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Original Research Paper

Anaesthesiology

AN OBSERVATIONAL STUDY TO EVALUATE THE USEFULNESS OF PROCALCITONIN AS A BIOMARKER OF SEPSIS IN THE EARLY STRATIFICATION OF ADULT PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT WITH SUSPECTED INFECTION.

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ABSTRACT Serum Procalcitonin(PCT) has become useful as a biomarker to assist in the diagnosis of sepsis, as well as related infectious or inflammatory conditions. It is a soluble protein liberated into the circulation of patients in response to severe systemic inflammation, in particular by bacterial infection. The aim of this study was to evaluate the usefulness of Procalcitonin as a biomarker of sepsis in the early stratification of adult patients admitted to the intensive care unit with suspected infection.Patients are randomly divided into two groups , **Group-1**: comprising those patients with a bacterial infection (SIRS with Sepsis) and **Group -2:** comprising patients without a bacterial infection (SIRS without Sepsis). we found that elevated PCT concentrations (> 0.5ng/ml) were detected in a significantly higher proportion of patients with SIRS with sepsis compared to those with SIRS without sepsis so we concluded that PCT is an excellent marker providing the additive effect to improve the predictive power for diagnosing sepsis, for assessing severity of sepsis, and also for predicting the outcome/prognosis.

KEYWORDS : PCT , Sepsis ,SIRS(systemic inflammatory response syndrome)

INTRODUCTION

The Systemic Inflammatory Response Syndrome (SIRS) is a generic term used to describe patients with fever and other signs of systemic inflammation. SIRS can be a non-specific manifestation of multiple clinical entities not associated with infection, or it can be a manifestation of systemic infection (i.e. sepsis). ***(Levy et al., 2003)***[1]. sepsis is an increasingly common cause of mortality and morbidity particularly in elderly, immunocompromised and critically ill patients ***(Vincent et al 2006)*** [2] **.** It is therefore unsurprising that there has been considerable interest, debate, and sometimes, arguments over the last two decades regarding the use of biomarkers to help in early screening of sepsis.

Serum Procalcitonin has become useful as a biomarker to assist in the diagnosis of sepsis, as well as related infectious or inflammatory conditions. It is a soluble protein liberated into the circulation of patients in response to severe systemic inflammation, in particular by bacterial infection. As a cut-off for the diagnosis of sepsis, plasma levels of ≥0.5ng/mL are interpreted as abnormal and suggest sepsis. After reaching peak levels, the circulating PCT concentration declines with a 50% plasma-disappearance rate of roughly 1-1½ days. It is also a useful monitor of the clinical course and prognosis ***(Meisner M et al 2014)*** [5].

This study was an attempt to assess the usefulness of Procalcitonin as a biomarker of sepsis in the early stratification of adult patients admitted to the intensive care unit with suspected sepsis at B.M.C. Medical College , Sagar , M.P.

The aim & objectives of the present study are:

1. To evaluate the usefulness of Procalcitonin as a biomarker of sepsis in the early stratification of adult patients admitted to the intensive care unit with suspected infection.

MATERIAL AND METHODS

The present prospective, cross-sectional, study was undertaken in the department of biochemistry of B.M.C. Medical College , Sagar , M.P. after it was approved and permitted by the ethical committee of the institute. The study cohort consisted of adult patients admitted to the ICU on suspicion of infection. The period of study extended from January 2021 to November 2021. Informed written consent was taken from all the subjects.

Inclusion Criteria's:

Patients (> 18 years of age) admitted to Intensive Care Units patients of B.M.C. Hoospital with SIRS, presenting with at least two positive criteria for sepsis were included in the study. We were used the American college of chest physician / Society of critical care medicine consensus conference criteria's to identify patients with sepsis, severe sepsis & septic shock ***(Bone et al., 1992).***

The diagnosis of SIRS was based on the satisfaction of 2 or more of the following previously reported criteria:

- Temperature > 38 degree Celsius or < 36degree Celsius
- Respiratory rate > 20 breaths/min.
- Heart rate > 90 beats/min.
- WBC count > 12000 cells/cubic mm or < 4000 cells/cubic mm or > 10% immature form.

Exclusion Criteria's:

Failure to obtain informed consent , Age less than 18 years, Trauma, Surgery, Burns, Cardiogenic shock, Acute pancreatitis, Patients with history of malignancy, Patients on drugs which stimulates cytokines (OKT3, Alemtuzumab etc) ,Paraneoplastic syndromes due to medullary thyroid carcinoma and small cell Carcinoma of lung Patients, satisfying inclusion criteria's were included in the study. On the basis of clinical, laboratory, and bacteriological reports patients were divided into two groups;

Group-1: comprising those patients with a bacterial infection (SIRS with Sepsis) and

Group -2: comprising patients without a bacterial infection (SIRS without Sepsis).

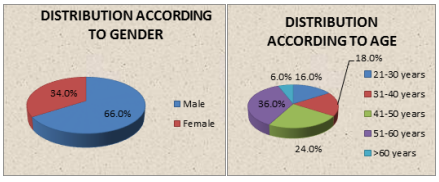
A clinical diagnosis of bacterial infection was established if a causative bacterium was isolated from samples, or if the patient was strongly suspected of having a bacterial infection according to clinical data and their clinical course as determined by the supervising consultant. After taking all aseptic precautions, Blood samples were drawn from all patients within 24 hours of admission to the ICU for blood culture and estimation of serum Procalcitonin. Day zero was defined as the first observational day at admission, and the next day was named day 1, then day 2, and so on. Body temperature, pulse, blood pressure and respiratory rate were recorded daily after admission into ICU. Symptoms and clinical signs, underlying diseases, and diagnosis at admission were recorded. After collecting the data it will be evaluated and compared between the study groups for diagnostic & prognostic value of Procalcitonin.

Statistical Analysis:

Statistical analysis was performed using statistical package for society survey (SPSS) for windows version 17. The t- test and Chi-square test was used to assess the significance of relations with categorical variables. In case of sparse data, the Fisher's exact probability was used as indicated. All variables were expressed as Mean ±SD and two-tailed "P" values below 0.05 were considered significant. The results was tabulated and graphically represented using Microsoft Office for Windows 2007.

OBSERVATION & RESULTS

The pie diagram shows the distribution of patients according to sex. In the present study, 66% of the study patients were males and 33% were females.



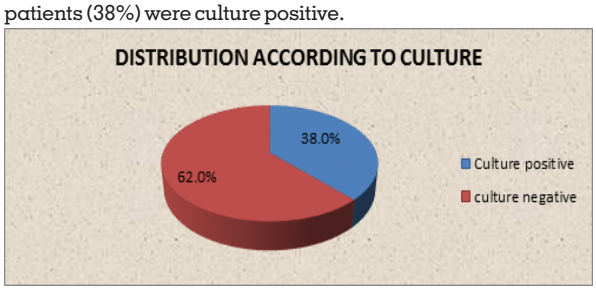
Graph 01: Pie diagram showing distribution according to gender & age.

Table No 01 : Distribution of study population according to culture. **(N=50)**

Culture	Number of patients	Percentage (%)
Culture negative	31	62
Culture positive	19	38
Total	50	100.0

The above table shows the distribution of patients according to culture.

In our study, 31 patients (62%) were culture negative and 19 patients (38%) were culture positive.



Graph 02: Pie diagram showing distribution of patients according to culture

Table No. 2 : Distribution according to SIRS status

(N=50)

SIRS status	Number of patients	Percentage (%)
SIRS without sepsis	29	58
SIRS with sepsis	21	42
Total	50	100.0

The above table shows the distribution of patients according to SIRS status. Out of total 50 patients, 21 (42%) were in SIRS with sepsis group while 29 patients (58%) in SIRS without sepsis group. In SIRS with sepsis group, 19 patients (38%) had positive cultures whereas 02 patients (04%) were culture negative but had strong clinical suspicion of having a bacterial infection according to their clinical course as determined by the supervising consultant.

Table No. 3 Correlation of SIRS status with Procalcitonin concentration

(N=50)

SIRS status	PCT concentration		Number of patients	P Value
	≤0.5 ng/mL	≥0.5 ng/mL		
SIRS without sepsis	20(40%)	09 (18%)	29 (58%)	<0.05
SIRS with sepsis	02 (04%) 19	19 (38%)	21 (42%)	

Chi-square 'X2' test applied. P value < 0.05 was taken as statistically significant

The above table also shows that elevated PCT concentrations (> 0.5ng/ml) were detected in a significantly higher proportion of patients with SIRS with sepsis compared to those with SIRS without sepsis (P = 0.0001 using Chi-square test).

Table No. 4 Correlation of degree of sepsis with Procalcitonin concentration

(N=21)

Procalcitonin (ng/mL)	Degree of sepsis			Significance
	Sepsis	Severe sepsis	Septic shock	
≤ 0.5ng/mL	02	00	00	***<0.05***
0.5 – 2.0ng/mL	04	00	00	
2.0 – 10.0ng/mL	03	06	01	
≥ 10.0ng/mL	00	03	02	
Total	09	09	03	

Fisher's Exact test was applied. P value < 0.05 was taken as statistically significant.

The above table shows that out of 50 patients, 21 patients (42.0%) met the criteria for sepsis according to ACCM/SCCP criteria's.

Among patients with SIRS with sepsis group, with increasing infection severity from sepsis through severe sepsis and septic shock, there was a significant parallel increase in the proportion of cases with high PCT concentrations at different cutoff points.

The relationship between PCT concentrations and the degree of sepsis was found to be statistically significant (P = 0.015 using Fisher's Exact test).

DISCUSSION

Our study population was a diverse group of critically ill adult patients with sepsis, admitted to the medical ICU. Out of 50 patients, 33 were males and 17 were females. We found a slightly higher percentage of males (66%) compared to females (34%) in the present study. Studies by previous workers also indicated a higher incidence among men. ***Martin et al.***[13] studied the demography, temporal incidence and changes in incidence and outcome of sepsis over 20 years in the United States reported that sepsis was more common in

men, accounting for 48.1% of cases on average per year and men were more likely to have sepsis than women with a mean annual relative risk of 1.28. ***Todi and group*** [14] reported from a multicenter trial done at 12 centers in India that sepsis was more common in males.

In the present study, incidence was more in patients aged over 50 years (42%) . The age distribution is similar to studies done around the world. A western study reported a higher incidence of sepsis in patients aged above 57 years (***Martin GS et al.2003***) [13].The mean age in an epidemiological study of sepsis in India was 54.9 years (***Todi S et al.2007)*** [14].

In our study, 21 patients (42.0 %) of patients was suffering from sepsis and 29 (58.0 %) had SIRS without evidences of bacterial infections . In our study, overall 19 (38%) culture proven cases of infection were recognized . Bacteremia is identified in only about 30% of patients with sepsis, depending on previous antibiotic treatment ***(Bates DW et al.1997)*** [17].The etiology of a presumed bacterial cause of fever cannot be detected in 50–80% of patients with suspected blood stream infection (***Müller B et al.2000)*** [10]. ***Schuetz P et al., (2009)*** [18] reported that in cases of severe sepsis or septic shock, the culture results is negative in more than 50% of the cases. ***Sinha M et al., (2011)*** [9] reported that the sensitivity of blood culture for making the diagnosis of sepsis was 63%. ***Nargis W et al., (2014)*** [12] reported that the etiology of a presumed bacterial cause of fever can be detected in 53.4% of patients with suspected blood stream infection.

In a study using a cut-off point of 2ng/mL, the sensitivity and specificity of PCT were 86% and 95% and patients had statistically significant correlation with the presence of sepsis ($p<0.0001$). The author concluded that PCT assay was found to be a useful biomarker of sepsis in critically ill patients with suspected sepsis admitted to ICU ***(Sinha M et al., 2011)*** [9].

In the present study we analyzed the plasma concentrations of PCT with respect to its potential use as a marker of sepsis. Elevated PCT concentrations (>0.5ng/ml) were detected at a significantly higher frequency among patients with infectious compared to those with non infectious SIRS .

The role of PCT in discriminating SIRS from sepsis is equivocal, although the majority of studies indicate higher values in patients with sepsis ***(Giamarellos et al., 2004*** [19]***; Jones et al., 2007*** [20]***; Uzzan et al., 2006*** [6]***)***. In contrast, some investigators reported that PCT is not very accurate in differentiating infection from inflammation in critically ill patients, where no significant difference was observed ***(Castelli et al., 2004*** [19]***; Tang et al., 2007*** [4]***)***. One of the causes of such ambiguous conclusions is the lack of a gold standard for infection. In the present study, culture results were used as a gold standard for infection. This could be partly responsible for the poor specificity we got (64.5%), since potentially infected patients with negative cultures would be misclassified into the SIRS without sepsis group. Furthermore, it has been documented that microbiology is not sensitive enough in sepsis diagnosis ***(De La Rosa et al., 2008)*** [20]. Another contributing factor for the low specificity is the multi-factorial nature of PCT induction ***(Schneider and Lam, 2007)*** [21].

Our results agreed with earlier findings which demonstrated that PCT alone does not possess a good discriminative value between septic and non septic ICU patients especially in a heterogeneous mix of diseases ***(Castelli et al., 2004)*** [19]. However, it may be useful together with full clinical assessment including signs of sepsis and bacteriological data.

The likelihood of a bacterial infection increases gradually with increasing Procalcitonin levels. We noticed that with choosing a higher cut-off point for serum PCT level, the sensitivity decreased but specificity increased. When the cut-off point was increased from >0.5ng/mL to >10ng/mL sensitivity decreased from 89.4% to 26.3% and specificity increased from 64.5%to 100% [Table no. 15]. ***Brunkhorst et al., (2000)*** [3] observed from their study that serum PCT levels increase with the increasing severity of the inflammatory response to infection. When the cut-off point was increased to 10ng/mL sensitivity decreased to 25.4% and specificity increased to 100%, PPV was 100% and NPV was 48%. These finding represent that use of a cut-off value in serum Procalcitonin for differentiating sepsis can be tailored according to the physicians' needs and the practicing situation (***Ahmadinejad et al., 2009***)[7].

The results of this study showed that, in a significant number of patients, PCT was a good indicator of severe sepsis and septic shock. We observed a significant increase in the proportion of cases with high PCT concentration in parallel with the degree of sepsis suggesting that PCT might be used not just as a marker of infection, but, more importantly, that it is a useful marker of infection severity. Increasing PCT concentrations during severe sepsis and septic shock were previously reported by many investigators ***(Chan et al., 2004*** [22]***; Ghorbani, 2009*** [23]***)***. Brunkhorst and co workers found that PCT demonstrated significant differences between sepsis, severe sepsis and septic shock on the first day after admission to the ICU or at the onset of inflammatory symptoms .. ***Sharma R & Vijaykumar M*** [16] in 2014 reported that high levels of PCT (>10ng/mL) was characteristically noted in patients with severe sepsis and septic shock.

Mortality was seen in 10 patients (20.0%) in the present study [Table no. 19]. Most of the sepsis patients who had mortality had high PCT level (> 2ng/ml) at the time of admission. A study by ***Martin et al., (2003)*** [13] showed that mortality in patients with sepsis from various centers varied between 16.8 and 31.8%. ***Sands et al., (1997)*** [24] studied sepsis in eight academic medical centers reported a mortality rate of 34%. Mortality could be attributed to age and various risk factors that are more common in that age group. An additional risk factor for increased mortality would be diabetes. Recently ***Nargis W et al., (2014)*** [12] from their study on 73 adult patients reported that the patients with PCT level more than 10ng/ml revealed mortality rate of 16.6%.

In this study, we found evidence that PCT may be an early prognostic marker in patients with sepsis since those who ultimately died demonstrated a significantly higher frequency of elevated PCT concentrations, on admission, than those who were alive at ICU discharge. This is in agreement with other studies (***Clec'h et al., 2004)*** [24],where higher PCT levels were demonstrated in patients with poor prognosis as early as the first day of the disease.

However, other studies documented that the course of PCT concentrations rather than the initial height plays a major role for prognosis ***(Jensen et al., 2006)*** [11]. ***Sudhir U et al., (2011)*** [8] ***and Azvedo et al., (2012)*** [14] reported that serum PCT level did not predict mortality and initial concentration was not significantly different between survivors and non-survivors. The prognostic value of the initial PCT concentration on admission still remains to be clarified.

Results of the present study confirm earlier findings that demonstrate serum PCT as among the most promising sepsis markers in critically ill patients, capable of complementing clinical signs and routine lab parameters suggestive of severe infection at the time of ICU admission. Procalcitonin can also be a good marker for predicting outcome in patients with sepsis.

CONCLUSION

The present study concluded that Procalcitonin (PCT) is a promising marker of sepsis especially at the time of admission into intensive care unit. It may guide physicians in their clinical decision making and their stepwise approach to the complex management of critically ill patients with sepsis. PCT is an excellent marker providing the additive effect to improve the predictive power for diagnosing sepsis, for assessing severity of sepsis, and also for predicting the outcome/ prognosis.

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