THE STUDY OF SERUM PROCALCITONIN LEVEL IN CORRELATION WITH SEPSIS

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ABSTRACT

BACKGROUND

Sepsis refers to the systemic response to serious infection. It can be response to the infection caused by any class of microorganism. The presence of bacteraemia is an indicator of disseminated infection and generally indicates a poorer prognosis when associated with localised disease. This study was undertaken to study the diagnostic and prognostic value of Procalcitonin (PCT) in patients with sepsis.

AIM

To study the diagnostic and prognostic value of Procalcitonin (PCT) in patients with sepsis.

MATERIALS AND METHODS

Fifty patients of age more than 18 years with sepsis admitted in KMC Hospitals, Mangalore, from August 2008 to June 2010 were subjects in the study after due permission from institution and informed consent from the patients. Diagnosis of sepsis was made according to criteria by ACCP/SCCM definition for sepsis. Definitive aetiological diagnosis requires isolation of microorganism from the blood and local site of infection, Gram stain and culture of the material from the primary site of infection for the microbial aetiology was taken. Other appropriate laboratory investigations depending upon requirement were done as mentioned in the investigations.

RESULTS

Out of total 50 patients, 23 patients were in group of sepsis, 14 were in group of severe sepsis while 13 had septic shock. Maximum number of the study patients were in the age group of 51-60 years. 52% of the study patients were male and 48% were female. Most common symptom in patients with sepsis was fever. Most common sign in the patient with sepsis is tachycardia followed by high temperature and then tachypnoea. Most common source of sepsis was respiratory infection followed by UTI.

CONCLUSION

Our data suggest the possibility that the addition of Procalcitonin into the standard workup of critically ill patients with suspected sepsis could increase diagnostic certainty and improve patient management.

KEYWORDS

Bacteraemia; Diagnostic; Procalcitonin; Prognostic.

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INTRODUCTION: Sepsis refers to the systemic response to serious infection. It can be response to infection caused by any class of microorganism. Any site of infection can result in sepsis or septic shock. Microbial invasion of blood stream is not essential for the development of sepsis.

However, blood cultures yield bacteria or fungi to approximately 20-40% of cases of severe sepsis and 40-70% of cases of septic shock.[1] The presence of bacteraemia is an indicator of disseminated infection and generally indicates a poorer prognosis when associated with localised disease. Sepsis is reported to be the most common cause of death in noncoronary intensive care unit. It is an increasingly common cause of mortality and morbidity particularly to elderly, immunocompromised and critically ill patients.

Approximately, 25-35% of patients with severe sepsis and 40-55% of patients with septic shock die within 30

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days.[2] The incidence of sepsis and septic shock has been increasing since the 1930s and all the recent evidence suggests that this rise will continue.

The reason for the increasing incidence are many; increased use of invasive devices such as intravenous catheters; widespread use of cytoxic and immunosuppressive drug therapies for cancer and transplantation, increased life span of patient with cancer and diabetics who are prone to develop sepsis and increase in infections due to antibiotic-resistant organisms.[2,3] Clinicians, intensivists and infectious disease specialists have employed different terminologies for similar, but overlapping clinical conditions. Previous large well-designed trials have not shown a reduction in overall mortality as interpretation of results have been obscured by the use of varying definitions for the following terms; Infection, bacteraemia, sepsis, septicaemia, sepsis syndrome, septic shock, etc.[4] The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus conference was held in 1991 with the goal of agreeing on a set of definitions that could be applied to the patients with sepsis and its sequalae.[5]

Severe infection and sepsis are common causes of morbidity and mortality in ICUs. Infection and sepsis are accompanied by clinical and lab signs such as changes in body temperature, leucocytosis and tachycardia. However, these signs and symptoms of systemic inflammation may have an infectious or noninfectious aetiology and are neither specific nor sensitive for sepsis. Patients with systemic infection and organ dysfunction or shock are often difficult to distinguish from patients with similar clinical signs and lab finding without infection. Bacteriological evidence of infection may not develop at the same time.[6]

Positive bacteriological results may be caused by contamination and negative results do not exclude sepsis. Since, these common clinical and lab measurements lack sensitivity and specificity other tests are needed to give an early marker of the infectious cause of a generalised inflammatory response to allow early diagnosis and the use of specific treatment. In patients with sepsis, early institution of appropriate antimicrobial therapy is associated with better outcome, so early diagnosis of sepsis is of prime importance. Moreover, widespread administration of antibiotic therapy carries probability of antibiotic resistance/drug toxicity and higher cost. Therefore, there is a necessity of an effective and appropriate marker to support or exclude the diagnosis. In response to infection, wide array of inflammatory mediators are released, but most of them are nonspecific. Role of C-reactive protein in correlation with severity is not clear. Microbiological culture require more time and neither they reflect host response to systemic infection nor the onset of organ dysfunction. Hence, some marker is required, which can add to diagnostic accuracy in patients with suspected sepsis. One such measurement, procalcitonin has recently become of interest as a possible marker of the systemic inflammatory response to infection.[7] This study was undertaken to study the diagnostic and prognostic value of Procalcitonin (PCT) in patients with sepsis.

MATERIALS AND METHODS: Fifty patients of age more than 18 years with sepsis admitted in KMC Hospitals, Mangalore, from August 2008 to June 2010 were subjects in the study after due permission from institution and informed consent from the patients. Diagnosis of sepsis was made according to criteria by ACCP/SCCM definition for sepsis. Definitive aetiological diagnosis requires isolation of microorganism from the blood and local site of infection Gram stain and culture of the material from the primary site of infection for the microbial aetiology was taken. Other appropriate laboratory investigations depending upon requirement were done as mentioned in the investigations.

Inclusion Criteria: Patient >18 years and <80 years fulfilling criteria for definition of Sepsis/Severe Sepsis/MODS defined by ACCP/SCCM.

Exclusion Criteria:

1. Age <18 years of age and >80 years of age.
2. Patients with malignancy.
3. Patients with trauma or surgery.

Diagnosis: Diagnostically sensitive findings in a patient with suspected or proven infection include hypothermia, tachycardia and leucocytosis or leucopenia. Acutely altered mental status, thrombocytopenia or hypotension also suggests the diagnosis. Definitive aetiological diagnosis required isolation of microorganism from blood or local site of infection. At least, two blood samples were sent for culture.

Procalcitonin Test Procedure: Serum or plasma was employed. Pipette 6 drops using the enclosed dropper pipette into the round cavity of the B.R.A.H.M.S. PCT-Q, incubate for 30 mins. at room temperature, after 30 mins. (max. 45 mins.) the PCT concentration range of the sample is determined. First, the validity of the test is checked with the help of the clearly visible control bind.

a. No band or only test band visible; tests, which show no control band are not valid and may not be evaluated.
b. Only control band visible: test, which show only a control band are negatively valid. The PCT concentrations are <0.5 ng/mL.
c. Control and test band visible: tests, which show both a control band and a test band are positively valid.

The PCT concentration range is determined by comparing the colour intensity of the test band with the colour blocks of the reference card.

BLOOD CULTURE: Specimen Collection: Preparation of site: Careful skin preparation is important to reduce the risk of introducing contaminants into the blood culture media. The vein from which blood is to be drawn must be chosen before the skin is disinfected. If the patient has an existing FV line, the blood is to be drawn below the existing line.

Specimen Collection: Blood for culture sensitivity and for routine investigations is collected. Other cultures taken were sputum, urine, pleural fluid, ascitic fluid, burn, wound swab according to primary infection present.

Blood: Two samples taken from each patient at the same time from different sites for culture sensitivity. In suspected endocarditis, three blood samples collected from different venepuncture sites over a period of 1 to 2 hrs.

Timing: Blood was obtained immediately once sepsis was suspected within 24 hrs. of admission to hospital before starting treatment.

Other Specimens:

1. **Sputum:** Expectorated sputum was collected by asking the patients to cough deeply and then expectorate into sterile screwed capped cup.
2. **Throat Swab:** In good light, tongue was depressed and affected area was swabbed using sterile cotton swab.
3. **Urine:** After taking appropriate aseptic precautions midstream portion of urine was collected in a wide mouthed sterile plastic cup and sent to laboratory within 1 hour.
4. **Body Fluids:** (Ascitic fluid, pleural fluid) - needle puncture site cleaned and disinfected with 10% solution of povidone, iodine and alcohol. Then, specimen was collected using sterile syringe, transferred to a sterile screw capped bottle and sent to laboratory.
5. **Wound Swab:** Pus was collected by means of sterile swab following thorough cleaning and decontamination and transported to laboratory. Blood culture bottle were observed and subcultures were done. Confirmed organisms were tested for antibiotic sensitivity.

RESULTS: In this study, total 50 patients were selected who were fitting into the inclusion criteria as mentioned in materials and method. Out of 50 patients, procalcitonin was positive in 47 (94%). 52% of the study patients were males and 48% were females as depicted in Table 1.

Sex	No. of Patients	Percentage
Male	26	52
Female	24	48

Table 1: Sex Distribution

Maximum number of the study patients were in the age group of 51-60 years as illustrated in Table 2.

Age Group	No. of Patients	Percentage
21-30	8	16
31-40	6	12
41-50	5	10
51-60	14	28
61-70	8	16
>70	9	18

Table 2: Age Group

Out of total 50 patients, 23 patients were in group of sepsis, 14 were in group of severe sepsis while 13 had septic shock as shown in Table 3.

Sepsis	No. of Patients	Percentage
Sepsis/SIRS	23	52
Severe sepsis	14	26
Septic shock	13	22

Table 3: Severity of Sepsis

Most common symptom in patients with sepsis was fever as elucidated in Table 4.

Symptoms	Percentage
Fever	83
Chills	15
Cough	40
Breathlessness	35
Altered sensorium	32
Vomiting	21
Loose stools	13
Pain abdomen	12
Jaundice	7
Headache	6
Burning micturition	6
Swelling of lower limb	6
Seizures	3

Table 4: Frequency of Symptoms in Patients

Most common sign in the patient with sepsis is tachycardia followed by high temperature and tachypnoea as illustrated in Table 5.

Signs	Percentage
Febrile	76
Tachycardia	91
Tachypnoea	65
Hypotension	37
Pallor	43
Icterus	30
Oedema	33
Petechiae	7
Subconjunctival haemorrhage	6
Lymphadenopathy	2
Altered sensorium	30

Table 5: Common Signs in Patients

Almost, all patients with sepsis had leucocytosis and high ESR as depicted in Table 6.

Lab Parameters	Percentage
Decreased haemoglobin (<10 gm%)	49
Leucocytosis (>12,000)	78
Leucopenia (<4,000)	6
Thrombocytopenia (<1,50,000)	55
Prolonged PT/INR	47
Altered RFT	67

Altered LFT	50
Raised bilirubin	0
Elevated enzymes	0
Decreased albumin	0
Raised ESR	73

Table 6: Laboratory Parameters

Total number of respiratory tract infections is seen in 20 and relationship between procalcitonin and sepsis in respiratory tract infection as depicted in Table 7.

Procalcitonin	Sepsis	Severe Sepsis	Septic Shock
<0.5	1	-	-
>0.5 <2	4	1	1
>2 <10	6	-	-
10	3	1	2

Table 7: Relationship between Procalcitonin and Sepsis in Respiratory Tract Infection

Total number of urinary tract infections is seen in 10 and relationship between procalcitonin and sepsis in urinary tract infection is shown in Table 8.

Procalcitonin	Sepsis	Severe Sepsis	Septic Shock
<0.5	1	0	0
>0.5 <2	2	0	1
>2 <10	1	0	1
>10	2	1	1

Table 8: Relationship between Procalcitonin and Sepsis in Urinary Tract Infection

Total number of gastrointestinal tract infections is seen in 10 and relationship between procalcitonin and sepsis in gastrointestinal tract infection as depicted in Table 9.

Procalcitonin	Sepsis	Severe Sepsis	Septic Shock
>0.5	0	0	0
>0.5 <2	1	0	0
>2 <10	1	1	1
>10	1	0	0

Table 9: Relationship between Procalcitonin and Sepsis in Gastrointestinal Tract Infection

Most common source of sepsis was respiratory infection followed by UTI as shown in Table 10.

Respiratory	20 (40%)
UTI	10 (20%)
GIT infection	4 (8%)
Others	6 (12%)
Source not identified	10 (20%)

Table 10: Source of Sepsis

Out of 50, total 20 (40%) patients had growth in culture, while rest 30 (60%) patients had no growth in culture. The relationship between procalcitonin and cultures in patients with sepsis is illustrated in Table 11.

Procalcitonin	Blood C/S	Urine C/S	Sputum C/S	Pus C/S	Ascetic Fluid C/S
>0.5	0	0	0	0	0
>0.5 >2	2	1	1	0	0
>2 <10	2	1	1	1	0
>10	3	3	2	2	1

Table 11: Relationship between Procalcitonin and Cultures in Patients with Sepsis

Out of total 50 patients, 20 were culture positive and among those 20, 70% had grown one negative organism in relative culture. Most common gram-negative organism grown was E. coli while most common gram-positive organism grown was MRSA as illustrated in Table 12.

Gm - ve	14 (70%)
Gm + ve	6 (30%)

Table 12: Organism Grown Culture

Even in culture-negative patient with sepsis, PCT level was consistent with severity of sepsis as shown in Table 13.

		<0.5	0.5-2	2-10	>10
No Growth	Sepsis	3	8	6	2
	Severe Sepsis	0	2	2	3
	Septic shock	0	0	2	2
Growth Present	Sepsis	0	1	1	2
	Severe Sepsis	0	1	2	4
	Septic shock	0	2	2	5

Table 13: PCT Culture in Relationship with Severity of Sepsis

PCT was positive in 47 out of total 50 patients and level of PCT was very high in patients with severe sepsis and septic shock as shown in Table 14.

Procalcitonin	Sepsis/SIRS	Severe Sepsis	Septic Shock
0.5	3	0	0
>0.5 >2	9	3	2
>2 <10	7	4	4
>10	4	7	7

Table 14: Diagnostic Value of Procalcitonin

Severity	Mean Score
Sepsis	4.9
Severe Sepsis	10.2
Shock	11.8

Table 15: Severity v/s. SOFA (Total No. of Patients with GIT = 5)

PCT level and mean SOFA score correlated well in patients with sepsis as depicted in Table 16.

Procalcitonin	SOFA
<0.5	6
0.5-2	8.4
2-10	10.6
>10	12.2

Table 16: PCT v/s. SOFA

Although, ESR is high in patients with sepsis. It doesn't correlate well with severity of sepsis as demonstrated in Table 17.

Procalcitonin	SOFA	ESR
<0.5	6	30
0.5-2	8.4	50
2-10	10.6	42
>10	12.2	53

Table 17: PCT v/s. SOFA v/s. ESR

In patients who had high mortality, PCT level was very high at the time of admission as depicted in Table 18.

Procalcitonin	Frequency	No. of Deaths	% Mortality
<0.5	3	0	0
0.5-2	14	4	20%
2-10	15	5	25%
>10	18	11	55%

Table 18: PCT v/s. Mortality

DISCUSSION: The Principal Findings of This Study in Critically Ill Patients with Sepsis are:

1. The confirmation of the previously described good diagnostic accuracy of PCT.
2. The addictive effect of PCT to improve the predictive power of routinely available sepsis parameters.
3. The good concordance of PCT levels with clinical evolution of septic patients.

Our study has several important implications for clinicians. First, as a new test for diagnosis, sepsis on admission, PCT offers a high level of accuracy that other currently available test cannot provide. The accuracy of PCT reference range, although not perfect, may guide physician in their clinical decision making and their stepwise approach to the complex management of critically ill patients with sepsis requiring several interventions in a short period. This test can be performed within 30 mins. and gives valuable information long before culture results are available. PCT is not only helpful in the diagnosis of sepsis, but also indicative of its severity. PCT has 94% sensitivity in the present study, which is similar to study done by Harbarth et al with reported sensitivity of 97%.[8] We can also see in our study as the severity of sepsis increases (According to ACCP definition), level of PCT also increases. Hence, very high level of PCT can be taken as the marker of severity of sepsis. Study done in United States over 20 years to know the demography, temporal incidence and changes in incidence and outcome showed that sepsis was more common in men, account for 48.1% of cases on average per year and men were more likely to have sepsis than women with mean annual relative risk of 1.28.[9]

Multicenter trial done at 12 centres across India showed that sepsis was more common in males (67%) than females.[10] In our study, among 50 patients of sepsis studied 26 patients were males (52%) and 24 patients were females (48%). Studies by previous workers also indicated a higher incidence among men. Multicenter trial done at 12 centres across India showed that sepsis was more common in elderly people and men.[10] Age of the study population was 54.9 years. A western study showed that sepsis was more common in the age group more than 56.9 years.[11] In our study, incidence was more in the age group over 50 years (60%) and the mean age of the study population was 52.5% years, which correlates with the above studies. Study by Sands KL et al showed that blood cultures were positive in about 28% of cases with gram-positive organisms being the most frequent isolate.[12] An Indian multicenter trial showed that though gram-positive infections were more common in western studies. In our country, gram-negative infections were more common than gram-positive infections.[10] In our study, a total of 50 adult patients with clinical diagnosis of septicaemia were studied. Blood culture was positive in 7 patients and the overall bacteriological positivity was 40%.

Positive cultures vary from 20 to 40% of cases of sepsis and hence our findings are consistent with other studies. Out of the 20 positive cultures, gram-negative organism was isolated in 14 patients and gram-positive organisms were isolated in 6 patients, which is similar to that seen in other studies. According to Calandra T et al, six common infection sites were identified in the causation of sepsis.[13] They were pneumonia, blood stream infections including infective endocarditis, intravascular catheter-related sepsis, intra-abdominal infections, urosepsis and surgical wound infections. Common source of sepsis in our 50 patients revealed the respiratory tract (40%) as being most common followed by urinary tract infection (20%), gastrointestinal infections (8%) and other infections (12%). In 20% of patients, primary source could not be identified. Urinary tract infections being the second most common focus maybe partly due to more number of elderly patients with risk factors like diabetes.

Our study population was a large, diverse group of critically ill adult patients with sepsis (Admitted to medical ICU). It was designed as a real-life study to closely resemble clinical practice. Therefore, we evaluated the combined role of PCT and other clinical indicators of inflammation as predictors of sepsis in which we explored the diagnostic accuracy of these different parameters from a clinical

perspective. Study by Martin GS et al showed that mortality in patients with sepsis form various centres varied between 16.8 to 31.8%.[9] In a study by Sands KE et al who studied sepsis in 8 academic medical centres showed that mortality was about 34%.[12] Mortality was attributed to age and various risk factors that are more common in that age group. In our study, mortality was seen in 20 patients (40%). In all those patient, PCT was positive and it was very high in almost 75% of them.

Higher SOFA score levels were associated with significantly higher PCT plasma concentrations.[14,15,16] In our study, SOFA score was calculated in 50 patients. The mean SOFA score was 11.90 when the PCT was >10, which correlates with the study done by Meisner M et al.[17] In our study, we can also see, as SOFA score increases, level of PCT also increases. The present results confirm earlier findings that demonstrate PCT is among the most promising marker of sepsis especially in critically inpatients capable of complementing clinical signs and routine lab parameters suggestive of severe infection at the time of admission. PCT measurement appears to be a better predictor to distinguish patients with sepsis and patients without sepsis when compared to blood cell counts or body temperature or ESR.

CONCLUSION:

1. In our study, incidence of sepsis was higher in patients aged >50 to 60 years with respiratory tract infection being the most common source of sepsis and gram-negative organisms were a more common as compared to gram-positive organisms.
2. Procalcitonin proved to be an excellent indicator of sepsis in critically ill patients with sensitivity of 94% and the level of PCT in patients with sepsis correlate well with severity of sepsis.
3. Higher level of procalcitonin is directly proportional to higher mortality in patients with sepsis and hence higher level of procalcitonin at admission in patients with sepsis is an indicator of poor prognosis.
4. Level of PCT correlate with degree of sepsis assessed by SOFA score.
5. Our results indicate that clinical variables are of modes diagnostic value for the diagnosis of sepsis including ICU admission. Thus, our data suggest the possibility that the addition of Procalcitonin into the standard workup of critically ill patients with suspected sepsis could increase diagnostic certainty and improve patient management.

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