ORIGINAL ARTICLE

The Clinical Implications of Hypophosphatemia Following Major Hepatic Resection or Cryosurgery

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Objectives: To determine the incidence and predisposing factors leading to postoperative hypophosphatemia after major hepatic surgery and the consequences of this electrolyte abnormality.

Design: A retrospective study.

Setting: A university tertiary care referral center.

Patients and Methods: Thirty-five consecutive patients undergoing either major hepatic resections or cryosurgery from July 1994 through January 1997 were retrospectively reviewed for the occurrence of hypophosphatemia and postoperative complications.

Main Outcome Measures: Prolonged ventilatory support, intensive care unit and hospital stays, and the incidence of postoperative complications.

Results: The overall incidence of hypophosphatemia in our series was 21 (67%) of 35 with a mortality rate of 1 (2.8%) in 35. Mean operative time, estimated blood loss, partial vascular occlusion time, and transfusion requirements were similar between the hypophosphatemic and the nonhypophosphatemic groups. The presence of postoperative complications was significantly greater in the hypophosphatemic group (17 [80%] of 21) vs the nonhypophosphatemic group (4 [28%] of 14) ($P<.05$). The incidence of antacid use in the hypophosphatemic group (14 [66%] of 21) was significantly higher than the use in the nonhypophosphatemic group (2 [14%] of 14) ($P<.05$).

Conclusions: Hypophosphatemia commonly occurs in major hepatic procedures. The presence of moderate hypophosphatemia is associated with the use of antacid therapy but no other perioperative or operative variables. The occurrence of hypophosphatemia correlates with an increased incidence of postoperative complications. Awareness of this entity can direct aggressive replacement of phosphates and avert the occurrence of severe hypophosphatemia and associated complications.

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MAJOR HEPATIC resection and cryosurgery have been used for the management of primary and metastatic tumors of the liver to provide prolonged survival and potential cure.[1] Recent advances in anesthetic and intraoperative management have reduced operative mortality to 0.6% to 2.7%.[2,3] Despite the refinement of surgical technique and advances in anesthetic management, major hepatic procedures are not without considerable morbidity, which ranges from 24% to 37%.[3,4] The postoperative period is affected by large fluid shifts and stimulation of hepatic enzyme systems. Postresectional hypophosphatemia has been reported by a few authors in case reports and a single reported series.[3,4] Phosphate is an essential anion with a main role in the formation of high-energy bonds. Phosphate is also necessary for the normal function of red blood cells, platelets, oxygen release from oxyhemoglobin, adenosine 5′-triphosphate synthesis, and the central nervous system. The clinical consequences of severe hypophosphatemia are well recognized and include impaired diaphragmatic contractility, ventricular irritability, myocardial depression, and insulin depression. George and Shiu[3] noted a significant correlation between severe hypophosphatemia (phospate level <0.32 mmol/L [<1.0 mg/dL]) and major postoperative complications in a series of patients undergoing formal hepatic lobectomies at Memorial Sloan-Kettering Hospital, New York, NY. The complications studied included cardiopulmonary depression, infection, hemorrhage, and liver failure. The purpose of our current study is to determine the incidence and predisposing factors leading to postopera-

PATIENTS AND METHODS

The medical records of 35 consecutive patients undergoing major hepatic procedures, including hepatic lobectomies and cryosurgery, between July 1994 and January 1997 were reviewed retrospectively. All operative procedures were performed by the senior author (L.B.J.). All minor resections (segmentectomies, wedge resections, and single-probe cryosurgery) were excluded. Eleven patients underwent operation for benign disease that included hemangiomas (8 patients), giant hepatic cysts (2 patients), and primary sclerosing cholangitis (1 patient). The indication for operation in 24 patients was malignant disease that included metastatic colon cancer (18 patients), primary hepatocellular carcinoma (4 patients), and other metastatic lesions (soft tissue sarcoma and Wilms tumor) (2 patients).

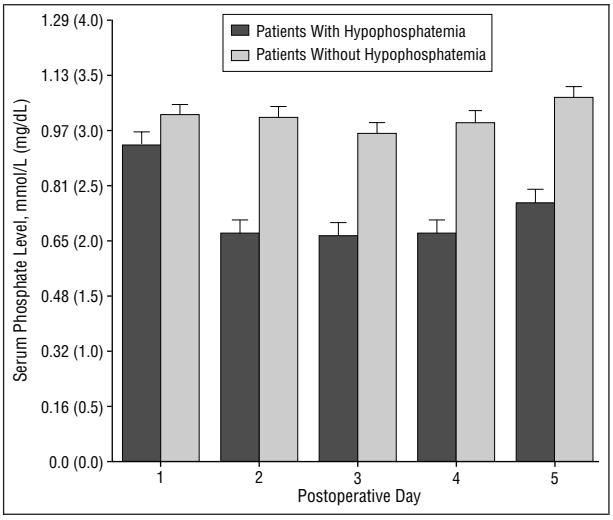
In all patients, age, sex, operative time, estimated blood loss, partial vascular occlusion time, transfusion of stored blood, autologous transfusion from intraoperative cell salvage, and the use of fresh frozen plasma, crystalloid, and colloid were analyzed. The postoperative variables analyzed included prolonged ventilatory support, intensive care unit and hospital stays, and complications. Postoperative laboratory values were examined, including white blood cell and platelet counts, prothrombin time, hematocrit, electrolyte, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, calcium, magnesium, and inorganic phosphate. Ionized phosphate and calcium values were not examined in this study. Data are presented as the mean ± SEM.

Statistical analysis was performed using Student *t* test or Mantel-Haenszel test as appropriate. The evaluation of hypophosphatemia was performed using analysis of variance. The χ^2 test was used to compare complications.

tive hypophosphatemia in major hepatic procedures and assess the impact of moderate hypophosphatemia (phosphate level <0.81 mmol/L [<2.5 mg/dL] and >0.32 mmol/L [>1.0 mg/dL]) on major postoperative morbidity.

RESULTS

There was an overall incidence of complications in 21 (67%) of 35 patients and perioperative mortality occurred in 1 (2.8%) of 35 patients. Of the 2 study groups, the first group (n = 21) was defined by the presence of hypophosphatemia (phosphate level <0.81 mmol/L [<2.5 mg/dL]) and the second group (n = 14) had a normal phosphate level (0.97-1.45 mmol/L [3.0-4.5 mg/dL]). In the group with hypophosphatemia, there were 11 men and 10 women with a mean (± SEM) age of 56.5 ± 12.2 years. In the group without hypophosphatemia, there were 10 men and 4 women with a mean (± SEM) age of 51.4 ± 18.2 years. Of the 21 patients with hypophosphatemia, there were 13 patients with colon cancer, 5 with hemangiomas, 2 with hepatomas, and 1 with primary sclerosing cholangitis. Of the 14 patients without hypophosphatemia, there were 5 with colon cancer, 3 with hemangiomas, 2 with hepatomas, 2 with cysts, and 2 with Wilms tumor and soft tissue sarcoma. Both groups had similar comorbidities, with a 14% incidence of cardiac disease in both groups. Type 1 diabetes mellitus was present in 4 (18%) of the 21 patients with hypophosphatemia vs 3 (21%) of the 14 patients without hypophosphatemia. Compromised immune systems due to chemotherapeutic administration in the last 6 months were present in 7 (21%) of the 35 patients in both groups. The level of preoperative nutrition measured by serum albumin levels was identical, with a mean value of 28 g/L in both groups. All patients had a serum phosphate level measured as an outpatient within 2 weeks of their operation. The mean phosphate level in the group with hypophosphatemia was 1.06 mmol/L (3.3 mg/dL) and 1.03 mmol/L (3.2 mg/dL) in the group without hypophosphatemia. The presence of hypophosphatemia was demonstrated in 21 (60%) of all 35 patients undergoing major hepatic procedures. A decrease in serum phosphate levels was noted in all patients on the first postoperative day with a nadir on the third day. We considered patients to have hypophosphatemia if they had a serum phosphate level less than 0.81 mmol/L (2.5 mg/dL) on either the first or second postoperative day. Both groups experienced a decrease from baseline with the levels in the hypophosphatemic group significantly lower than those in the nonhypophosphatemic group (**Figure**). Furthermore, the phosphate levels were found to be significantly different between the hypophosphatemic group vs the nonhypophosphatemic group during the first 5 postoperative days using analysis of variance analysis ($P<.005$).



Comparison of mean (± SEM) postoperative serum phosphate levels between patients with hypophosphatemia and those without hypophosphatemia measured on each of the first 5 postoperative days.

Operative time, estimated blood loss, and partial vascular occlusion time were examined and found to be similar between both groups. Intraoperative blood transfusion was examined in both groups with blood products

Table 1. Intraoperative Data*

	Group	
	Hypophosphatemia	Nonhypophosphatemia
Operating time, h:min	6:21 ± 0:10	7:31 ± 3:30
Partial vascular occlusion, min	23.5 ± 22.0	19.0 ± 12.6
Packed red blood cells, U	1.75 ± 1.51	4.00 ± 4.15
Cell saver, U	1.35 ± 2.31	1.11 ± 1.96
Fresh frozen plasma, U	1.60 ± 2.29	3.56 ± 2.79
Crystalloid, mL	7267 ± 3272	12 000 ± 4268

*Data are presented as mean ± SEM.

Table 2. Postoperative Care Data*

	Group	
	Hypophosphatemia	Nonhypophosphatemia
Ventilatory support, d	1.56 ± 1.33	0.70 ± 0.82
Intensive care unit stay, d	3.09 ± 6.60	1.82 ± 1.32
Hospital stay, d	16.22 ± 12.09	11.22 ± 7.03

*Data are presented as mean ± SEM.

encompassing packed red blood cell, cell saver, and fresh frozen plasma units and volume expanders including colloids and crystalloids. A trend toward an increased requirement for red blood cell and fresh frozen plasma transfusions was present in the nonhypophosphatemic group, but it was not significant (**Table 1**). The associated morbidity of hypophosphatemia was examined by reviewing the need for prolonged ventilatory support and length of both intensive care unit and total hospital stay. A trend toward prolonged ventilatory support and prolonged intensive care unit and hospital stay was present in the hypophosphatemic group, but it was not significant (**Table 2**).

The incidence of postoperative complications was significantly greater in the hypophosphatemic group (17 [80%] of 21) vs the nonhypophosphatemic group (4 [28%] of 14) ($P<.05$). Postoperative complications included pancreatitis, pulmonary infection, gastrointestinal hemorrhage, wound infection, and ileus (**Table 3**). The overall mortality in the series was low, with a single death in the hypophosphatemic group (2.8%).

Cryotherapy has emerged as a new therapeutic approach for the management of unresectable liver tumors and an adjunct to hepatic resection. As this technique is refined, the use of this surgical adjunct may become more widespread. Hypophosphatemia occurred in 5 (71%) of 7 patients who underwent cryotherapy with no significant increase in complication rates. Cryotherapy results in a significant but transient elevation in aminotransferases in both hypophosphatemic ($P<.002$) and nonhypophosphatemic ($P<.04$) groups who underwent cryotherapy (**Table 4**).

Table 3. Postoperative Complications

	No. of Patients	
Type of Complication	Hypophosphatemia (n = 21)	Nonhypophosphatemia (n = 14)
Pancreatitis	4	1
Pulmonary	3	1
Infection	5	0
Prolonged ileus	3	0
Gastrointestinal bleeding	2	2
Total (%)	**17** (80)	**4** (28)*

**Student* t *test,* $P<.05$ *vs hypophosphatemia.*

Patients with hypophosphatemia who underwent cryotherapy required ventilatory support for a longer mean period (2.2 days) vs patients with hypophosphatemia who underwent resection (1.6 days) and patients in the nonhypophosphatemia group (0.6 days) ($P<.002$). Despite this increased need for ventilatory support there was no significant increase in intensive care unit or hospital stay.

Phosphate replacement was initiated in the postoperative period for serum phosphate levels below 0.97 mmol/L (3.0 mg/dL) (normal range, 0.97-1.45 mmol/L [3.0-4.5 mg/dL]). By the first postoperative day, the average replacement requirement in the hypophosphatemic group was 15 mmol/d of either sodium phosphate or potassium phosphate, increasing to a peak of 25 mmol/d by the third postoperative day. Phosphate requirement after the third postoperative day then began to decline. Patients in the nonhypophosphatemic group required a mean replacement of 5 mmol/d of either sodium phosphate or potassium phosphate.

Antacid therapy was more prevalant in the hypophosphatemic group (14 [66%] of 21) vs the nonhypophosphatemic group (2 [14%] of 14). Antacids were usually administered by nasogastric tube or orally in the form of 30 mL of aluminum-containing antacids 4 times daily. Evaluation of the 2 groups demonstrated a significant correlation between the use of antacids and the occurrence of hypophosphatemia ($P<.05$). Other variables analyzed included the levels of serum albumin, alkaline phosphatase, bilirubin, and liver aminotransferases.

COMMENT

Phosphate is an essential component in multiple metabolic processes and the normal function of red blood cells, leukocytes, platelets, and oxyhemoglobin.[5] Hypophosphatemia has been reported in various clinical scenarios, including diabetes mellitus, pancreatitis, gram-negative sepsis, respiratory alkalosis, starvation, and antacid therapy.[6-11] Hypophosphatemic syndrome was first observed after refeeding severely malnourished individuals in World War II concentration camps.[12,13] This syndrome was associated with life-threatening cardiopulmonary and neurologic complications. Severe hypophosphatemia was also noted in patients receiving phos-

Table 4. Cryotherapy Groups vs Resection Groups*

	Patients With Hypophosphatemia		Patients Without Hypophosphatemia	
	Cryotherapy	Resection	Cryotherapy	Resection
Peak aspartate aminotransferase level, U/L	2722 ± 884†	462 ± 60	719 ± 24	440 ± 102
Ventilatory support, d	2.2 ± 0.9‡	1.3 ± 0.3	1.0 ± 0.0	0.6 ± 0.2
Intensive care unit stay, d	2.0 ± 0.4	1.8 ± 4.8	3.0 ± 0.9	2.0 ± 0.3
Nadir phosphate levels, mmol/L (mg/dL)	0.52 ± 0.0 (1.6 ± 0.0)	0.68 ± 0.03 (2.1 ± 0.1)	0.90 ± 0.03 (2.8 ± 0.1)	0.97 ± 0.06 (3.0 ± 0.2)
Complications, No. (%)	4/5 (80)	12/18 (66)	0/2 (0)	4/12 (33)

*Data are presented as mean ± SEM, unless noted otherwise.
†$P<.001$.
‡$P<.002$.

phate-free hyperalimentation.[8,14,15] Recently, a similar phenomenon was recognized in patients with trauma with clinically significant hypophosphatemia.[16-19] Severe hypophosphatemia has also been recognized in elective aortic aneurysm and bypass surgery to affect patient morbidity.[20]

A minor fraction of the total body phosphate exists in inorganic form and requires several days to be converted to the organic form. Hypophosphatemia does not become clinically important in the normal physiologic state due to the large organic phosphate reserve pool.[20-22] However, during acute fluid shifts like those experienced in the postoperative period, significant hypophosphatemia can occur. Hypophosphatemia related to hepatic surgery does not rest solely on postoperative fluid shifts. Hypophosphatemia results from a combination of fluid shifts, the extent of hepatic resection, and the patient's phosphate reserve. The consequences of hypophosphatemia are the deprivation of phosphate from the generation of adenosine 5′-triphosphate and 2,3-diphosphoglycerate leading to increased hemoglobin-oxygen affinity and subsequent tissue anoxia. Respiratory muscle weakness and cardiac dysfunction have been repeatedly described in association with low serum phosphate levels.[5]

The period following major intra-abdominal operations has been associated with moderate but transient hypophosphatemia. Glucose administration in the postoperative period increases oxidative phosphorylation, especially in those patients noted to be severely malnourished in the perioperative period.[23-25] A subsequent high metabolic state is then imposed resulting in a severe and precipitous decrease in serum phosphate levels. Hypophosphatemia has also been reported in association with episodes of acute liver failure. During major hepatic resections a period of rapid hepatic regeneration and early mitotic division in the residual hepatic substance is experienced. Islami et al[26] and Fisher et al[27,28] described a canine subtotal hepatectomy model that led to rapid uptake of radiolabeled phosphate and increased mitotic counts in the regenerating residual liver, resulting in hypophosphatemia.

Hypophosphatemia commonly occurs in major hepatic procedures including major hepatic resection and cryosurgery. The occurrence of moderate hypophosphatemia is associated with the use of antacids but not with any other perioperative or operative variables studied. Those patients experiencing hypophosphatemia demonstrated a trend toward prolonged intubation and intensive care unit and hospital stays. A clinically significant increase in morbidity was demonstrated in the hypophosphatemic group. Patients in the cryosurgery cohort required prolonged ventilatory support and had significant morbidity, which was shared with the hypophosphatemic resection group. However, we cannot demonstrate a direct causal relationship. When hypophosphatemia occurs, an aggressive replacement approach with the administration of as much as 45 mmol/d of either sodium or potassium phosphate beginning on the first postoperative day can avert severe hypophosphatemia. However, overaggressive infusions must be avoided secondary to the complications of hypocalcemia, hypotension, and renal dysfunction.

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Plasma Homocysteine as a Risk Factor for Vascular Disease: The European Concerted Action Project

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Context.—Elevated plasma homocysteine is a known risk factor for atherosclerotic vascular disease, but the strength of the relationship and the interaction of plasma homocysteine with other risk factors are unclear.
Objective.—To establish the magnitude of the vascular disease risk associated with an increased plasma homocysteine level and to examine interaction effects between elevated plasma homocysteine level and conventional risk factors.
Design.—Case-control study.
Setting.—Nineteen centers in 9 European countries.
Patients.—A total of 750 cases of atherosclerotic vascular disease (cardiac, cerebral, and peripheral) and 800 controls of both sexes younger than 60 years.
Measurements.—Plasma total homocysteine was measured while subjects were fasting and after a standardized methionine-loading test, which involves the administration of 100 mg of methionine per kilogram and stresses the metabolic pathway responsible for the irreversible degradation of homocysteine. Plasma cobalamin, pyridoxal 5′-phosphate, red blood cell folate, serum cholesterol, smoking, and blood pressure were also measured.
Results.—The relative risk for vascular disease in the top fifth compared with the bottom four fifths of the control fasting total homocysteine distribution was 2.2 (95% confidence interval, 1.6-2.9). Methionine loading identified an additional 27% of at-risk cases. A dose-response effect was noted between total homocysteine level and risk. The risk was similar to and independent of that of other risk factors, but interaction effects were noted between homocysteine and these risk factors; for both sexes combined, an increased fasting homocysteine level showed a more than multiplicative effect on risk in smokers and in hypertensive subjects. Red blood cell folate, cobalamin, and pyridoxal phosphate, all of which modulate homocysteine metabolism, were inversely related to total homocysteine levels. Compared with nonusers of vitamin supplements, the small number of subjects taking such vitamins appeared to have a substantially lower risk of vascular disease, a proportion of which was attributable to lower plasma homocysteine levels.
Conclusions.—An increased plasma total homocysteine level confers an independent risk of vascular disease similar to that of smoking or hyperlipidemia. It powerfully increases the risk associated with smoking and hypertension. It is time to undertake randomized controlled trials of the effect of vitamins that reduce plasma homocysteine levels on vascular disease risk. *JAMA.* 1997;277:1775-1781

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