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EFFECT OF HYPOPHOSPHATEMIA ON POST OPERATIVE OUTCOMES IN CARDIAC SURGERY

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Contribution

MN, AAK conceived the idea and planned study. FA, MID helped in collection, assembly and interpretation of the data. MN did critical revision of the article for important intellectual content. All authors contributed significantly to the submitted manuscript.

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ABSTRACT

Objective: To establish association of phosphorus levels with surgical outcome of patients in our setup.

Methodology: This was an case control study conducted at Department of Cardiac Surgery, Civil Hospital Karachi from May 2015 to August 2015 . Phosphorus levels were measured at three points of hospital stay; a) preoperatively b) immediately post operatively and c) at first post operative day. Patients were divided in two groups according to immediate post operative phosphate levels; those with hypophosphatemia (<2.7 mg/dl) and a control group with normal phosphate levels (2.7-4.5 mg/dl). Pre and post operative management including duration of Heart Lung Machine, cross clamp, duration of ventilation, ICU Stay, cardio active support needed and amount of blood loss ,use of IABP and mortality were recorded.

Results: A total of 55 patients were included in the study .Hypophosphatemia was found in 27.3% patients immediately after surgery and 38.2% patients at first post operative day. No significant difference was found in intra operative management of patient. However, post operative course of both groups differed significantly in two groups in terms of duration of ventilation (11.9±11.6 versus 6.1±5.5 hours, p=0.002), duration of ICU stay (3.5±1.5 versus 2.4±0.7 days, p=0.01) and duration of inotropic support needed (45.5±31.2 versus 25.0 ±12.4 hours, p=0.001). Patients with hypophosphatemia had significantly more blood loss (998.7±1217.8 versus 526.8±322.0, p=0.001) and received more blood transfusions post operatively (1.80±2.09 versus 0.8±0.9, p=0.009). No significant difference of post operative mortality was found in both groups (15.3% versus 3.2%, p=0.07).

Conclusion: Hypophosphatemia is documented in one third of postoperative cardiac surgery patients and is associated with prolonged ventilation, duration of ICU stay and inotropic support with more blood loss.

Key Words: CABG, Ionotropic support , ICU, Ventilation, Post-operative

INTRODUCTION

Hypophosphatemia is common in ICU patients especially those undergoing cardiac surgery with extracorporeal circulation.[1,2] Hypophosphatemia (below 2.50 mg/dl) was observed in 50% of postoperative patients after Cardiac Surgery patients. [3] Previous studies reported that 88% of cardiac patients had significant deficiency one or more electrolyte as compared to 20% of control individuals; p <0.001), with a significant difference of phosphate levels observed in both groups, (phosphate 0.43 +/- 0.22 versus 0.92 +/- 0.32, p= 0.001).[2]

Zazzo et al. reported that mortality is significantly higher in hypophosphatemic patients (30% versus 15.2%; p= 0.05).[4] Patients undergoing cardiac surgery on heart lung machine encounter an acute phase reaction which was correlated to several post operative complications.[5] Another study reported that significant hypophosphatemia (0.8 mg/dl) was present in 34.3% of patients and associated with adverse surgical outcomes in terms of prolong ventilation, need of cardio active support and prolonged hospital stay.[6]

However prevalence of hypophosphatemia and its affect on surgical outcomes is not documented in our setting. This study is designed to evaluate phosphorus levels pre and post operatively with postoperative monitoring of patients and to establish association of phosphate levels with surgical outcome of patients.

METHODOLOGY

This was case control study conducted at Department of Cardiac Surgery, Civil Hospital Karachi from May 2015 to August 2015. All patients admitted in cardiac surgery department undergoing open heart surgeries with cardio pulmonary bypass including Coronary Artery Bypass Grafting (CABG), Aortic or Mitral Valve replacement, Atrial and Ventricular Septal Defect Closures were recruited in this study.

Patients of age <18 or >75 years undergoing CABG with valve replacement or Double valve replacement or post infarct ventricular septal defect were excluded from this study.

Following measures were taken during all surgeries:

- Standardized anesthesia was given for complete sedation.
- Patients were kept on heart lung machine during whole procedure.
- Anterograde/retrograde cardioplegia was given to arrest cardiac contractility.
- Core temperature kept at 30 ^{0}C during CPB.
- Hemodilution was achieved by intravenous (I/V) crystalloid fluids to keep the hematocrit 20-22.
- After completion of procedure patients were shifted immediately to cardiothoracic ICU.

Standard post operative care included:

- Mechanical ventilation on Continuous Mandatory Ventilation (CMV)
- Cardio active support was given (Nor adrenaline/ Adrenaline/milrinon) to maintain Mean Arterial Pressure (MAP) between 60 – 90 mm Hg.
- Analgesia was given through Intravenous (I/V) route if required.
- Weaning from mechanical ventilation done if patients are thermodynamically stable, absence of significant bleeding (<100 ml/hr), adequate urine output (> 1ml/kg/hr), oxygen saturation > 95%, FiO_2<40%, maintaining $PaCO_2$ by Arterial Blood Gases (ABGs) and patient able to respond and follow directions.
- After wards, patients were placed on T Piece for 30 minutes and extubated if no signs of respiratory or cardiac distress.
- Patients shifted from ICU to ward at least 24-48hours of stay in ICU.
- Patients were observed in ward for hemodynamic stability, adequate urine output, consciousness, mobility, adequate anticoagulation for valve replacement surgeries (maintaining INR between 2-3) and wound healing and discharged accordingly.

Data was collected through structured questionnaire which included base line investigations preoperatively and electrolyte levels (Sodium, Potassium, Chlorine, Calcium, Magnesium, Phosphorus) at three points of hospital stay; a) preoperatively, b) immediately post operatively and c) at first post op day. Patients were divided in two groups according to immediate post operative phosphate levels; those with hypophosphatemia (<2.7 mg/dl) and a control group with normal phosphate levels (2.7-4.5 mg/dl).

Per operative management (durations of cardiopulmonary bypass, duration of cross clamp, units of packed cells and FFPs transfused and intra operative fluids) were recorded. Post-op management (duration of ventilation, duration of ICU Stay, duration of cardio active support needed, amount of blood loss and post op transfusions, use of Intra Aortic Balloon Pump (IABP), duration of post-op hospital stay and post-op mortality) was also recorded and surgical outcome was measured on above mentioned parameters in both groups.

After completing data collection, patients were divided in two groups; with normal phosphate levels (2.7 - 4.5mg/dl) and very low phosphate levels (significant hypophosphatemia,

<0.8 mg/dl). Then these groups were compared to evaluate how phosphate levels affected post operative management of patients. SPSS software 16 was be used to evaluate and compare findings of this research.

RESULTS

A total of 55 patients were included in the study with mean age of study population was 43.21±16.11 years. Out of them 35 (63.6%) were males. Ischemic Heart Disease (IHD) was most prevalent found in 30 (54.5%) patients, followed by mitral stenosis (MS) and mitral regurgitation (MR) with prevalence of 10 (18.2%) each. CABG was performed in 54.5% and valve replacement in 41.8% cases.

Hypophosphatemia was found in 15 (27.3%) patients immediately after surgery and 21 (38.2%) patients at first post operative day. Majority of patients 43(78.2%) had normal phosphate levels pre operatively which decreased to only 29 (52.7%) at first post operative day. (Table 1)

No significant difference was found in intra operative management of patient except for ionotropic support needed

Table 1: Level of Phosphates at Different Periods of Hospital Stay (n=55)

SERUM PHOSPUROUS LEVELS	PRIOR TO SURGERY	IMMEDIATELY AFTER SURGERY	FIRST POST-OP DAY
NORMAL (2.7-4.5 mg/dl) MEAN (± SD)	43 (78.2%) 3.39 (±0.48)	32 (58.2%) 3.57 (±0.62)	29 (52.7%) 3.45 (±0.57)
HYPOPHOSPHATEMIA (<2.7 mg/dl) MEAN (± SD)	10 (18.2%) 2.46 (±0.15)	15 (27.3%) 2.22 (±0.83)	21 (38.2%) 2.05 (±0.55)
HYPERPHOSPHATEMIA (>4.5 mg/dl) MEAN (± SD)	2 (3.6%) 5.05 (±0.63)	8 (14.5%) 5.03 (±0.15)	5 (9.1%) 4.94 (±0.23)

at the time of ICU Admission. Patients undergoing Valve Replacement with hypophosphatemia need ionotropic support in 100% of cases in comparison only 53.3% cases with normal phosphate levels needed it. (Table 2)

However, post-operative course of both groups differed in two groups in terms of duration of ventilation (11.9 ±11.6 versus 6.15 ±5.5 hours, p=0.002), duration of ICU stay (3.5±1.5 versus 2.4±0.7 days, p=0.01), duration of cardio active support needed (45.5±31.2 versus 25.0 ±12.4 hours, p=0.001), duration of drains required (45.0 ±25.7 versus 33.7±11.3 p=0.01), and need of re-intubation (20% versus 0%, p= 0.04).

Patients with hypophosphatemia had significantly more blood loss (998.7±1217.8 versus 526.8±322.0, p=0.001) and received more blood transfusions post operatively (1.8±2.0 versus 0.8±0.9, p=0.009). IABP was needed in 3 patients and they all fall in hypophosphatemia group (25% patients, p=0.036) and all underwent CABG surgery. No significant difference of post-operative mortality was found in both groups (15.3% versus 3.2%, p=0.07).

Significant difference was observed between CABG versus Valve Replacement (VR) surgeries. Patients undergoing VR with hypophosphatemia needed prolonged ICU stay (3.3 ±1.0, p=0.00). Duration of hospital stay was also increased in VR with an average of 7.4 days (±2.6) versus 4.6 days (±1.1) (p=0.01). Patients with VR needed greater post-operative inotropic support (50% of patients with hypophosphatemia versus non with normal phosphate levels (p=0.001))

However amount of blood loss was significantly higher in CABG with hypophosphatemia (1200±1420.8 versus 644.3± 368.4, p=0.007) and increased duration of drain removal (50.9±29.3 versus 39.9±11.7, p=0.006) while no significant difference was observed in VR (33.4±10.8 versus 27.9 ±6.9, p=0.119).

Post-operative transfusion of PCVs was significantly higher in CABG with hypophosphatemia (1.8±2.0 versus 0.8 ±0.9, p=0.04) but not significant in VR with hypophosphatemia (0.6±0.8 versus 0.6±0.61, p=0.25). (Table 3)

DISCUSSION

Hypophosphatemia was found in 27.3% patients [2.22±0.83)] immediately after surgery and 38.2% [2.05±0.55)] patients at first post op day. It is observed that hypophosphatemia has deleterious effect on outcome of patients in terms of duration of ventilation (p=0.002), duration of ICU stay (p=0.013) and duration of cardio active support needed (p=0.001). Moreover, patients with hypophosphatemia have significantly more blood loss (p=

Table 2: Intra-Operative Course of Patients During Study Period (n=55)

PARAMETER	HYPOPHOSPHATEMIA	NORMAL PHOSPHATE LEVELS	P-VALUE
UNITS OF PCV TRANSFUSED CABG VALVE	0.87 (±1.06) 1.00 (±1.247) 0.60 (±0.548)	0.41 (±0.79) 0.38 (±0.719) 0.47 (±0.915)	0.255 0.051 0.451
UNITS OF FFPs TRANSFUSED CABG VALVE	Nil	Nil	
DURATION ON HEART LUNG MACHINE (Minutes) CABG VALVE	96.66 (±6.75) 104.70 (±15.18) 80.60 (±37.28)	79.03 (±27.58) 96.00 (17.07) 64.33 (±25.02)	0.466 0.303 0.239
Time OF CROSS CLAMP (Minutes) CABG VALVE	65.86 (±20.60) 74.10 (±13.96) 49.40 (±23.22)	54.37 (±21.80) 65.06 (±14.25) 45.00 (±23.32)	0.429 0.175 0.961
INTRA OPERATIVE FLUIDS (ml) CABG VALVE	2148.5 (±581.78) 2222.8 (±244.63) 2000 (±984.25)	1958.8 (±432.14) 2113.9 (±244.63) 1829.3 (±532.18)	0.479 0.466 0.219
Ionotropic support at ICU Admission CABG VALVE	15 (100%) 10 (100%) 5 (100%)	23 (71.87%) 15 (93.75%) 8 (53.33%)	0.074 0.636 0.000

0.001) and received more blood transfusions post operatively (p=0.009).

Normal phosphorus levels are important in several biological processes. [5]As Phosphate is main component of ATP, lower phosphorus levels lead to depleted intracellular stores of ATP and cellular dysfunction. Due to this effect hypophosphatemia is related to impaired myocardial contractility.[6] There are several mechanisms behind hypophosphatemia including decrease gastro intestinal absorption, increase renal excretion and redistribution of phosphorus into intracellular compartment.[1,7] Among them most important causal factor is redistribution across cell membrane which may resulted from high serum levels of catecholamines including epinephrine and nor epinephrine.[8] Moreover cardiac surgery increases proinflammatory cytokines which aggrevate intracellular membrane shift of phosphorus. [5,9]

Effect of hypophosphatemia has been widely studied and associated with rhabdomyolysis, hemolysis, left ventricular dysfunction and may lead to cardiac and respiratory failure.[1,7] Many researches showed hypophosphatemia as important finding among cardiac surgery patients.[2,3] Our study showed that hypophosphatemia present in 18.2% of cases pre operatively which increases to 27.3% immediately post op and further 38.2% at first post op day. This is consistent with previous research which showed that significant hypophosphatemia is more evident in post operative period.[6] No significant difference was observed in intra operative course of two groups except that patients with hypophosphatemia undergoing valve replacement needed ionotropic support at ICU Admission in 100% cases versus only 53.3% of normal phosphatemic group (p=0.00). However, previously it is showed that no significant difference was there at ICU admission but they need greater than one ionotropic drug at ICU admission (42.3% versus 28.2%, p=0.05)[6]

Duration of ventilation was higher in hypophosphatemic group (p=0.002) which is consistent with previous study (p= 0.05).[6] This may be explained by impaired contractility of diaphragm due to low serum inorganic phosphate levels. [10] Due to this effect it was difficult to wean off patients from mechanical ventilator which resulted in prolong ICU stay as evident in our study. Moreover, it might resulted in increase chances of reintubation as our study also showed(p=0.040). Duration of cardioactive support increased in hypo-phosphatemic group (p=0.001) consistent with previous research (p=0.005).[6] It is also implicated that phosphorus replacement therapy resulted in improve cardiac output which might be explained by better

Table 3: Post Operative Course of Patients During Study Period (n=55)

PARAMETER	HYPOPHOSPHATEMIA Mean ± SD	NORMAL PHOSPHATE LEVELS Mean ± SD	P VALUE
Duration of ventilation (hours)	11.90 (±11.65)	6.15 (±5.56)	0.002
CABG	11.95 (±13.55)	7.77 (±6.62)	0.040
VALVE	11.80 (±7.85)	4.70 (±3.89)	0.013
Duration of ICU stay (days)	3.50 (±1.57)	2.40 (±0.71)	0.013
CABG	3.35 (±1.02)	2.81 (±0.75)	0.120
VALVE	3.80 (±2.48)	2.06 (±0.25)	0.000
Duration of hospital stay (Post -Op days)	6.20 (±2.00)	5.25 (±2.14)	0.652
CABG	5.60 (±1.42)	5.87 (±2.70)	0.320
VALVE	7.40 (±2.60)	4.66 (±1.17)	0.013
Duration of inotropic support needed (Hours)	45.50 (±31.28)	25.03 (±12.48)	0.001
CABG	57.88 (±33.23)	25.81 (±12.77)	0.002
VALVE	23.20 (±2.38)	23.80 (±12.58)	0.017
Ionotropic Support (=2drugs required)	3 (20%)	9 (28.12%)	0.74
CABG	3 (30%)	4 (23.52%)	0.666
VALVE	0 (0%)	5 (50%)	0.000
Amount of Blood Loss (ml)	998.67 (±1217.80)	526.88 (±322.09)	0.001
CABG	1200 (±1420.81)	644.38 (±368.45)	0.007
VALVE	596.00 (±586.96)	413.33 (±228.99)	0.038
Duration of drains placement (Hours)	45.06 (±25.71)	33.79 (±11.32)	0.010
CABG	50.90 (±29.38)	39.90 (±11.78)	0.006
VALVE	33.40 (±10.80)	27.93 (±6.98)	0.119
Post-Op Transfusion of PCV	1.40 (±1.84)	0.72 (±0.81)	0.009
CABG	1.80 (±2.09)	0.81 (±0.98)	0.049
VALVE	0.60 (±0.89)	0.67 (±0.617)	0.251
Post-Op Transfusion of FFPs	0.60 (±1.40)	0.06 (±0.35)	0.00
CABG	0.50 (±1.26)	0.12 (±0.50)	0.049
VALVE	0.80 (±1.78)	0.00 (±0.00)	0.000
IABP use	3 (20%)	0 (0%)	0.015
CABG	3 (30%)	0 (0%)	0.036
VALVE	0 (0%)	0 (0%)	0.000
Re-Intubation Needed	3 (20%)	0 (0%)	0.040
CABG	3 (10%)	0 (0%)	0.069
VALVE	0 (0%)	0 (0%)	0.000
Post-Op Mortality	2 (13.33%)	1 (3.125%)	0.076
CABG	2 (20%)	1 (6.25%)	0.405
VALVE	0 (0%)	0 (0%)	0.000

contractile function of myocardium.[14]

Patients with hypophosphatemia have more blood loss (p= 0.001) which resulted in increase rate of post operative transfusions (p=0.009). Greater blood loss resulted in prolong duration of drain placement (p=0.010). Severe hypophosphatemia is a rare cause of intravenous hemolysis but not much data available on it.[16]

In this study effect of hypophosphatemia was also compared between CABG and Valve Replacement surgeries. It is noted that effect of hypophosphatemia on valve replacement surgeries was greater in terms of prolong ICU (p=0.00) and hospital stay (p=0.013). Moreover, hypophosphatemic group undergoing VR surgeries have greater duration of ventilation (p=0.013) and cradioactive support (p=0.01). From these results it might be postulated that myocardial and diaphragm contractility affects VR surgeries more. But this effect needs to be studied in future studies. Our study showed no significant difference of post operative mortality among two groups (15.38% versus 3.22%, p=0.076). However, Hypophosphatemia ($p \leqslant 0.6$ mmol/L) has been reported in up to 20% of critically ill ICU patients with significant increase ICU mortality (p= .004).[12] Moreover, it has been studied that correction of hypophosphataemia resulted in improvement of symptoms.[13]

Phosphorus replacement therapy can be given either through oral or intravenous route. Recommended dosage for oral administration is of 2.5 to 3.5 g (80 to 110 mmol) per day given in two to three divided doses per day.[1] Intravenous phosphorus replacement is safely recommended up to 1mmol/kg at speed of 7.5 mmol/hr and proved to normalize serum phosphorus level in 60% of cases.[14]

CONCLUSION

Hypophosphatemia is documented in one third of postoperative cardiac surgery patients and is associated with prolonged ventilation, duration of ICU stay and inotropic support with more blood loss. On the basis of this study it is recommended that serum phosphorus levels should be routinely monitored post operatively and appropriate replacement should be given.

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