Diagnostic and Prognostic Significance of Procalcitonin and CRP in Septicaemia

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ABSTRACT

BACKGROUND

Sepsis is a major cause of morbidity and mortality. Early diagnosis and treatment with adequate antimicrobial therapy are essential for successful treatment. Despite the use of available treatment modalities, mortality and morbidity in sepsis remain high. Cost of therapy and burden over the society increase as the diagnosis is delayed. The prognosis also worsens with delayed diagnosis and treatment. The study was designed to assess the levels of serum procalcitonin and CRP in patients with septicaemia and determine as to whether serum procalcitonin level and CRP levels correlate with the severity of septicaemia or not and correlate (procalcitonin, CRP and both) with survival outcome in cases of sepsis.

METHODS

All patients were subjected to detailed clinical examination and investigations. Patient's clinical profile, progression of disease and outcome were recorded. Serum procalcitonin level and various other relevant factors were also measured in all the study subjects. Patients admitted at Nehru Hospital, BRD Medical College, Gorakhpur were included in the study. A total of 60 patients were included in the study. The study period was from August 2017 to December 2017.

RESULTS

Procalcitonin is a useful marker for severity of infection. Increased level of procalcitonin is highly specific for infection. Low procalcitonin level cannot be used safely to exclude the presence of infection. Higher level of serum procalcitonin predicts mortality better than other available parameters. High CRP levels (more than 2 times than normal value) are also associated with high mortality but somewhat is inferior in predicting the outcome. High procalcitonin level along with raised CRP, best correlates with the poor outcome.

CONCLUSIONS

Although sepsis is mainly a clinical diagnosis and its severity can be assessed by scores like APACHE II, serum procalcitonin is a better marker for the assessing severity of the sepsis. Serum procalcitonin can aid in early diagnosis as it appears in blood earlier than other markers. Procalcitonin and CRP together predict mortality better than other markers.

KEYWORDS

Procalcitonin, CRP, Sepsis, Septic Shock, Severe Sepsis, Sepsis-Related Organ Failure Assessment Score

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BACKGROUND

Sepsis is a major cause of morbidity and mortality. Early diagnosis and treatment with adequate antimicrobial therapy are essential for successful treatment. Despite the use of available treatment modalities, mortality and morbidity in sepsis remains high. Cost of the therapy and burden over the society increases as the diagnosis is delayed. The prognosis also worsens with delayed diagnosis and treatment. Various diagnostic markers like TNF α, IL6, IL 1 β, C reactive protein (CRP) and lipopolysaccharide binding proteins are available but in septicaemia they are increased briefly or intermittently. Out of these markers CRP is most widely used. The common problem for the mediator is its nonspecific nature and variable correlation with severity of the disease. Procalcitonin (PCT) has recently been proposed as a marker of bacterial infection in critically ill patients, and its levels related to the severity of sepsis. PCT has also several advantages over other inflammatory markers like its earlier increase in response to an infection that is maintained even with immunosuppressive medications. It has better negative predictive value and a better correlation with outcome (mortality). In addition to clinical and microbiological parameters PCT may further help to differentiate blood contamination from blood stream infection. In healthy individuals, concentration of PCT are substantially below 0.1 mg/l. The most potent stimulator for PCT induction is bacterial endotoxins. Patients with viral and localised bacterial infections have lower plasma PCT levels than with septicaemic infections.

Recent studies show that PCT might not just be a marker of infection, but more importantly a good marker of severity of infection. There are numerous 'severity of illness scoring systems', but most commonly used scoring systems are APACHE (acute physiology and chronic health evaluation), MPM (mortality probability model) and SAPS (simplified acute physiology score) system. These systems are difficult to calculate and have not been validated in prediction of mortality. Moreover, they cannot be used as diagnostic tool. PCT appears to be a diagnostic tool as well as a good marker of severity of infection.

Objectives

1. To determine the levels of serum PCT and CRP in patients with septicaemia.
2. To see whether serum PCT level correlates with severity of septicaemia and survival outcome.
3. To evaluate as to whether PCT alone or PCT and CRP together are better predictor of outcome.
4. To evaluate as to whether PCT measurement can help in differentiating between bacterial and other kinds of inflammatory process.

METHODS

The patients who had symptoms suggestive of sepsis were included in the study. Patients were selected from those admitted in indoor of the department of medicine, Nehru hospital, BRD Medical College.

Inclusion Criteria

1) Bacteraemia- presence of bacteria in blood as evidenced by positive blood culture.
2) Septicaemia- presence of microbes or their toxins in blood.
3) Systemic inflammatory response syndrome- 2 or more of the following conditions-
   a) Fever (oral temperature >38^{0}C or Hypothermia <36^{0}C)
   b) Tachypnoea (> 24 breath /minute)
   c) Tachycardia (Heart rate >90/minute)
   d) Leucocytosis (>12000/μL), Leucopoenia (<4000/μL) or 10% Band cells.
4) Sepsis – SIRS that has a proven or suspected microbial aetiology.

Exclusion Criteria

1) Patients having thyroid tumours.
2) Patients suffering from carcinoma of lungs.

All investigations were done at pathology department, blood culture at microbiology department and serum for Procalcitonin was taken and sent to reference lab (path care, Hyderabad). APACHE II score and CRUB – 65 score was calculated at the time of admission to assess the severity of illness.

RESULTS

Patients admitted at Nehru Hospital, BRD Medical College, Gorakhpur were taken for the study. A total of 60 patients were included in the study. The study period was from August 2017 to December 2017. All the patients were subjected to detailed clinical examination. Patient's clinical profile, progression of disease and outcome were recorded and following observations were made. Total 60 patients were enrolled in the study. Out of them 32 (53.34%) were male and 28 (46.66) were female. 18 (30%) male and 14 (23.33%) female patients were <50 years of age.

Age	Male	%	Female	%	Total	%
< 50	18	30	14	23.33	32	53.33
> 50	14	23.34	14	23.33	28	46.67
Total	32	53.34	28	46.66	60	100

Table 1. Age and Sex Distribution

Presenting Complains	No. of Patients	%
Fever	56	93.33
Breathlessness	20	33.33
Cough	14	23.33
Burning Micturition	12	20
Headache	12	20
Vomiting	12	20
Pain in Abdomen	8	13.33

Table 2. Symptoms

The most common presenting symptom was fever. It was present in 56 (93.33%) patients. The next common symptoms were breathlessness in 33.33% and cough in 23.33% patients. Tachycardia (P.R. >90) was present in all the patients included for the study. Hypotension (systolic B.P. <90 mmHg) was present in 22 (36.66%) patients. Tachypnoea (respiratory rate >24) was present in 52 (86.66%) patients. The temperature of more than 38^0 C was present in 56 (93.33%) patients and less than 36^0 C in 4 (6.67%) patients. Anaemia was present in 54 (90%) patients. TLC was raised (>12000 cells/mm^3) in all 60 patients. DLC was predominantly Polymorphic in 56 (93.33%) and Lymphocytic predominance in 4 (6.67%) patients. Serum Creatinine was raised (>1.5 mg/dl) in 38 (63.33%) patients. Blood Urea was raised (>40 mg/dl) in 42 (70%) patients. SGPT was raised (>40 IU/L) in 44 (73.33%) patients. Blood culture was negative in all patients included in the study.

Pulse		
Pulse Rate	No. of Patients	%
>90	60	100
<90	0	0
Blood Pressure		
Systolic B.P.	No. of Patients	%
< 90	22	33.66
> 90	38	63.34
Respiratory Rate		
Resp. Rate/min.	No. of Patients	%
< 24	8	13.34
> 24	52	88.66
Temperature		
Temperature	No. of Patients	%
> 38^0 C	56	93.33
< 36^0 C	4	6.67
Haematological and Biochemical Investigations		
Haemoglobin		
Hb (gm %)	No. of Patients	%
<6	4	6.67
6 – 9	18	30
9 – 12	32	53.33
> 12	6	10
Total Leucocyte Count		
TLC (cells/mm^3)	No. of Patients	%
> 12000	60	100
4000-12000	0	0
< 4000	0	0
Differential Leucocyte Count		
DLC (cells/mm^3)	No. of Patients	%
Polymorph dominant	56	93.34
Lymphocyte dominant	4	6.66
Serum Creatinine & Blood Urea		
S. Creatinine (mg/dl)	No. of Patients	%
< 1.5	22	36.67
> 1.5	38	63.33
B. Urea	No. of Patients	%
< 40	18	30
> 40	21	70
SGPT		
SGPT (IU/L)	No. of Patients	%
< 40	16	26.67
> 40	44	73.33
Blood Culture		
Negative in all cases		

Table 3. Clinical Examination

S. PCT Level (mg/L)	S.CRP Level (mg/L)	Patients No. (%)	Survival No. (%)	Death No. (%)
< 0.1	<50	22 (36.6)	22 (100)	0 (0)
0.1-0.25	>50	22 (36.6)	16 (72.7)	6 (27.3)
> 0.25	>50	16 (26.7)	6 (37.5)	10 (62.5)

Table 4. Serum Procalcitonin (PCT) Level and Mortality

$X^2 2df = 9.2549$. $p < 0.05$

All the patients who had normal serum Procalcitonin (<0.1 mg/L) no mortality occurred. In those, whom serum Procalcitonin was between 0.1–0.25 mg/L and CRP level between >50, 27.3% (6 out of 22) patient died and in patients whom s. Procalcitonin was >0.25 and CRP >50, mortality was 62.5%. Chi Squire Test was applied and found statically significant ($p<0.05$) that mortality was significantly high in raised S. PCT group. The correlation between APACHE II score, Serum Procalcitonin, CRP and mortality was found significant.

	Apache II < 25			**Apache II > 25**		
Focus of Infection	**Patients No. (%)**	**PCT > 0.1**	**Death**	**Patients No. (%)**	**PCT >0.1**	**Death**
Septic meningitis	7 (25)	3 (10.7)	2 (7.1)	6 (18.8)	6 (18.8)	3 (9.4)
Pneumonia	9 (32.1)	3 (10.7)	1 (3.6)	7 (21.9)	6 (18.8)	2 (6.3)
Septic Abortion	3 (10.7)	0	0	4 (12.5)	4 (12.5)	3 (9.4)
Complicated UTI	2 (7.1)	0	0	4 (12.5)	4 (12.5)	1 (3.1)
Diabetic foot	6 (21.4)	2 (7.1)	1 (3.6)	5 (15.5)	4 (12.5)	1 (3.1)
Acute Pancreatitis	1 (3.6)	0	0	3 (9.4)	3 (9.4)	1 (3.1)
Pyothorax	0	0	0	3 (9.4)	3 (9.4)	1 (3.1)
Total (60)	28 (46.6)	8 (28.6)	4 (14.3)	32 (53.4)	30 (93.8)	12 (37.5)

Table 5. Relation between Focus of Infection, Apache II and Serum Procalcitonin (PCT) Levels

Out of 60 patients 16 were suffering from pneumonia, 13 septic meningitis, 11 diabetic foot, and 7 septic abortion, 6 complicated UTI, 4 acute Pancreatitis and 3 Pyothorax. APACHE II score of <25 is indicator of lesser severity of illness. Patients were divided in two groups, APACHE II score <25 and APACHE II score >25. In APACHE II score <25 group, 28 patients were included. Out of those 28 patients serum Procalcitonin was raised in 8. Total of 4 patients died in this group. In all the 4 patients who died, serum procalcitonin level was raised. The mortality rate in the group of APACHE II score <25, according to APACHE II score is 14.28% (4 out of 28 patients) and mortality rate of raised serum Procalcitonin is 50% (4 out of 8 patients). In APACHE II score >25 group, 32 patients were included. Out of those 32 patients serum Procalcitonin was raised in 30. Total of 12 patients died in this group. In all the 12 patients who died, serum procalcitonin level was raised. The mortality rate in the group of APACHE II score >25, mortality rate according to APACHE II score is 37.5% (12 out of 32 patients) and mortality rate of raised serum Procalcitonin is 40% (12 out of 30 patients).

CRP level >50 correlates with mortality but 8 patients with much higher level survived (>200 mg/L) and even lower level (50 to 100 mg/L) 6 patients expired.

DISCUSSION

Sepsis is a major cause of morbidity and mortality.[1] Rapid detection of sepsis is difficult because the initial signs of diseases are usually nonspecific.[2] Early diagnosis of severe infection and prompt initiation of adequate antimicrobial therapy are essential for successful treatment.[3] Various diagnostic markers like TNF α, IL6, IL 1β[4, 5] C reactive

protein (CRP) [6, 7] and lipopolysaccharide binding protein are available but in septicaemia they increased briefly or intermittently. Out of these markers, C reactive protein is most widely used. The common problem for the mediator is its nonspecific nature and variable correlation with severity of the disease. Procalcitonin has recently been proposed as a marker of bacterial infection in critically ill patients.[8,9] In bacterial infection and sepsis, procalcitonin levels are increased in the blood which can be used for diagnosis of sepsis and more importantly, its level is related to the severity of sepsis.[8,9,10]

There are numerous 'severity of illness scoring systems' but most commonly used scoring systems are APACHE (acute physiology and chronic health evaluation), MPM (mortality probability model) and SAPS (simplified acute physiology score) system. The new definition of sepsis known as SEPSIS-3 was announced at the 45th Critical Care Congress in the beginning of 2016. The SIRS criteria have been criticized for wide sensitivity and lack of specificity for sepsis (which is primarily induced by infection) while SOFA score has been enhanced as a diagnostic criterion for sepsis. These systems are difficult to calculate and have not been validated in prediction of mortality. More over them cannot be used as diagnostic tool.

PCT appears to be a diagnostic tool as well as a good marker of severity of infection. This study include 60 patients of clinically diagnosed sepsis (having at least 2 features of SIRS) of various aetiologies. All patients underwent detailed clinical examination, haematological investigations, blood culture. Serum Procalcitonin was measured in all cases at the time of admission. Repeat measurement of PCT was not done. Total 60 patients were enrolled in the study. Out of them 32 (53.34%) were male and 28 (46.66) were female. 18 (30%) male and 14 (23.33%) female patients were <50 years of age (Table - 1). The most common presenting symptom was fever. It was present in 56 (93.33%) patients. The next common symptoms were breathlessness in 33.33% and cough in 23.33% patients (Table -2). Tachycardia (P.R. >90) was present in all the patients included for the study. Hypotension (systolic B.P. <90 mmHg) was present in 22(36.66%) patients. Tachypnoea (respiratory rate >24) was present in 52 (86.66%) patients. The temperature of more than 38^0 C was present in 56 (93.33%) patients and less than 36^0 C in 4 (6.67%) patients.

Anaemia was present in 54 (90%) patients. TLC was raised (>12000 cells/mm^3) in all 60 patients. DLC was predominantly Polymorphic in 56 (93.33%) and Lymphocytic predominance in 4 (6.67%) patients. Serum Creatinine was raised (>1.5 mg/dl) in 38 (63.33%) patients. Blood Urea was raised (>40 mg/dl) in 42(70%) patients. SGPT was raised (>40 IU/L) in 44(73.33%) patients. Blood culture was negative in all patients included in the study (Table - 3). TLC >12000 or <4000 cell/mm^3, pulse rate >90 / minute, respiratory rate >24/minute and temperature >38^0C or <36^0C are essential diagnostic criteria for SIRS. In our series of patients increased TLC and tachycardia were found in all (100%) patients, tachypnoea in 86.66% and raised temperature in 93.33% patients. Serum procalcitonin level was more than 0.25 mg/L in 16 (26.66%) patients out of which 10 (62.5%) died. In 22 (36.66%) patients, serum procalcitonin was between 0.1 – 0.25 mg/L, 6 (10%) patients died in this group. In the group of 22 (36.66%) patients with normal serum procalcitonin levels (<0.1 mg/dl) no mortality was noted. This correlates with the studies by Assicot M et al that serum procalcitonin level is raised in the patients with septicaemia (Table – 4).

Out of 60 patients 16 were suffering from pneumonia, 13 septic meningitis, 11 diabetic foot, and 7 septic abortion, 6 complicated UTI, 4 acute Pancreatitis and 3 Pyothorax. APACHE II score of <25 is indicator of lesser severity of illness. Patients were divided in two groups, APACHE II score <25 and APACHE II score >25. In first group (n= 28). 4 patients died, while 8 patients were found to have raised serum Procalcitonin. It was also noticed that 4 patients who died, serum procalcitonin level was raised. The mortality rate in the group of APACHE II score <25, according to APACHE II score is 14.28% (4 out of 28 patients) and mortality rate of raised serum Procalcitonin is 50% (4 out of 8 patients). In APACHE II score >25 group, 32 patients were included. Among them 30 showed raised serum Procalcitonin. It was also noticed that 12 patients who died, serum procalcitonin level was found to be raised. Thus the mortality rate in the group of APACHE II score >25, according to APACHE II score is 37.5% (12 out of 32 patients) and mortality rate of raised serum Procalcitonin is 40% (12 out of 30 patients).

In our study Procalcitonin was raised in 38 (63.33%) patients. According to Corsino Ray et al, Procalcitonin was found to be raised in 92.6%[11] other studies have also reported rise of procalcitonin in 80–90% cases of sepsis. In our study those patients who had APACHE II score >25, Procalcitonin was raised in 93.8% which is comparable to previous studies. It seems that in previous studies, less severe patients (APACHE II score <25) of sepsis or various aetiologies of sepsis were not taken for the study. In our study all (100%) the patients who had APACHE II score >25 and sepsis was due to septic meningitis or complicated UTI or septic abortion, had 100% raised. Procalcitonin (TABLE – 5) Muller B ET al[8] and Becker KL ET al[12] also found the same type of results.

CRP level >50 correlates with mortality but 8 patients with much higher level of CRP survived (>200 mg/L) and even lower level of CRP (50 to 100 mg/L) 6 patients expired. We found significant difference in mortality in patients with raised serum procalcitonin vs. normal serum procalcitonin level. Various clinical and laboratory parameters like Hb, TLC, DLC, serum creatinine, blood urea, SGPT which have conventionally been used in the definition of sepsis and multiorgan dysfunction syndrome. We compared the level of these parameters amongst patients with serum procalcitonin <0.1 mg/L and patients with serum procalcitonin level >0.1 mg/L. The difference between two groups was calculated by t test and was not found significant. It was noted that higher level of serum procalcitonin predicts mortality. Although serum procalcitonin is not very sensitive in diagnosing sepsis, it is better marker to predict mortality more accurately. High levels of Procalcitonin and raised CRP

together predicts mortality better than procalcitonin or CRP alone.

CONCLUSIONS

Procalcitonin is a useful marker for severity of infection. High procalcitonin level is highly specific for infection. Low procalcitonin level cannot be used safely to exclude the presence of infection. Higher level of serum procalcitonin predicts mortality better than other parameters available. Thus, from the present study, we can conclude that although sepsis is mainly a clinical diagnosis and its severity can be assessed by scores like APACHE II, serum procalcitonin is a good marker for the assessing severity of the sepsis. Serum procalcitonin can aid in early diagnosis as it appears in blood earlier than other markers. The only problem with serum procalcitonin is its cost and lack of easy availability. High levels of Procalcitonin and raised CRP together predict mortality better than procalcitonin or CRP alone.

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