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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 12 (4): 393-396, 2009
ISSN 1028-8880

Procalcitonin Role in Differential Diagnosis of Infection Stages and Non Infection Inflammation

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Abstract: The aim of this study is evaluation of procalcitonin role in the diagnosis of infectious and non infectious inflammation. This cross-sectional study was conducted in one hundred patients in Baqiyatallah Hospital of Iran in 2008. Patients suspected to infection were recruited to study. They were divided to four groups as: systemic inflammatory response syndrome, sepsis, sepsis syndrome and septic shock. Procalcitonin quantitative was assayed by immunoluminometric kit manufactured in Germany. Procalcitonin level was divided to four groups in <0.5 ng mL^{-1} compatible for SIRS, 0.5-2 ng mL^{-1} for sepsis and 2-10 ng mL^{-1} for sepsis syndrome and >10 ng mL^{-1} for septic shock. Data was analyzed by SPSS 13 for window software; T student test, ANOVA and Chi-square were used. In this study 53(53%) of subjects were men with mean age of 56.16±19.5 years old. The diagnosis was SIRS in 36%, sepsis in 38%, sepsis syndrome in 14% and septic shock in 12% of cases. Procalcitonin level was less than 0.5 ng mL^{-1} in 61% and more than 10 ng mL^{-1} in 10% of patients. Procalcitonin level showed significant association with septic shock, positive blood culture and mental dysfunction. Ultimately this study showed that high level of procalcitonin can differentiate septic shock from SIRS and other stages of infection. Dysfunction of mental status and high level of procalcitonin can determine septic shock.

Key words: Sepsis, sepsis syndrome, septic skock, SIRS, procalcitonin

INTRODUCTION

Sepsis is used for definition of systemic inflammatory response caused by infectious agents. Despite the use of new treatment modalities, improvements in technology and increased experience, mortality rates in sepsis remain high (Larosa and Opal, 2008). Noninfectious factors are responsible for systemic inflammatory response syndrome (SIRS) such as trauma, burns, hemorrhages, hypothermia, pancreatitis, collagen vascular disease, malignancy (Rivers *et al*., 2008) and surgery had similar clinical presentation to sepsis and therefore differential diagnosis remains difficult (Canan *et al*., 2003). Sepsis remains one of the greatest challenges in critical care medicine. Furthermore, the clinical signs or most typical laboratory findings of sepsis occur later, when multiple organ system failure has already occurred and mortality considerably increased (Fioretto *et al*., 2008). Rapid detection of bacterial sepsis is difficult because the first signs of disease are usually non-specific (Volante *et al*., 2004). Definition of systemic inflammatory response syndrome (SIRS) include two or more of following parameters; fever or hypothermia, respiratory rate more than 20 min^{-1}, heart rate more than 90 min^{-1}, leukocytosis or leukopenia and more than 10% band cell. Sepsis is SIRS plus documented infection etiology. Sepsis syndrome or septicemia is sepsis plus organs failure and septic shock is sepsis plus refractory hypotension and shock (Arkader *et al*., 2006). Early diagnosis of severe infections and the prompt initiation of adequate antimicrobial therapy are essential for successful treatment and need to focus on biochemical mediators capable to distinguish infection from SIRS and indicating the severity and prognosis of diseases (Whicher *et al*., 2001). The lack of specific early markers of infection may be responsible in part for withholding, delaying or unnecessary antimicrobial treatment in critically ill patients. In the last decade researchers have found procalcitonin (PCT) to have an important role in the diagnosis of bacterial infection (Santuz *et al*., 2008). Procalcitonin is a prohormone of calcitonin, normally produced by thyroid gland C-cells in response to hypocalcaemia. Under normal conditions, very low concentrations of PCT in serum (<0.1 ng mL^{-1}) are observed (Whicher *et al*., 2001). More significantly, inflammatory processes induce extra thyroid production of PCT, the levels of which increase after 3 to 4 h, peaking at around 6 h, with a plateau of up to 24 h and can remain elevated for up to 48 h (Jose *et al*., 2007).

Serum PCT elevated levels is strongly associated with systemic bacterial infections (Christ-Crain, 2005).

Which can also accurately differentiate between systemic bacterial infection and non-infectious acute inflammatory states (Pierre *et al*., 2008).

As PCT is not commonly used in our country for diagnosis of sepsis or SIRS therefore, we decided to evaluate it in admitted patients with clinical presentation of infection.

MATERIALS AND METHODS

This is a cross-sectional study that was conducted in one hundred patients that admitted to emergency ward of Baqiyatallah Hospital as a Referral Hospital in Tehran, the capital city of Iran in 2008. Patients suspected to infection that had signs and symptoms of systemic inflammatory response syndrome were recruited to the study. Demographic data such as age, sex and consumption of antibiotics before admitting were obtained from each person. Blood samples 10 mL from each person were obtained for blood culture, ESR, CRP, CBC and Procalcitonin (PCT). Vital signs as fever, hypothermia, heart rate, respiratory rate and blood pressure were recorded. Patients were divided into four different groups according to diagnosis: systemic inflammatory response syndrome as non infectious condition, sepsis, sepsis syndrome and septic shock as infectious conditions. Procalcitonin (PCT) was assayed by immunoluminometric assay compatible to order of its kit. Blood samples were immediately centrifuged for PCT assay and we determinated quantitative of PCT according to instructions of the kit manufactured by BRAHMS Diagnostica, Berlin, Germany. This test can detect PCT level less than 0.1-500 ng mL^{-1} ; the overall sensitivity of this test is about pg mL^{-1}.

PCT quantity level was divided to four groups; PCT<0.05 ng mL^{-1} compatible for SIRS, PCT = 0.05-2 ng mL^{-1} for sepsis, PCT 2-10 ng mL^{-1} for sepsis syndrome and PCT>10 ng mL^{-1} for septic shock. Data was analyzed by SPSS 13 for window software. T student test, ANOVA, Tukey HSD, Scheffe test and Chi-square were used and $p<0.05$ was accounted as significant difference.

RESULTS

In this study, 53(53%) of patients were men. The mean age was 56.16±19.59 (Mean±SD); range 12-98 years old. Vital signs and mental status are shown in Table 1. Ultimate diagnosis was SIRS in 36%, sepsis in 38%, sepsis syndrome in 14% and septic shock in 12% of cases. Laboratory data are shown in Table 2. PCT was less than 0.5 in 61%, 0.5-2 in 29% and more than 10 in 10% of patients. Mean of PCT was 5.43±20.81; range 0.1-197 ng mL^{-1}. The association of PCT in septic shock with sepsis syndrome ($p<0.000$), sepsis ($p<0.000$) and SIRS ($p<0.000$) were significant (Table 3). PCT in SIRS, sepsis and sepsis syndrome didn't show significant difference that showed in Fig. 1. Between vital signs such as fever, heart rate, respiratory rate and blood pressure with PCT there was no significant difference. Between laboratory findings and PCT no significant association was found. Between diagnosis groups and WBC ($p>0.142$), ESR ($p>0.165$), CRP ($p>0.949$) there was no significant association either, but blood culture was significantly associated with diagnosis groups and blood cultures were highly positive in septic shock and significantly associated with high levels of PCT ($p<0.021$). Mental status was an important clinical condition significantly associated with stage of infection and was almost seen in all patients with septic shock ($p<0.05$).

Table 1: Vital signs and mental status in patients

Vital sign	Limit	Frequency	Percent
Fever	Yes	78	78.0
	No	22	22.0
Heart rate	<90 min^{-1}	83	83.0
	>90 min^{-1}	17	17.0
Respiratory rate	<20 min^{-1}	27	27.0
	>20 min^{-1}	73	73.0
Blood pressure	Hypotension	2	2.0
	Normal	38	38.0
	Hypertension	20	20.0
Mental status	Stupor	14	14.0
	Normal	86	86.0

Table 2: Laboratory data in patients

Laboratory test	Limit	Frequency	Percent
WBC	Leucopenia	4	4
	Normal	57	57
	Leukocytosis	32	32
Hemoglobin	Normal	82	82
	Anemia	18	18
Platelet	Normal	94	94
	Thrombocytopenia	6	6
ESR	<30 mm h^{-1}	31	31
	30-100 mm h^{-1}	60	60
	>100 mm h^{-1}	9	9
Pyuria	Positive	40	40
	Negative	60	60
Blood culture	Positive	21	21
	Negative	79	79
Urine culture	Positive	15	15
	Negative	85	85

Table 3: Mean level of PCT in septic shock and SIRS, sepsis, sepsis syndrome

			95% Confidence Interval		
	Diagnosis	Mean difference of PCT	Lower Bound	Upper Bound	p-value
Septic shock	SIRS	31.4642	15.3307	47.5977	0.000
	Sepsis	28.6922	12.4405	44.9438	0.000
	Sepsis Syndrome	29.8903	10.5146	49.2659	0.001

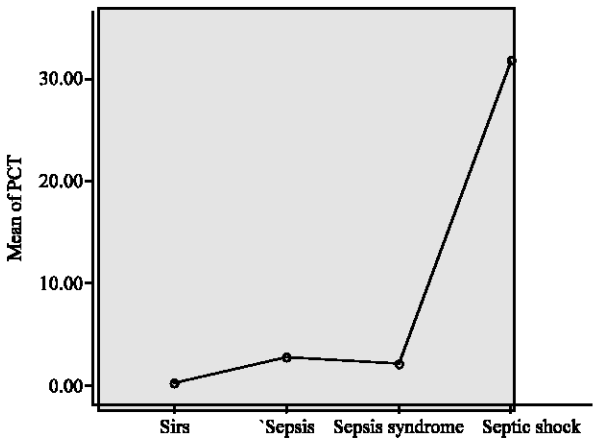

Fig. 1: Association between PCT and SIRS, Sepsis, Sepsis syndrome and Septic shock

More than 88% of patients used antibiotics and almost all of them at last consumed one third generation cephalosporin and between antibiotic and PCT level there was not any significant association ($p>0.06$). The most frequent diagnoses of SIRS were: 7% collagen-vascular diseases (lupus, Wagner and Rheumatoid arthritis) and 2% malignancy.

DISCUSSION

This study showed that procalcitonin (PCT) can differentiate septic shock from SIRS. Septic shock is a critical and life-threatening stage of infection and it may cause high mortality if treatment is delayed. PCT more than 10 ng mL^{-1} strongly was showed septic shock and it can be used as a maker for serious systemic infection and septic shock.

Septic shock is a more severe form of sepsis syndrome plus hypotension that doesn't response to serum therapy and already differentiation from other acute causes of hypotension is difficult. Septic shock patients may present with hypothermia as a paradox presentation, therefore a marker that can differentiate between infection and other causes of hypotension is very important and it seems that PCT assay is very helpful in this regard (Fioretto *et al*., 2008).

In this study PCT level could not differentiate between malignancy and sepsis. As large sample size of patients with malignancy is needed for confirmation (Quintana *et al*., 2008).

Some collagen-vascular disease (CVD) present as SIRS and may be mistaken with infection, in these research, PCT levels did not increase in CVD such as Lupus, Reumthoid arthritis therefore, PCT can differentiate between CVD and sepsis if it was not superimposed with infection (Quintana *et al*., 2008).

In this study, PCT levels could not differentiate between SIRS, sepsis and sepsis syndrome that is opposite to earlier studies and which may be due to use of antibiotics before admission of patients to this hospital (Endo *et al*., 2008). Erythrocyte Sedimentation Rate (ESR) and C-Reactive Proteins (CRP) are acute phase reactants that can not differentiate between SIRS and infection according to this findings which is similar to earlier studies results (Barati *et al*., 2008).

In severe sepsis mental dysfunction is a guide for start of early antibiotic therapy and sepsis with diminished mental status have poor prognosis and in this study positive blood culture, high PCT levels and mental dysfunction significantly suggested septic shock, therefore septic shock should be considered in patients with high PCT levels and confusion (Siami *et al*., 2008).

Patients with SIRS do not need antibiotic therapy which is hastily started obscuring early diagnosis and causing long time hospitalization. This problem can be prevented by PCT assay before antibiotic therapy that it can lead to early diagnosis and diminish occupation of bed in hospital and prescription of antibiotics (Chirouze *et al*., 2002).

Leukocytosis and leukopenia are markers for severe infection and patients with leukopenia had poor prognosis in comparison to patients with leukocytosis in sepsis, but in this study these two parameters were not significant related to PCT levels in stages of infection. Furthermore, PCT can determine septic shock better than white blood cell count (Barati *et al*., 2008).

Antibiotics were used by general practitioners before admission of patients to hospital, can subside the infection or diminish the severity of infection and reduce PCT level. For this reason PCT level assay after antibiotic therapy only can determine response to treatment but if the infection is resistant to antibiotic therapy, PCT levels may remained high (Nobre *et al*., 2008).

Blood culture is needed for diagnosis of infectious disease and it helps to choose specific antibiotic therapy. In this study patients with sepsis had more positive blood cultures than other cases, therefore blood culture is needed for specific bacterial diagnosis early in admission (Charles *et al*., 2008).

Hypothermia as a paradox clinical manifestation showed severe sepsis and septic shock, but in here fever and hypothermia did not have association with PCT which is opposite to earlier studies and may be due to early usage of antibiotics and antipyretic drugs (Maniaci *et al*., 2008).

Limitation of this study is: because this hospital is referral center, most of the patients have confused antibiotics before admission and evaluation of PCT before beginning of antibiotics is difficult and therefore further study is recommended in a primary hospital in the future.

CONCLUSION

These findings suggest that high level of PCT can differentiate septic shock from SIRS and other less severe stage of infection, on other hand dysfunction of mental status contemporaneous high level of PCT confirmed septic shock. Therefore even in patients that took antibiotics for a short time, PCT assay can help to determine the diagnosis of septic shock.

ACKNOWLEDGMENT

I thank from Health Research Center of Baqiyatallah University of Medical Sciences for the financial support of this research.

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