Original Research Article

Significance of hypophosphatemia as an indicator of Gram negative sepsis

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Abstract

Hypophosphatemia has long been reported to be associated with sepsis and has been correlated with sepsis severity. This prospective study was undertaken at the SKIMS university for a period of two and a half years to determine whether hypophosphatemia could serve as a rapid lab parameter in sepsis patients especially Gram negative sepsis. One hundred patients of sepsis, documented by blood culture were studied. Patients were divided into two groups. First group included 48 patients with Gram positive sepsis and second group included 52 patients with Gram negative sepsis. All the information was collected including physical examination, laboratory parameters, haematological and biochemical analysis, chest x ray and cultures. Hypophosphatemia was seen in 65.4% of Gram negative patients and only in 27.1% of gram positive patients. Among hypophosphatemic patients significant difference was noted in pulse, systolic BP, blood sugar levels, bilirubin and prothrombin time, whereas insignificant difference was noted in TLC, platelet count, urea, creatinine, calcium and albumin levels.

Keywords: hypophosphatemia, platelet, Medicine.

Introduction

One of the oldest syndromes in medicine is sepsis. In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection[1]. In 2003, a consensus panel endorsed most of the concepts in sepsis, with the limitation that signs of a systemic inflammatory response, such as tachycardia or an elevated white-cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions[2]. Pneumonia is the most common cause, accounting for about half of all cases, followed by intraabdominal and urinary tract infections[3-6]. Blood cultures are usually positive in only one third of cases, and in up to a third of cases, cultures from all sites are negative[3,5,7,8]. *Staphylococcus aureus* and *Streptococcus pneumonia* are the most common gram-positive isolates, whereas among Gram-negative organisms *Escherichia coli*, klebsiella species, and *Pseudomonas aeruginosa* usually predominate[5,8]. Severe sepsis and septic shock were highly lethal before the modern intensive care was available. Even with intensive care, rates of in-hospital death from septic shock were often in excess of 80% as recently as 30 years ago[9]. However, with advances in care, and prompt initiation of therapy to treat the underlying infection and support of failing organs, mortality is now closer to 20 to 30% in many series[3,10]. Prompt recognition of sepsis is essential to reduce the early mortality as the cultures take long time to show the results. Hypophosphatemia develops in the early stages of sepsis and correlates with the severity of the clinical condition of the patient[11,12]. A high incidence of hypophosphatemia was observed in patients with sepsis during the first 24 hr of hospitalization and serum inorganic phosphate (Pi) levels <2 mg/ dl were especially suggestive of Gram negative sepsis[13,14]

Keeping in view serious consequences of hypophosphatemia in sepsis and its quick availability, it is imperative to find hypophosphatemia at the earliest so that good gram negative antibiotic coverage could save many lives before cultures are available.

Materials and Methods

This study was a prospective observational study, conducted in the department of internal medicine in collaboration with department of microbiology SKIMS for a period of two and a half years. Only those patients were included in the study in whom sepsis was documented and confirmed on positive blood cultures. Patients with other causes of hypophosphatemia like metabolic alkalosis, chronic alcoholism, CCF were excluded from this study. Blood culture positive patients were divided into two groups viz Gram positive and Gram negative and comparison made between two groups with regard to different clinical and lab parameters with special emphasis on phosphorus levels. Phosphorus levels were determined through enzymatic method. Cultures were done as per policy protocols of the department of microbiology SKIMS. In statistical analysis, all values were expressed as means ± SE, and for comparisonbetween means we used the paired t-test. Avalue of $P < 0.05$ was considered as statistically significant.

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Results

The study population consisted of 100 patients of blood culture documented sepsis. Different clinical and laboratory parameters were taken to compare two groups with special emphasis on blood phosphate levels

The mean age of patients was 32.22±19.66(11.2±13.48 days) with range of 3 to 68 years and male to female ratio of 61:39(1.56). Among the study population 100 cases, 48 were gram positive and 52 were gram negative. In the population of 100 cases, hypophosphatemia (phosphorus levels of less than 3 mg/dl) was observed in 47 patients and 53 did not have hypophosphatemia. Among gram positive cases, 13(27.1%) were hypophosphatemic and among gram negative cases, 34(65.4%) were hypophosphatemic, a statistically significant value($p<0.05$).

In gram positive group, the commonest organism was staphylococcus aureus (40%) and others were streptococcus viridans (5%) and enterococci (3%). In gram negative group the commonest organism was klebsiellaaerogenes (17%) and others were E.coli (14%), pseudomonas aeruginosa(13%), Acinetobacter (6%), proteus mirabilis and Citrobacterfreundii (1%) each.

With regards to clinical parameters statistically significant difference between two groups was observed in pulse, systolic BP and temperature. Gram negative patients had more tachycardia($p=0.045$) were more febrile($p=0.035$) and had more of systolic hypotension($p=0.001$).Renal insufficiency was noted more commonly in gram negative sepsis, albeit with statistically insignificant difference ($p>0.05$).

Similarly with regards to lab parameters, statistically significant difference was observed in blood sugar, bilirubin, SGOT and albumin.Moderate hyperglycemia($p=0.00$), moderate hyperbilirubinemia ($p=0.036$), higher SGOT($P=0.013$) and hypoalbuminemia ($p=0.047$) was observed more commonly in gram negative sepsis.

In the gram negative group, urine culture was positive in 30 patients, out of which 6 had pseudomonas aeruginosa, 14 had E.coli and 10 had klebsiellaaerogenes.

In the Gram positive group, urine culture was positive in 6 patients only and all of them were E.coli, so urine was seen as a source of infection in 57.5% of gram negative patients and 12.5% of gram positive patients who had additional gram negative bacteriuria.

Table 1:Age and sex distribution of patients in group A and group B

Parameters	Group A	Group B
M`ale	30(49.2%)	31(50.8%)
Female	18(46.2%)	21(53.8%)
Mean age ± SD(Years)	33.04±19.46	31.44±20.07
Mean age ± SD (Days)	11.56±18.33	11.09±8.73
Standard error or mean	3.116	3.135
Total(100)	48	52

Table 2:Abnormal clinical parameters in hypophosphatemic and non hypophosphatemic patients

Parameters	Hypophosphatemia	Non hypophosphatemia	p value
Pulse			
Normal	9(19.1%)	21(39.6%)	0.026
Tachycardia	38(80.9%)	32(60.4%)	
Temperature			
Afebrile	5(10.9%)	12(23.5%)	0.102
Febrile	41(89.1%)	39(76.5%)	
Systolic BP			
Nonhypotensive	18(50%)	35 (87.5%)	0.000
Hypotensive	18(50%)	5(12.5%)	

Table 3:Comparison of abnormal laboratory parameters of patients in group A and group B

Parameters	Group A (Gram +ve)	Group B (Gram -ve)	p value
TLC			
Normal	9(18.8%)	16(30.6%)	0.372
Leucopenia	12(25.0%)	12(23.1%)	
Leucocytosis	27(56.2%)	24(46.3%)	
Platelet count			
Normal	28(58.3%)	27(51.9%)	0.520
Thrombocytopenia	20(41.7%)	25(48.1%)	
Blood sugar			
Normal	33(68.8%)	16(30.8%)	0.000
Raised	15(31.2%)	36(69.2%)	
Blood urea			
Normal	42(87.5%)	42(80.8%)	0.359
Raised	6(12.5%)	10(19.2%)	
Serum creatinine			
Normal	39(81.3%)	34(65.4%)	0.074
Raised	9(18.7%)	18(34.6%)	
Albumin			
Normal	28(58.3%)	20(38.5%)	0.047
Hypoalbuminemia	20(41.7%)	32(61.5%)	
SGOT			
Normal	29(60.4%)	43(82.7%)	0.013
Raised	19(39.6%)	9(17.3%)	
SGPT			

Normal	28(58.3%)	31(59.6%)	0.896
Riased	20(41.7%)	21(40.4%)	
Calcium			
Normal	27(56.2%)	26(50.0%)	0.532
Hypocalcemia	21(43.8%)	26(50.0%)	
Phosphorus			
Non hypophosphatemia	35(72.9%)	18(34.6%)	0.000
Hypophosphatemia	13(27.1%)	34(65.4%)	

Table 4:Distribution of Organisms (Blood Culture) In Group A and Group B

Group A (Gram +ve)	
Enterococci	3%
Staphylococcus aureus	40%
Streptococcus viridans	5%
Group B (Gram -ve)	
Acinetobacter	6%
Klebsiellaaerogenes	17%
Pseudomonas aeruginosa	13%
E.coli	14%
Proteus mirabilis	1%
Citrobacterfreundii	1%

Discussion

Sepsis is one of the common medical conditions which if not diagnosed and treated urgently, leadsto high morbidity and mortality. The early diagnosis of sepsis rests on some preliminary laboratory tests like leucocyte count(leucocytosis/ leucopenia), platelet count(thrombocytopenia) and absolute or relative hypophosphatemia. Among the basic laboratory parameters, only the hypophosphatemia has been found helpful in quick diagnosis and determining the etiology of sepsis, i;e, higher incidence of hypophosphatemia has been documented in gram negative than gram positive sepsis.

The present study was undertaken with an aim to study the significance of hypophosphatemia in terms of documenting higher incidence in gram negative sepsis. Among gram positive cases, 13(27.1%) were hypophosphatemic and among gram negative cases, 34(65.4%) were hypophosphatemic, a statistically significant value($p<0.05$) whereas Riedler GF et al showed almost similar incidence of 69% hypophosphatemia in gram negative sepsis and 24% incidence in gram positive sepsis.

Hypophosphatemia has been regarded as an independent risk factor for 28-day mortality in sick ICU patients[15]. A higher mortality of around 80% was observed in severe hypophosphatemic septic patients by Shor R et al[16] The mechanism of hypophosphatemia in sepsis is still not clear , however, Barak V et al linked the hypophosphatemia to increase in various cytokines like TNF alpha and IL- 6[17].

Hypophosphatemia develops early in sepsis and correlates with severe sepsis[18,19].

Hypophosphatemia in sepsis increases the mortality through various effects like myocardial depression, arrhythmias, decreased oxygen delivery to tissues and impaired response to vasopressive agents[12, 20, 21]. Our study revealed staphylococcus aureus (40%) as the commonest gram positive pathogen and klebsiellaaerogenes (17%), E.coli (14%) and pseudomonas aeruginosa (13%) were common in gram negative group. Reidler GF et al reported staph aureus as the commonest gram positive organism and E. Coli as the commonest gram negative organism.

Our study revealed that hypophosphatemia is more common in gram negative sepsis and this group demonstrated adverse features like fever, tachycardia, hypotension, renal insufficiency, hyperglycemia, hypoalbuminemia and jaundice with transaminitis. These reports are consistent with Reidler GF study which showed increased mortality associated with these adverse features. Garner et al showed that sepsis mortality could be decreased with infusion of phosphates[22].

Our study concludes that hypophosphatemia is observed in sepsis, more commonly in gram negative sepsis and its presence makes sepsis more worse. The fact that cultures do not come positive in all sepsis patients and have longer turn around time, it becomes imperative to use rapidly available tests like serum phosphorus to diagnose sepsis early so that higher mortality associated with it is reduced.

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