrating drugs used in the present study were mainly furosemide and mannitol. Furosemide, a loop diuretic, has a mild inhibitory effect on carbonic anhydrase and may result in a decrease in the blood phosphate concentration, but since furosemide mainly acts on the loop of Henley, it generally does not increase phosphate excretion.[9] Mannitol is an unabsorbable polysaccharide that increases urine production by osmotic diuretic action. Although mannitol causes an increase in urine production, it also has an insignificant effect in increasing the plasma phosphate concentration and therefore should not cause significant hypophosphatemia.[10] The results of this study show that hypophosphatemia is associated with the use of dehydrating drugs, suggesting there are unknown mechanisms involved, which should be further investigated in future research.

The incidence of stress hyperglycemia was found to be very high in severely ill patients, thus insulin was administered to control the patient's blood glucose concentration to avert

serious consequences such as impairment of innate immune functions. The mechanism of RFS is that when people are hungry, their basal metabolic rate slows down, their insulin concentration decreases and their glucagon concentration increases. During the fasting phase in critically ill patients, gluconeogenesis, after the depletion of glycogen, can exhaust physiological concentrations of electrolytes and vitamins. When re-feeding is initiated, whether oral, enteral or parenteral nutrition, metabolism shifts from protein and fat metabolism to glucose breakdown, which causes a significant increase in the secretion of insulin, and an increased uptake of glucose and electrolytes such as phosphate, potassium and magnesium, eventually leading to hypophosphatemia, hypokalemia and hypomagnesemia.[11] These mechanisms lead to the development of RFS, which can be further deteriorated by the insulin strategy commonly used in ICU management. Under normal circumstances, insulin has a slight effect on the intracellular transfer of glucose and phosphate, but when patients have osmotic diuresis, or when patients were malnourished or alcoholic, the use of insulin may lead to severe hypophosphatemia.[12]

Earlier studies found that both enteral and parenteral nutrition can also lead to hypophosphatemia,[13] with enteral nutrition even more prone to the induction of hypophosphatemia. One possible reason is that following low-amounts of enteral nutrition being administered, insulin secretion is maintained at a low concentration, which can expedite phosphate intracellular transfer faster than the rate from enteral nutrition. Another possibility is that enteral nutrition stimulates more insulin secretion than intravenous nutrition, due to the generation of enteral gastroinsulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), both of which significantly increase insulin secretion.[14] Other studies found that among 213 patients in a surgical ICU, 126 (59%) developed hypophosphatemia, 83 (66%) developed RFS and 43 (34%) developed hypophosphatemia without refeeding.[15] These findings suggest that there are other factors are involved in the development of hypophosphatemia besides refeeding. In the present study, the patients were refed with either phosphate-enriched enteral or parenteral nutrition, and we did not find a significantly higher incidence of RFS.

Continuous renal replacement therapy (CRRT) has become the preferred method of blood purification in the ICU due to its ability to provide slow and stable ion removal, optimized fluid control, and a similar physiological treatment process, especially for patients with hemodynamic instability.[16] Since CRRT can remove electrolytes such as sodium, potassium and phosphorus from the body, it is possible to develop hypophosphatemia within 24 h to 48 h of the initiation of CRRT, if the replacement fluid does not contain phosphate.[17] In addition to the duration of blood purification, the treatment dose of blood purification also affected the

removal of blood phosphate. The higher the treatment dose of blood purification, the higher the removal rate of blood phosphate. One study reported that the incidence of hypophosphatemia when using CRRT in high-dose and low-dose groups was 65.1% and 54%, respectively.[18] In this study, the blood purification method used for patients was CRRT, but unfortunately since our study is retrospective, relevant data on therapeutic doses could not be obtained. Thus, we did not draw any conclusion on the impact of CRRT on the concentration of serum phosphate.

Hypophosphatemia often occurs in clinical practice; however, it remains undermanaged. Subramanian et al[19] reported that 42% of patients with hypophosphatemia did not receive appropriate treatment. Therefore, it is necessary to carry out further research and other initiatives on the pathogenesis and awareness of hypophosphatemia and to enhance the understanding of clinicians on the harm caused by hypophosphatemia. Even though the iatrogenic intervention of dehydrating drug usage was the only risk factor found in this study, beside routine measurements attention should also be paid to the monitoring of patients' blood phosphate concentrations, supplementation of phosphate and vitamin B1, especially before insulin treatment, to prevent the occurrence of hypophosphatemia over time during clinical treatment.

There were several limitations to our study: (1) it study was a single-center retrospective study with some loss of experimental data, which might subsequently limit further analysis of the risk factors; (2) the sample size was not large enough due to results of laboratory examinations; (3) many other potential risk factors for hypophosphatemia were not integrated into this study; (4) the factors investigated in the study may not fully reflect the real clinical situation. Therefore, further studies with a large sample size in multi-centers and randomized controls will be required to establish further risk factors for hypophosphatemia.

Conclusion

The use of dehydrating drugs was found to be the only significant risk factor for the development of hypophosphatemia in ICU patients. APACHEII, SOFA, modified NUTRIC scores as well as the length of a patient’s stay in ICU was likely associated with aggravation of hypophosphatemia.

AUTHOR DISCLOSURE

The authors declare that they have no conflicts of interest.

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Table 1. Clinical characteristics and baseline data of patients with different blood serum phosphorus concentrations

	Normal group	Mild group	Moderate group	Severe group	*p*-value
Gender, n (%)					
Male	22 (73.3)	22 (73.3)	17 (56.7)	19 (63.3)	0.44
Female	8 (26.7)	8 (26.7)	13 (43.3)	11 (36.7)	
Age (years), mean±SD	59.0±16.0	60.5±23.0	58.0±17.0	51.5±22.0	0.42
Hypoproteinemia, n (%)	21 (70.0)	21 (70.0)	22 (73.3)	22 (73.3)	0.98
Albumin (g/L), mean±SD	30.8±10.0	31.8±9.2	29.0±13.0	28.3±11.6	0.65
Elevated creatinine, n (%)	9 (30.0)	9 (30.0)	9 (30.0)	11 (36.7)	0.93
Creatinine (μmol/L), mean±SD	84.5±53.0	83.5±58.0	88.5±64.0	89.5±58.0	0.90
Diabetes, n (%)	3 (10.0)	5 (16.7)	3 (10.0)	8 (26.7)	0.25
APACHEII score, mean±SD	15.5±6.0	14.5±7.0	17.0±9.0	18.0±12.0	0.22
SOFA score, mean±SD	6.0±5.0	6.5±3.0	5.0±4.0	7.0±5.0	0.43
Modified NUTRIC score, mean±SD	3.0±3.0	3.0±2.0	3.0±3.0	3.5±3.0	0.48
Total length of hospital stays (d), mean±SD	16.5±20.0	18.5±31.0	17.0±13.0	16.0±22.0	0.89
ICU stays (h), mean±SD	93.0±70.0	102.0±90.0	109.0±78.0	115.5±95.0	0.55

APACHEII: acute physiology and chronic health evaluation II; ICU: intensive care unit; NUTRIC: NUTrition Risk in Critically ill; SOFA: Sequential Organ Failure Assessment.

Table 2. Treatment and outcomes among patients with different degrees of hypophosphatemia

	Normal group	Mild group	Moderate group	Severe group	*p*-value
Amount of total insulin (iu), mean±SD	44.0±74.1	56.0±69.0	146.4±218.7	271.4±278.6	0.004
Days without nutritional support, mean±SD	2.0±2.0	2.5±3.0	2.0±2.0	2.0±1.0	0.43
Duration of blood purification (h), mean±SD	129.5±95.0	117.0±0.0	62.0±54.0	78.0±98.0	0.17
Energy in enteral nutrition (kcal), mean±SD	2,400.0±2,100.0	1,416.0±3,044.0	2,430.0±7125.0	3,157.5±5,220.0	0.45
Energy in parenteral nutrition (kcal), mean±SD	1,000.0±300.0	1,775.0±4,000.0	1,400.0±2,000.0	2,775.0±3,300.0	0.14
Total mannitol (g), mean±SD	675.0±575.0	525.0±550.0	600.0±500.0	550.0±425.0	0.99
Total furosemide (mg), mean±SD	238.8±189.0	86.4±100.0	90.0±313.3	90.0±251.2	0.75
Total adrenaline (mg), mean±SD	10.0±18.7	11.9±20.7	24.8±44.5	21.1±51.8	0.56
Total norepinephrine (mg), mean±SD	28.5±0.0	1.6±0.0	3.4±2.8	1.3±0.0	0.28
Total dopamine (mg), mean±SD	2,068.0±0.0	80.0±0.0	727.2±0.0	500.8±841.6	0.44
Enteral nutrition, n (%)	18 (60.0)	16 (53.3)	17 (56.7)	14 (46.7)	0.76
Parenteral nutrition, n (%)	8 (26.7)	10 (33.3)	10 (33.3)	12 (40.0)	0.75
Blood purification, n (%)	2 (6.7)	1 (3.3)	3 (10.0)	3 (10.0)	0.87
Dehydrating drugs, n (%)	17 (56.7)	22 (73.3)	24 (80.0)	26 (86.7)	0.06
Catecholamines, n (%)	10 (33.3)	11 (36.7)	16 (53.3)	16 (53.3)	0.26

Table 3. Univariate logistic regression analysis

	OR (95% CI)	*p*-value
Gender		
Female	1.0	0.37
Male	0.66 (0.26-1.65)	
Age (year)	0.99 (0.95-1.02)	0.36
Hypoproteinemia		
No	0.90 (0.36-2.22)	0.82
Albumin (g/L)	0.98 (0.93-1.04)	0.49
Elevated creatinine		
No	0.90 (0.37-2.21)	0.82
Creatinine (μmol/L)	1.00 (1.00-1.00)	0.49
Diabetes		
No	0.51 (0.14-1.90)	0.32
APACHEII score	1.04 (0.97-1.11)	0.29
SOFA score	1.04 (0.90-1.20)	0.61
Modified NUTRIC score	0.91 (0.73-1.14)	0.41
Total length of hospital stays (day)	1.01 (0.98-1.03)	0.64
ICU stays (h)	1.01 (1.00-1.01)	0.17
Amount of total insulin (iu)	1.01 (1.00-1.03)	0.14
Days without nutritional support	1.14 (0.81-1.61)	0.46
Duration of blood purification (h)	0.98 (0.94-1.02)	0.25
Energy in enteral nutrition (kcal)	1.00 (1.00-1.00)	0.45
Energy in parenteral nutrition (kcal)	1.00 (1.00-1.00)	0.08
Total mannitol (g)	1.00 (1.00-1.00)	0.94
Total furosemide (mg)	1.00 (1.00-1.00)	0.52
Total adrenaline (mg)	1.02 (0.98-1.06)	0.29
Total norepinephrine (mg)	0.46 (<0.01->999.9)	0.91
Total dopamine (mg)	0.99 (0.85-1.15)	0.85
Enteral nutrition		
No	1.0	0.46
Parenteral nutrition		
No	1.0	0.37
Blood purification		
No	0.85 (0.17-4.32)	0.84
Dehydrating drugs		
No	1.0	0.01
Catecholamine drugs		
No	0.55 (0.23-1.30)	0.17

APACHEII: acute physiology and chronic health evaluation II; ICU: intensive care unit; NUTRIC: NUTrition Risk in Critically ill; SOFA: Sequential Organ Failure Assessment.

Table 4. Multivariate logistic regression analysis

	OR (95% CI)	*p*-value
Age (years)	0.99 (0.95-1.02)	0.43
Gender (male *vs* female)	0.55 (0.21-1.45)	0.23
Dehydrating drugs (yes *vs* no)	3.26 (1.31-8.11)	0.01