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Original Research Article

Post hepatectomy hypophosphatemia and its association with initial liver insufficiency and morbidity

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ABSTRACT

Background: Hypophosphatemia after liver resection is a frequent issue, only a small subset of patient requires correction. This group of patients associated with morbidity was evaluated.
Methods: Liver resections were retrospectively analysed between Jan 2015 and March 2018. We evaluated the association of hypophosphatemia (defined as serum phosphate <2mg/dl) and the occurrence of initial liver insufficiency (ILI) [Elevation of total bilirubin above 2mg/dl above the preoperative values and INR more than 1.7]. Any association of hypophosphatemia with post-operative major morbidity (Clavien Dind0 grade 3 and 4 complications) was also studied.
Results: A total of 86 patients were analysed during the study period, 28 patients were excluded as per the exclusion criteria and 58 patients were included in the study. Majority of the patients in our study populations were above 60yrs of age with male preponderance. Hepatocellular carcinoma was the frequent indication for surgery. Significant hypophosphatemia was seen in 15 patients reaching nadir values on Post-operative day 3. Clavien Dindo Grade- 3,4 complications was seen in 7 patients and 8 patients had Initial liver insufficiency.
Conclusions: This study tried to evaluate only the subset of patients who had significant hypophosphatemia who required replacement with initial liver insufficiency and morbidity. We have found association of hypophosphatemia with initial liver insufficiency and morbidity. Hence, authors advocate early identification and correction to avoid possible complications.

Keywords: Hypophosphatemia**,** Initial liver insufficiency, Post hepatectomy

INTRODUCTION

Phosphate is one of the essential electrolytes which are involved in many vital enzymatic activities. The complex interaction between magnesium, calcium and phosphate in maintaining the musculoskeletal system cannot be underestimated. Phosphate is present in nucleic acids like DNA and RNA. It is the source of energy in our day to day activities in the form of ATP.

Liver tissue contains 0.3% of phosphate by weight.[1] This phosphate can become less in many instances in our body which is termed as hypophosphatemia. Many surgeries like open heart surgeries are associated with hypophosphatemia.[2,3] Of relevance to this paper is the hypophosphatemia after hepatectomy which is more profound and frequent and associated with complication.[4] Initial liver insufficiency (ILI) is seen after hepatectomies which will resolve in due course. But whether this initial liver insufficiency associated with a correctable issue like hypophosphatemia needs to be studied in detail.

Many theories are proposed to elaborate the relationship between hypophosphatemia and liver surgeries like, rapid

influx due to regeneration, renal loss etc. none of the theories has stood the test of time and validated appropriately.[5,6]

Liver regeneration and metabolic activity peaks in POD 3 and stabilizes by post-operative day 5-7. Further phosphate mobilization from bones may take up to 1week. Hence the initial measurement and adequate supplementation is necessary for adequate homeostasis during the early post-operative period.

This study looks to the possible relation between initial liver insufficiency, post-operative complications with hypophosphatemia and it also looks at the relevance of correcting the hypophosphatemia.

Authors have hypothesized that initial liver insufficiency and early postoperative complications is associated with hypophosphatemia.

METHODS

This study is a retrospective study of a prospectively maintained database. Institutional data between Jan 2015 and March 2018 was analysed. Patients undergoing elective hepatectomy and fulfilling the inclusion and exclusion criteria as elaborated below were analysed.

Inclusion criteria

- Patient undergoing elective hepatectomy
- Serum phosphate measurement with in post-operative day 7.

Exclusion criteria

- Serum phosphate not measured with in post-operative day 7
- Chronic renal failure patients
- Emergency hepatectomy for trauma, tumour bleeds etc.
- Child B, C cirrhosis
- Age < 12 and >70years
- Patients on aluminum-based antacids, TPN, causing interference with phosphate levels in the serum
- Major blood transfusions.

Initial liver insufficiency is defined for the study as

- Hypophosphatemia is defined as serum level less than 2mg/dl.
- Major Hepatectomy defined as resection of 3 or more segments and major blood transfusion defined as transfusion of more than 5 units of blood.

Serum phosphate was measured on post-operative day-2, 3 till 7 and additional measurement done as required. Cut off for substituting phosphate was when serum phosphate level was less than 2.0mg/dl. Phosphate was administered as an intravenous injection. The dose was repeated as required. 30 days post-operative morbidity, readmission, mortality was analysed using Clavien Dindo.[7]

RESULTS

A total of 86 patients were analysed during the study period, 28 patients were excluded as per the exclusion criteria and 58 patients were included in the study.

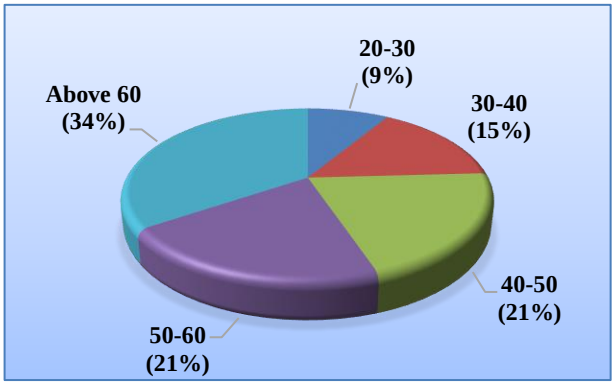

Figure 1: Age distribution of patients.

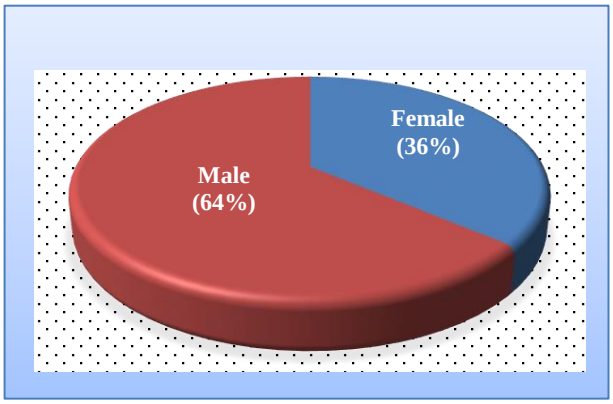

Figure 2: Sex distribution of patients.

Majority of the patients were above 60 yearrs of age which was about 34%, least number of patients was seen in the age group between 20-30age groups (Figure 1). Male to female ratio was 64:36 and there was a male preponderance (Figure 2).

Table 1: Distribution of patients by disease.

Disease	Frequency	Percent
Benign	15	25.86
Carcinoma colon with liver metastasis	4	6.90
Carcinoma gall bladder	6	10.34
Cholangiocarcinoma	5	8.62
Hepatocellular carcinoma	25	43.10
Others	3	5.17
Grand Total	58	100.00

Hepatocellular carcinoma was the major disease of present study patients about 43%. Second most common was benign 26%, which included - recurrent pyogenic cholangitis, haemangioma etc. Carcinoma colon with liver metastasis was the least set of patients 4 (7%) (Table 1).

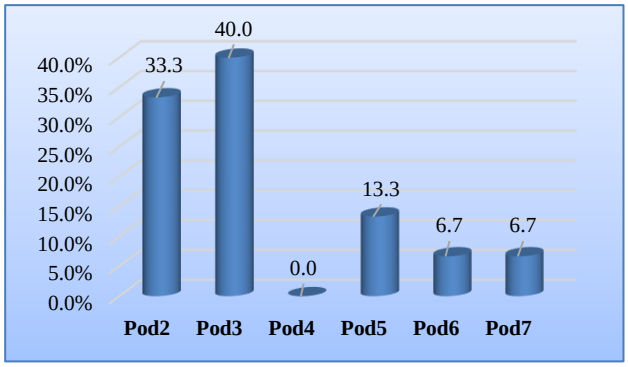

Figure 3: Post- operative day phosphate levels.

In present study Hypophosphatemia was seen in 37 patients out of the 58 patients. But the total number of patients experiencing hypophosphatemia which required correction was-15, hence we have used only this subset of patients for present analysis. Peak incidence was noted in POD 3, which had 6 patients (40%), followed by POD 2 with 5 patients (33%) (Figure 3). Elevation of bilirubin was seen in 8 patients (14%), elevation of INR seen in 7 patients (12%). Initial liver insufficiency is defined as presence of either elevated bilirubin or INR. This was seen in total 8 patients (13.7%) of the total number of 58 patients (Figure 4).

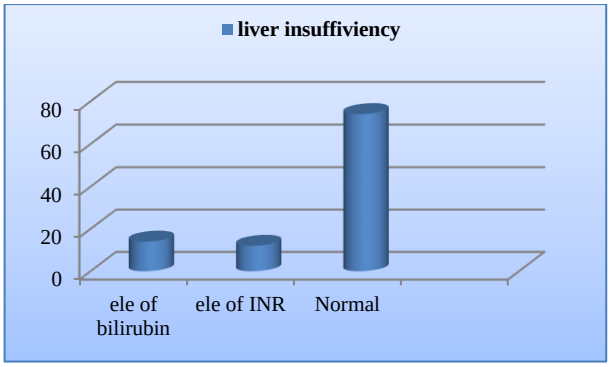

Figure 4: Elevation of bilirubin and elevation of INR.

Complications arising in post-operative period were defined based on Clavien Dindo complication grading. We have taken into account grade 3, 4 as one group. A total of 7 patients (12%) had Calvein Dindo grade 3, 4 complications (Figure 5).

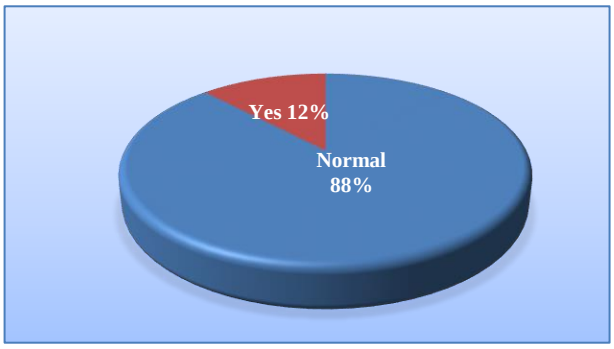

Figure 5: Clavien Dindo Grade - 3,4.

Table 2: Chi square test to see association between the hypophosphatemia and initial liver insufficiency.

		Initial liver insufficiency			Chi-square value	P value
		Normal	Yes	Total		
Serum Phosphate levels.	Normal	41	2	43	11.686	0.001
	Low	9	6	15		
	Total	50	8	58		

Table 3: Chi square test to see association between the hypophosphatemia and Clavien Dindo Grade - 3, 4 complications.

		Clavien Dindo Grade – 3,4			Chi-Square Value	P-Value
		Normal	Yes	Total		
Serum Phosphate levels.	Normal	41	2	43	8.621	0.003
	Low	10	5	15		
	Total	51	7	58		

15 patients had hypophosphatemia and 8 patients had initial liver insufficiency. Of the 8 patients who had initial liver insufficiency 6 patients had hypophosphatemia. On chi square analysis p-value was <0.001which was statistically significant (Table 2). 15 patients had hypophosphatemia and 7 patients had

Clavien Dindo Grade - 3, 4 complications. Of the 7 patients who had Clavien Dindo Grade 3, 4 complications 5 patients had hypophosphatemia. On chi square analysis p-value was <0.003which was statistically significant (Table 3).

DISCUSSION

Phosphorus does not exist in free biological form; it is usually present as phosphate (PO4). There exists a complex interaction in the body between phosphate, calcium and magnesium. The movement of these minerals during absorption from intestine, reposition in bone, and excretion from kidney is guided by many hormones.[8]

This study is a retrospective study trying to evaluate the possible association of hypophosphatemia with initial liver insufficiency and early post-operative complications.

In present study we operated predominantly on patients who were above 60 years of age. There was a male predominance.

Hepatocellular carcinoma was the major disease of present study patients (43%). Second most common was benign (26%), which included - recurrent pyogenic cholangitis, haemangioma etc.

Malcolm and his colleagues showed occurrence of hypophosphatemia in 96% of the patients and in fact told early development of hypophosphatemia within 72 hours is beneficial and indicates good liver regeneration. While delayed development is associated with morbidity.[9]

In present study Hypophosphatemia was seen in 37 patients (64%). Of these only 15 patients required corrections (26%), hence these patients were included in the study. With this we have tried to exclude all the patients who will have transient hypophosphatemia who might not be significantly associated with complications.

Is hypophosphatemia a normal physiological sequel after hepatectomy or is it associated with major complications? Some study has shown complications associated with hypophosphatemia and have suggested aggressive monitoring and in fact advocated parenteral replacement aggressively.[10,11] While others have shown that hypophosphatemia is not associated with major complications.[12,13]

Authors have used Clavien Dindo classification to study the surgical complications7. In present study authors found statistically significant association observed between the occurrence of hypophosphatemia and occurrence of Clavien Dindo 3, 4. (P-value < 0.01). Lee and his colleagues did not show any association with complications occurring with hypophosphatemia.[13]

Early identification of post- operative hepatic insufficiency is very important to give the best supportive care. Many markers have been evaluated, like aspartate aminotransferase to platelet count ratio, albumin, serum C-reactive protein (CRP) levels, but serum bilirubin and INR/ prothrombin has been accepted by many.[14-16]. This is also recommended by the International Study Group of Liver Surgery (ISGLS) who have put forward grading system using these parameters.[17] Hence, we decided to evaluate the initial liver insufficiency by using these two parameters.

Authors found a statistical significance between the occurrence of Hypophosphatemia and Initial Liver Insufficiency. (P-value <0.01). Authors have not analysed hypophosphatemia in between major and minor hepatectomies separately. This is because significant trauma to liver will be there in even non-segmental resections or non- anatomical resections. Also, many studies have repeatedly showed no significant hypophosphatemia in major liver resections.

Authors have also not bifurcated hypophosphatemia into mild, moderate or severe as present sample size is less.[18] This study has not evaluated any parameters relating to the renal loss of phosphates.

The pathophysiology of hypophosphatemia is still controversial. The debate continues predominantly between the theories of excessive influx into the liver and urinary phosphate loss. The theories supporting the controversies are discussed below.

The urinary phosphate loss is probably due to derangement of normal hepatorenal messaging system. Further the recent studies have proposed an existence of a novel phosphaturic factor called phosphatonins. The exact mechanism of synthesis and metabolism has not been elaborated in any of the studies.[5,6,19]

Empirically ascribed amplified phosphate utilization by the regenerating hepatocytes. This hypothesis is supported by canine models subjected to sub-total hepatectomy that led to rapid uptake of radiolabeled phosphate and increased mitotic counts in the regenerating residual liver, resulting in HP.[20,21]

Is routine administration of phosphate advisable after hepatectomy? This is still controversial. The pathophysiology of hypophosphatemia, the novel investigations and rational of administration has been evaluated Dutta and his colleagues.[22] Studies by Tan and colleagues do not endorse the routine administration of hyper alimentation with supra therapeutic phosphorus because of its potential morbidity.[12]

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