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Serum Procalcitonin as a marker of infection in chronic kidney disease patients on hemodialysis in sepsis

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Abstract:
Introduction: *The use of Procalcitonin (PCT) as a bacterial diagnostic marker is controversial in patients on hemodialysis (HD). Infections account for considerable morbidity and mortality in patients on HD. Hence, early diagnosis of bacterial infections is important to make a prognostic assessment of its severity. If PCT can be used as a primary marker for bacterial infections in patients on HD, these infections can be diagnosed and treated early. Therefore, we investigated whether PCT could function as a primary diagnostic marker of bacterial infections in patients on HD.*
Aim: *1) To measure and show that serum procalcitonin levels will be increased in patients with chronic kidney disease in sepsis on hemodialysis, and will be clinically significant. 2) To compare the serum procalcitonin levels in patients on hemodialysis with sepsis; with procalcitonin level of patients on hemodialysis without sepsis*
Methods: *A total of 80 patients of chronic kidney disease on hemodialysis admitted in M S Ramaiah Hospital during the period October 2012 to september2014, were included in the study and were divided into 40 cases and 40 controls considering the inclusion and exclusion criteria.*
Results: *Raised Serum procalcitonin was significantly more associated with CKD patients on hemodialysis in sepsis with P<0.001. When procalcitonin was measured in CKD patients on hemodialysis in sepsis, the sensitivity and specificity was 92.50, and 100.00 respectively, with a cut-off >5ng/ml.*
Conclusion: *Procalcitonin is a good marker of bacterial infection even in patients undergoing hemodialysis. In patients undergoing hemodialysis, procalcitonin cut off level of >5ng/ml indicates sepsis.*
Keywords: *Chronic kidney disease; Hemodialysis; Procalcitonin; Sepsis.*

I. Introduction

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalization at all stages of CKD. The second commonest cause of death among patients with ESRD is septicemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Epidemiological studies suggest that ESRD patients have a higher risk of contracting bacterial infections and that the three most commonly seen infectious complications are urinary tract infections (UTI), pneumonia, and sepsis. Overall, the annual percentage of mortality secondary to sepsis is approximately 100 to 300 fold higher in dialysis patients.[4]

The use of PCT as a bacterial diagnostic marker is controversial in patients on hemodialysis (HD).[5-7] Infections account for considerable morbidity and mortality in patients on HD.[8] Hence, early diagnosis of bacterial infections is important to make a prognostic assessment of its severity. If PCT can be used as a primary marker for bacterial infections in patients on HD, these infections can be diagnosed and treated early. Therefore, we investigated whether PCT could function as a primary diagnostic marker of bacterial infections in patients on HD. We investigated whether serum PCT levels were influenced by HD and determined the cut-off level of PCT in patients on HD.

Aims and Objectives

1. To measure and show that serum procalcitonin levels will be increased in patients with chronic kidney disease in sepsis on hemodialysis, and will be clinically significant.
2. To compare the serum procalcitonin levels in patients on hemodialysis with sepsis to procalcitonin level of patients on hemodialysis without sepsis.

II. Materials And Methods

The study was a prospective observational cross-sectional analytical study, where continuous data was enumerated after fulfilling the inclusion criteria. A total of 80 patients of chronic kidney disease on hemodialysis admitted during the period October 2012 to September 2014, were included in the study and were divided into 40 cases and 40 controls considering the inclusion and exclusion criteria.

Inclusion criteria

1. Chronic kidney disease patients on hemodialysis with sepsis
2. Should satisfy criteria for 1) Sepsis or
   2) Severe sepsis or
   3) Septic shock

As per International guidelines for management of severe sepsis and septic shock: 2008 published by Society of Critical Care Medicine.[9]

3. Should satisfy criteria for chronic kidney disease as per guide lines of Kidney Disease Outcome Quality Initiative of the National Kidney.[10]

Exclusion criteria

1. Patients age below 18 years.
2. Patients who underwent major surgery.
3. Patients with severe burns.
4. Patients on treatment with OKT3 antibodies

Laboratory methods

Serum procalcitonin, blood cultures, blood urea, serum creatinine, complete blood count, chest x-ray, urine routine, serum electrolytes were done in all the patients.

Statistical methods

Descriptive and inferential statistical analysis was carried out in the present study. Results of continuous measurements are presented as mean ± SD (min-max) and results of categorical measurements are presented in numbers (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups.

III. Results

The mean age of patients in cases was 51.98±14.84 and the mean age of patients in controls was 54.48±12.23. 58 patients (72.5%) in the study group were men and 22 patients (27.5%) were women. Fever (100.0%) was the most common presenting symptom in our study group, followed by cough (30.0%) and burning micturition (17.5%). In our study, diabetes mellitus and hypertension were most common co-morbid conditions (Table 1). The cases group had fulfilled the SIRS criteria with mean heart rate of 111.05±13.37 beats per minute, mean temperature being 100.11±1.67 in Fahrenheit, mean respiratory rate being 24.73±6.19, and the mean total count being 15156.23±8059.46 cells/cubic millimeter (Table 2). Pallor and edema were most common clinical signs seen in the patients. Pallor was seen in 65% and 67.5% in cases and controls respectively. Edema was seen in 30% and 25% in cases and controls respectively. In cases bronchopneumonia was the most common cause of sepsis (32.5%), followed by urosepsis in 27.5% and septic encephalopathy in 12.5% (Table3).

In our study anemia of chronic disease was seen in both cases and controls with mean hemoglobin being 8.46±1.61 in cases and 8.65±1.12 in controls. Leukocytosis was predominantly associated with sepsis group when compared to the non sepsis group with significant p value. The mean creatinine value was high in sepsis group when compared to the non sepsis group with moderately significant p value. The mean platelet count was less in sepsis group when compared to the non sepsis group with moderately significant p value (Table 4). In cases 7(17.5%) had sputum culture positive and 11(27.5%) had blood culture positive and 8(20.09%) had urine culture positive (Table 5). ESBL Escherichia coli was the most common organism isolated from blood and urine, whereas pseudomonas was the most common organism isolated from sputum. In cases all the patients had procalcitonin level more than 5 and in controls 32(80.0%) had procalcitonin between 0.5-2 and 8(20.0%) between 2 and 5 (Table 6).

Table 1: Co morbid conditions

Co morbid conditions	Cases (n=40)		Controls (n=40)		P value
	No	%	No	%	
Diabetes	28	70.0	32	80.0	0.302
Hypertension	27	67.5	33	82.5	0.121

Table 2: Vital parameters

Vital parameters	Cases	Controls	P value
Pulse rate	111.05±13.37	83.95±10.19	<0.001**
SBP (mm Hg)	132.78±43.16	146.48±23.64	0.082
DBP (mm Hg)	76.51±22.17	89.60±14.10	0.002**
Temperature (^{0}F)	100.11±1.67	98.73±0.28	<0.001**
Respiratory rate	24.73±6.19	18.50±4.64	<0.001**

Table 3: Causes of sepsis

Causes of sepsis	Cases (n=40)	
	No	%
Bronchopneumonia	13	32.5
Urosepsis	11	27.5
Septic encephalopathy	5	12.5
Acute Gastroenteritis with sepsis	3	7.5
Left diabetic foot	3	7.5
Sepsis with septic shock	2	5.0
CAPD related infection	1	2.5
Gluteal abscess	1	2.5

Table 4: Lab parameters: a comparison in two groups

Lab Parameters	Cases	Controls	P value
Hemoglobin (gm/dl)	8.46±1.61	8.65±1.12	0.549
Total count (cells/mm3)	15156.23±8059.46	7128.82±2258.57	<0.001**
ESR (at end of 1st hour)	79.97±39.24	70.22±37.67	0.276
Platelet count (cells/mm3)	1.71±1.41	2.31±0.82	0.024*
Serum creatinine (mg/dl)	8.06±2.71	6.95±2.37	0.054
Blood urea (mg/dl)	60.32±35.76	45.23±25.43	0.033*

Table 5: Culture findings: Sputum, Blood and Urine

	Cases (n=40)		Controls (n=40)		P value
	No	%	No	%	
Sputum Culture					0.012*
• Negative	33	82.5	40	100.0	
• Positive	7	17.5	0	0.0	
1. Acinetobacter	1	2.5	0	0.0	
2. Gram positive cocci	2	5.0	0	0.0	
3. Gram negative cocci	1	2.5	0	0.0	
4. Pseudomonas	3	7.5	0	0.0	
Blood Culture					<0.001**
• Negative	29	72.5	40	100.0	
• Positive	11	27.5	0	0.0	
1. Acinetobacter	1	2.5	0	0.0	
2. Enterococcus	2	5.0	0	0.0	
3. Methicillin sensitive Staphylococcus aureus (MSSA)	3	7.5	0	0.0	
4. Methicillin resistant Staphylococcus aureus (MRSA)	1	2.5	0	0.0	
5. ESBL E.coli	4	10.0	0	0.0	
Urine Culture					0.005**
• Negative	32	80.0	40	100.0	
• Positive	8	20.0	0	0.0	
1. ESBL E.coli	4	10.0	0	0.0	
2. Enterococcus fecalis	3	7.5	0	0.0	
• Mixed bacterial flora	1	2.5	0	0.0	

Table 6: Serum Procalcitonin

Serum Procalcitonin	Cases		Controls	
	No	%	No	%
0.5-2	0	0.0	32	80.0
2-5	0	0	8	20.0
5-50	23	57.5	0	0.0
51-100	3	7.5	0	0.0
>100	14	35.0	0	0.0
Total	40	100.0	40	100.0

IV. Discussion

Procalcitonin is the prohormone of the hormone calcitonin. In healthy people, plasma PCT concentrations are found to be below 0.05 ng/ml, but PCT concentrations can increase up to1000 ng/ml in patients with sepsis, severe sepsis or septic shock. PCT values in the range of 0.5 and 2ng/ml represent a grey zone with uncertainty as far as the diagnosis of sepsis is concerned. PCT levels more than 2ng/ml are highly suggestive of an infectious process with systemic consequences. Concentrations more than 10ng/ml are almost exclusively found in patients with severe sepsis or septic shock. Bacterial endotoxins and pro-inflammatory cytokines are powerful stimuli for the production of PCT.

Since the mid-1990s, there has been an increasing use of PCT measurements in identifying systemic bacterial infections. The short half-life (25–30 hours in plasma) of PCT, coupled with its virtual absence in health and specificity for bacterial infections, gives it a clear advantage over the other markers of bacterial infection. Recent data demonstrated that serum PCT is also an accurate indicator of severe infection and sepsis in patients with chronic kidney disease (CKD) requiring intermittent hemodialysis (HD).[5,6] Moderately increased PCT was observed in CKD with and without renal replacement therapy (RRT) in the absence of infections. [6] However, the extent of PCT elevation in CKD with and without RRT, its underlying factors and the origin of PCT under these conditions remain to be elucidated

Serum Procalcitonin as a diagnostic marker of sepsis has been largely studied in adult population and is an established marker of sepsis with a sensitivity of 90-96%. Studies in the patients on maintenance hemodialysis are lacking in this regard in the country and worldwide. Hence this study was conducted in our hospital to study the usefulness of serum PCT in the diagnosis of sepsis in the chronic kidney disease on maintenance hemodialysis.

In our study, diabetes mellitus and hypertension were the two most common co-morbid conditions. This is in concordance with study done by Borja Quiroga et al where diabetes mellitus was the most common co morbid condition.[11] In our study, bronchopneumonia (32.5%) was the most common cause of sepsis. This is in concordance with studies done by Stefan Herget-Rosenthal et al and Ken -Ichi Mori et al, where pneumonia was the most common cause of sepsis.[6,12] In our study, the mean WBC count was higher in infection group when compared to the non infection group, this is in correlation with the study done by Ken-Ichi Mori et al, were the infection group had significantly higher WBC counts ($P < 0.01$).[12] This finding is also in correlation with the study done by Stefan Herget-Rosenthal et al where all the patients with severe infections and sepsis had higher values of WBC than patients without infections.[6] In our study, raised Serum procalcitonin was significantly more in sepsis group with P value <0.001. This correlates with a study done by Ken-Ichi Mori et al where the infection group had significantly higher procalcitonin ($P < 0.01$).[12] Similar finding was noted by Stefan Herget-Rosenthal et al and Borja Quiroga et al where patients with severe infections and sepsis showed significantly higher procalcitonin values.[6,11] In our study, gram negative bacteria like pseudomonas (7.5 %) was the most common organism isolated from sputum in patients with sepsis. This is in concordance with the study done by Ren W et al where gram negative bacteria like E coli (15.85%) and pseudomonas (14.63%) were the most common organisms isolated. [13] In our study, ESBL E.coli (10%) was the most common organism isolated from urine in patients with sepsis. This is in concordance with a study done by Falah S et al where E.coli (15%) was the most common organism isolated from urine.[14]

The normal reference range for procalcitonin is < 0.5, but in our study, 80% of the controls had procalcitonin between 0.5-2 and 20% had procalcitonin between 2 and 5. This is in concordance with a study done by Handan Akbulut et al. [15] In their study, mean plasma concentration of procalcitonin in CKD patients on hemodialysis was 2.13±0.7 ng/mL. This can be explained by the fact that CKD is a chronic inflammatory state which causes raised procalcitonin level in CKD patients without sepsis.

In our study all the patients of CKD with sepsis had a procalcitonin level of more than 5, hence a cut off of more than 5 for procalcitonin was calculated as a marker of sepsis in these patients with a Sensitivity of

92.50,Specificity of 100.00, AUC=96.1%, SE=0.023 with P value <0.001**.** But in a study conducted by Stefan Herget-Rosenthal et al, patients with and without infections were well discriminated by the PCT cut-off value of 1.5 ng/ml. [6] The difference in the cut-off value was attributed to the difference in the kit used to estimate the procalcitonin level in the two studies. Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

V. Conclusions

Procalcitonin is a good marker of bacterial infection even in patients undergoing hemodialysis. Procalcitonin should be used as marker of sepsis in all patients of chronic kidney disease on hemodialysis in sepsis. Furthermore, the mean plasma concentration of procalcitonin was elevated in chronic kidney disease, patients on maintenance hemodialysis compared to reference range, so in our study we had observed that the procalcitonin cutoff level should be set at 5ng/mL to indicate sepsis.

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