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Refeeding hypophosphatemia: a potentially fatal danger in the intensive care unit*

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Aim: To determine the overall and comparative incidence of refeeding hypophosphatemia (RH) between enteral and parenteral nutrition in general adult intensive care unit (ICU) patients.

Materials and methods: This study was performed as a retrospective analysis. A total of 117 patients who received enteral and parenteral nutrition were included in the study. Demographic characteristics, type of nutrition, daily energy intake, and serum phosphorus levels before and after the initiation of the nutrition were recorded for 7 days.

Results: The mean age of the patients was 65.8 ± 16.7 years. RH was found in 61 patients (52.14%). There was no significant difference in RH with regard to nutrition type (P = 0.756). The duration of the ICU stay was longer in the patients with RH compared with the patients without RH [median: 12 (3–68) and 8.5 (3–41) days, respectively; P = 0.025]. The mortality rate was higher in patients with RH compared with patients without RH (P = 0.037).

Conclusion: The incidence of RH was quite high in our medical ICU. The mortality rate and the duration of ICU stay were higher in the patients with RH than those without RH.

Key words: Enteral nutrition, parenteral nutrition, refeeding hypophosphatemia

1. Introduction

Phosphate is an integral component of the nucleic acids that form DNA and RNA. Phosphate bonds of adenosine triphosphate carry the energy required for all cellular functions (1). Hypophosphatemia is frequently observed in critically ill patients and it is related to increased mortality and morbidity (2–6). Depending on the severity of the hypophosphatemia, the patient may complain about muscle weakness and generalized weakness as mild symptoms, and it can even lead to respiratory failure and death (1,7). Typical causes of hypophosphatemia in critically ill patients are sepsis, postoperative state, trauma, fluid therapy, refeeding, acid-base disorders such as respiratory alkalosis and metabolic acidosis, medications such as glucose/insulin therapy, catecholamines, diuretics, and renal replacement therapy (8).

Refeeding hypophosphatemia (RH) was first observed in starved ex-prisoners of World War II when nutrition was initiated (9). RH is an underappreciated but clinically important entity, characterized by acute electrolyte abnormalities, mainly hypophosphatemia, fluid retention, and dysfunction of various organs and systems, which can result in significant morbidity and occasionally death (6,10,11). RH is a life-threatening constellation of cardiovascular, pulmonary, hepatic, renal, neuromuscular, metabolic, and hematological abnormalities following inappropriate alimentary resuscitation in severely malnourished or starved individuals (12).

Clinical manifestations of refeeding syndrome predominate when carbohydrates are reintroduced. A sudden swing from fat and protein catabolism to carbohydrate metabolism stimulates a catastrophic increase in insulin production. This increase in insulin secretion results in intracellular shifts of glucose with obligatory cellular uptakes of phosphate, magnesium, and potassium. In addition, this sudden introduction of carbohydrate can reduce water and sodium excretion, resulting in the expansion of the extracellular fluid compartment and fluid overload, pulmonary edema, and/or cardiac decompensation (13). Several additional clinical features may also be observed during this time, including hypophosphatemia, hypopotassemia,

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hypomagnesemia, hyperglycemia, and thiamin deficiency (14). Hypophosphatemia can cause cardiac arrhythmia, respiratory failure, rhabdomyolysis, and confusion (14–16). Although several risk factors for RH were described, poor oral ingestion, recent weight loss, and systemic disease such as malignancy were reported in the majority of patients (15).

Normal plasma phosphorus ranges between 0.80 and 1.41 mmol/L in adults. Low serum phosphate concentrations (<0.80 mmol/L) are present in 5%–10% of hospitalized patients. The prevalence of RH varies from 25% to 45% in patients treated in intensive care units (ICUs) or outpatient services (4,17,18).

The aim of this study was to determine the overall and comparative incidence of RH between enteral nutrition (EN) and parenteral nutrition (PN) in a general adult hospital in critically ill patients.

2. Materials and methods

This study was performed retrospectively between January 2010 and June 2011 in a medical intensive care unit (MICU). Patients who were older than 18 years of age, were treated in the MICU for longer than 48 h, and received either EN or PN with full access to available medical records were included in the study. A total of 163 patients were included. Forty-six of these patients were excluded from the study because they had hypophosphatemia before the initiation of nutrition and so 117 patients were included in the analysis. The patients with chronic renal failure or diabetic ketoacidosis and those receiving antacid medications were excluded. Age, sex, body weight, and demographic parameters were recorded. Primary diagnosis, APACHE II scores, and underlying diseases such as diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, cirrhosis, cerebrovascular disease, and malignancies were also recorded. The method of nutrition and the energy intake on days 1, 2, 3, and 4 were analyzed. Durations of hospital, ICU stay, and mechanical ventilation and outcomes of the patients (dead or alive) were recorded. The levels of serum potassium (K), magnesium (Mg), and phosphorus (P) prior to nutrition and on days 1–7 were recorded. Hypophosphatemia was defined as a serum P level of ≤2.4 mg/L (0.77 mmol/L), severe hypophosphatemia as serum P level of ≤1 mg/dL (0.32 mmol/L) (15), hypopotassemia as a serum K level of ≤3.5 mmol/L, and hypomagnesemia as a serum Mg level of ≤0.7 mmol/L (1). The patients received daily infusions of P, K, and Mg based on ICU electrolyte protocol. The energy requirements of the patients were calculated as being in the acute stage at 20–25 kcal/kg and in the subacute stage at 30 kcal/kg.

2.1. Method of nutrition in patients

All patients received EN, but PN was given if EN was contraindicated. In patients with EN, nutrition was started with 20 mL/h. The nutritional goal was reached by increasing by 20 mL/4 h. EN solutions used were Nutrison Protein Plus Multifibre (Nutricia), Nutrison Protein Plus (Nutricia), Pulmocare (Abbott), Jevity Plus (Abbott), Oxepa (Abbott), and Novasource Diabetes (Nestle Health Care Nutrition). For PN, standard forms were used [OliClinomel N4 (Eczacibasi-Baxter), Kabiven Peripheral (Fresenius Kabi)], and custom solutions free of phosphate prepared in our hospital were used for central PN.

Most patients received nutrition for at least 4 days; however, 1 patient received nutrition for 2 days and 8 patients for 3 days due to death or discharge. Serum phosphorus, potassium, and magnesium levels were recorded in 113, 106, 89, 78, and 70 patients on days 3, 4, 5, 6, and 7, respectively.

2.2. Statistical analysis

SPSS 15.0 was used for the statistical analysis. Continuous variables with normal distribution are presented as mean ± SD. Median values were used where normal distribution was absent. Statistical analysis for the parametric variables was performed using the Student t-test between the 2 groups. The Mann–Whitney U test was used to compare nonparametric variables between the 2 groups. Qualitative variables are given as percentages and the correlation between categorical variables was investigated using the chi-square test. The Pearson correlation analysis test was used to determine the association between the quantity of energy intake and the phosphorus level.

3. Results

The mean age for all patients was 65.8 ± 16.7 years. Of the 117 patients, 70 (59.8%) were male. RF was found in 61 patients (52.14%). There was severe hypophosphatemia in 6 (9.8%) of these patients. Parenteral nutrition was given to 40 patients (34.2%), 58 patients received EN (49.6%), and 19 patients received PN + EN (16.2%). RF was found in 47.5% of the patients with PN, in 55.17% of the patients with EN, and in 52.6% of the patients with EN + PN. There was no significant difference for RH with regard to nutrition type (P = 0.756). Demographic and laboratory data are shown in the Table. The mean APACHE II score was 26.6 ± 7.0. APACHE II scores were not different among patients with and without RH (P = 0.556). The duration of ICU stay was longer in the patients

with RH compared with patients without RH [median: 12 (3–68) and 8.5 (3–41) days, respectively; P = 0.025)]. The duration of mechanical ventilation [median: 10 (1–67) and 8 (2–31) days, respectively] and the length of hospital stay [median: 13 (3–68) and 10 (5–43) days, respectively] were similar in patients with RH and without RH (P = 0.120 and P = 0.229). The mortality rate was higher in patients with RH compared with patients without RH (P = 0.037). Energy intake of the patients was recorded during the first 4 days, as shown in the Table, and there was no statistically significant difference among patients with RH and without RH. RH was found to occur at rates of 23%, 28%, 22%, 10%, 8%, 5%, and 3% on days 1, 2, 3, 4, 5, 6, and 7, respectively. Seventy percent of the patients experienced at least 1 chronic disease and 20% of the patients had a malignancy. There was no correlation between the energy intake and the phosphorus level (Figure). Hypopotassemia and hypomagnesemia were present in 62.3% and 45.9% of the patients with RH. Hypomagnesemia and hypopotassemia were significantly more frequent in the patients with RH than those without RH (Table).

4. Discussion

In this study, we observed a high incidence of RH among the critically ill patients in our MICU receiving EN and PN solutions. There was no statistically significant difference between EN and PN for RH.

Hypophosphatemia has a higher incidence in critically ill patients. Hypophosphatemia is commonly missed due to nonspecific signs and symptoms and phosphorus level measurements are not included in most of the biochemistry panels (8).

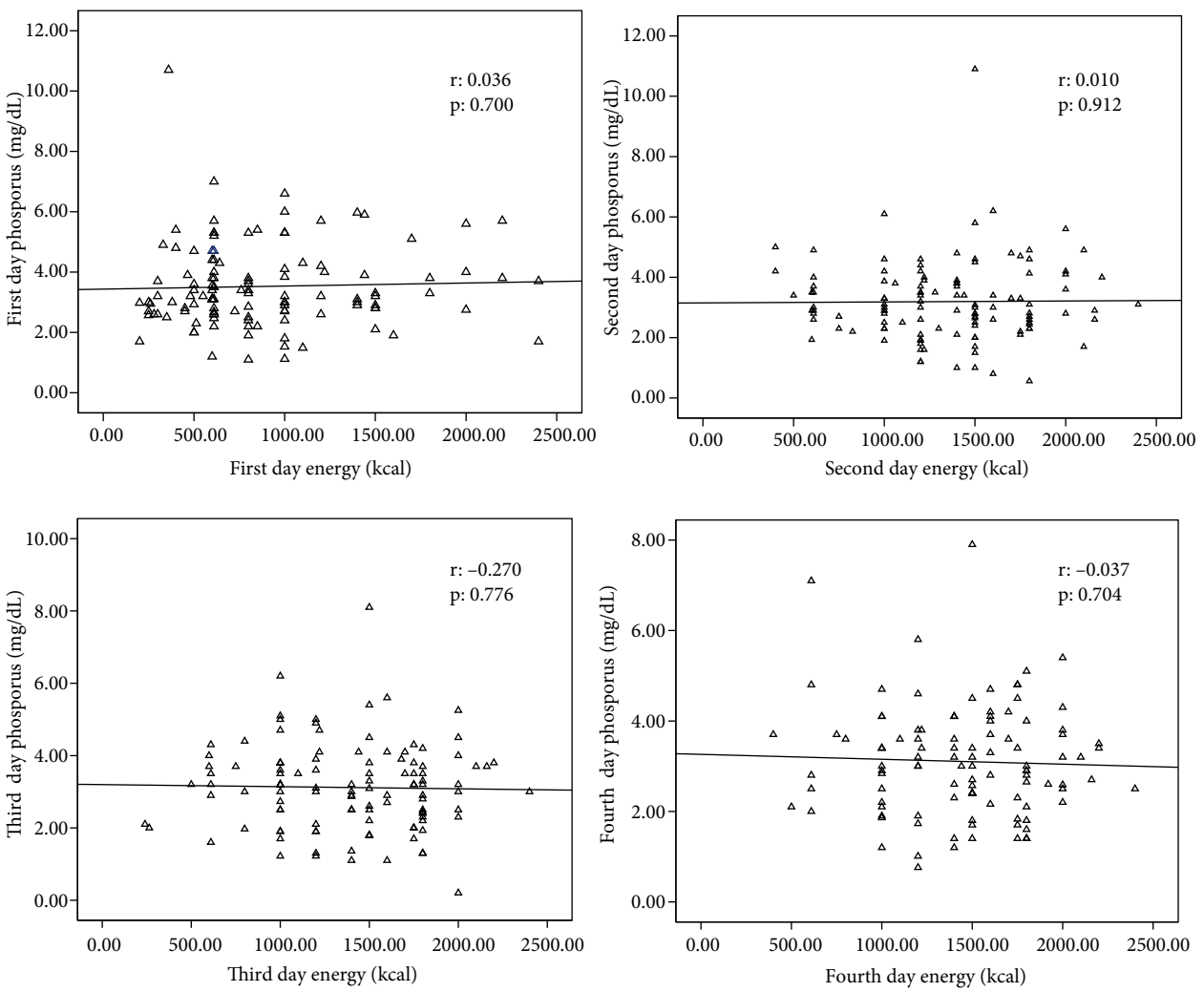

Figure. The relationship between daily energy and phosphorus levels.

Table. Demographic and laboratory features of patients.

Variables	Total, n = 117	Patients		P
		With RH, n = 61	Without RH, n = 56	
Age, years	65.8 ± 16.7	64.8 ± 17.9	66.8 ± 15.3	0.525
APACHE II score	26.6 ± 7	26.3 ± 6.2	27.0 ± 7.5	0.556
Nutrition type				
PN, n (%)	40 (34.2)	19 (31.1)	21 (37.5)	
EN, n (%)	58 (49.6)	32 (52.5)	26 (46.4)	0.756
PN + EN, n (%)	19 (16.2)	10 (16.4)	9 (16.1)	
Energy given				
Day 1 (kcal)	886 ± 499	906 ± 496	865 ± 506	0.656
Day 2 (kcal)	1455 ± 1337	1332 ± 423	1348 ± 459	0.845
Day 3 (kcal)	1377 ± 444	1381 ± 456	1373 ± 435	0.919
Day 4 (kcal)	1445 ± 418	1449 ± 432	1441 ± 407	0.924
Day 1 P level (mg/dL)	3.52 ± 1.40	2.94 ± 1.03	4.14 ± 1.48	<0.0001
Day 2 P level (mg/dL)	3.19 ± 1.32	2.54 ± 0.95	3.88 ± 1.33	<0.0001
Day 3 P level (mg/dL)	3.09 ± 1.21	2.48 ± 1.03	3.75 ± 1.05	<0.0001
Day 4 P level (mg/dL)	3.12 ± 1.22	2.45 ± 0.90	3.88 ± 1.11	<0.0001
Hypomagnesemia, n (%)	41 (35)	28 (45.9)	13 (23.2)	0.010
Hypopotassemia, n (%)	60 (51.3)	38 (62.3)	22 (39.3)	0.013
Days in ICU (days)	10 (3–68)	12 (3–68)	8.5 (3–41)	0.025
Days in mechanical ventilation (days)	8.5 (1–67)	10 (1–67)	8 (2–31)	0.120
Length of hospital stay (days)	12 (3–68)	13 (3–68)	10 (5–43)	0.229
Mortality, n (%)	88 (75.2)	50 (83.3)	38 (66.7)	0.037

Hypophosphatemia can result in cardiac arrhythmia, respiratory failure, rhabdomyolysis, and confusion (14–16). Hypopotassemia may lead to muscle paralysis, rhabdomyolysis, muscle necrosis, respiratory failure, and myocardial contraction disorders and hypomagnesemia may cause changes in electrocardiography, tetanus, and convulsions (19). Altered diaphragmatic contractility, respiratory muscle fatigue, and respiratory failure were detected in the patients with malnutrition and hypophosphatemia, which resulted in longer durations of mechanical ventilation (20–23). Reversible myocardial depression, reduction in oxygen binding capacity of the red blood cells, leukocyte dysfunction, and neuromuscular complications were reported (23–26). As a result, hypophosphatemia may result in organ dysfunctions. Mortality and morbidity rates in patients with hypophosphatemia may be higher due to the factors mentioned above.

Data regarding RH incidence in critically ill patients are very limited. There were significant discrepancies between the studies regarding the incidence of RH (4,18,27). In a study by Marik and Bedigian (18), performed in both medical and surgical ICU patients, they reported RH incidence of 34%, which was lower than our results. This may have been due to the lower APACHE scores of their patients compared to the APACHE scores of our patients. In our study, the mean age was 65 years and 70% of patients had a chronic disease while 20% had a malignancy. Advanced age, chronic disease, and malignant disorders may contribute to hypophosphatemia by causing malnutrition. In another study, Hoffman et al. (4) found the rate of hypophosphatemia to be 45% in an ICU. However, this rate was for all causes of hypophosphatemia, not just for RH (4).

RH was commonly observed in patients receiving PN due to high levels of glucose in PN solutions, which

stimulates insulin secretion, and this hyperinsulinemic state leads to hypophosphatemia, hypopotassemia, and hypomagnesemia (18). However, recent studies showed that RH was more prevalent in patients receiving EN compared to those receiving PN solutions (6,17,28). This could be explained by 3 different mechanisms. EN may result in hyperinsulinemia due to the incretin effect and thus RH may develop. The incretin effect, identified in the 1960s, describes the greater insulin secretion when a patient is given an oral bolus of glucose over an intravenous bolus (29). This is related to the production of enteral gastro-insulinotropic peptide and glucagon-like peptide-1, both of which act to increase insulin secretion from the pancreatic islet β cells. As a second possible reason, phosphate in EN solutions might be digested with more difficulty from intestines when compared with phosphate in PN solutions. Thirdly, levels of phosphate may be lower in EN solutions.

EN may lead to more frequent RH if energy introduction is provided in a relatively shorter period of time. In a retrospective study performed by Vignaud et al. (5), in 68 patients with anorexia nervosa treated in 30 different ICUs in France, they found that refeeding syndrome more frequently occurred for patients receiving high calories on the first day of the treatment. In patients with malnutrition, rapid intake of energy may result in hyperinsulinemia and thus the development of RH (15). We did not find a significantly higher rate of RH for EN patients compared to PN. This may be related to multiple factors. The risk of refeeding syndrome and concomitant hypophosphatemia is largely correlated to the degree of malnutrition. We do not have data about the degree of malnutrition in our patients. How malnutrition is managed is important, because it determines the risk for RH. We also cannot compare the supplied amount of the calories, and macro- and micronutrients, used in EN and PN.

Another form of nutrition is combined PN and EN. This form of nutrition was performed when we could not reach nutritional goals with EN. There was also no difference for RH between PN + EN and EN-only and PN-only patients.

In our study, the duration of ICU stay and the mortality rate of patients with RH were higher compared to patients without RH. There exist data showing that hypophosphatemia may be related to increased mortality rate; however, there are very limited data showing the relation between mortality rate and RH. Hoffmann et al. (4) showed a 30% mortality rate in hospitalized patients with severe hypophosphatemia. There was no increased mortality rate in the first 7 days of ICU stay in a study performed by Zeki et al. (17), and, similarly, Lubart et al. (30) did not find an increased mortality rate for 7 days and 1 month in 40 elderly patients with RH. In a study performed in 55 septic patients, severe hypophosphatemia increased mortality rates by 8-fold (2). In a recent study by Fu et al. (3), hypophosphatemia increased mortality rate and duration of ICU stay in critically ill patients. Our data showed slightly increased duration of mechanical ventilation and hospital stay, but this did not reach statistical significance. Marik and Bedigian (18) showed a significant increase in the duration of mechanical ventilation and hospital stay in patients with RH.

Symptoms of hypophosphatemia may be relevant in patients with a serum phosphorus level of <0.65 mmol/L. However, life-threating severe hypophosphatemia was observed when serum phosphorus levels were <0.32 mmol/L (2,3). It was claimed that there is a negative correlation between serum phosphorus levels and mortality rate in hypophosphatemic, critically ill patients (3). Marik and Bedigian (18) found severe hypophosphatemia in 6 (9.8%) of 61 patients with RH. In our study, we found severe hypophosphatemia in 6 (5.1%) of 117 patients. However, mortality rate was not higher in this patient group ($P > 0.05$). This could be explained by the limited number of patients with severe hypophosphatemia in our study.

This study had several limitations, such as a retrospective design, unavailability of the scoring systems regarding malnutrition, and missing data on the daily dosage of intravenous phosphorus, magnesium, and potassium replacements at the time of the treatment.

In conclusion, we found a quite high incidence of RH in an MICU when compared with previous studies. The mortality rate and the duration of ICU stay were higher in the patients with RH than those without RH. Patients at risk should receive nutrition by slow infusions and serum phosphorus, potassium, and magnesium levels should be monitored for appropriate replacement strategies.

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