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Procalcitonin and quantitative C-reactive protein role in the early diagnosis of sepsis in patients with febrile neutropenia

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Abstract

Background: Neutropenia with fever is a common syndrome in patients with hematologic malignancies who have a high risk of infectious diseases. As early diagnosis of infection in such patients is really important, the aim of this study was to investigate the sensitivity and specificity of procalcitonin (PCT) and C-reactive protein (CRP) in the diagnosis of sepsis in febrile neutropenic patients in a referral malignant care center of Isfahan in 2010-2011. **Materials and Methods:** In this analytical cross-sectional study, all the febrile neutropenic patients who were admitted in the referral malignant care center in 2010-2011 were evaluated. The data from every individual, including sex, age, admission time, and duration of fever before taking antibiotics were collected. Sixty-four subjects were involved in the study. Blood samples of the subjects were obtained and the levels of PCT, CRP, Absolute neutrophil count (ANC), and white blood cell count were measured, and blood cultures were obtained. According to the test results, the 64 subjects were divided into two groups including patients with sepsis and without sepsis. **Results:** Mean value of PCT in the sepsis group was 28.65 ± 2.68 and in the non-sepsis group was 2.48 ± 0.66, with a *P* value of 0.000. In case of CRP, the sepsis group had a mean of 159.48 ± 9.73 and the non-sepsis group had a mean of 126.17 ± 10.63 ($P = 0.015$). Sensitivity and specificity were analyzed by using receiver operating characteristic (ROC) curve and were found to be 92.5% and 97.3%, respectively, for PCT and 70.5% and 42.1%, respectively, for CRP. **Conclusion:** PCT can be considered as a predictive factor and a diagnostic marker for the diagnosis of sepsis in febrile neutropenic patients.

Key words: C-reactive protein, fever, neutropenia, procalcitonin

Introduction

Neutropenia is a granulocyte disorder that manifests with a decrease of neutrophils. Some of the causes include infectious diseases, hematologic disorders, and malignancies. Depending on the duration of neutropenia, the disease can be divided into two types: Acute and chronic.

Neutropenia with fever is one of the most common syndromes in leukemic patients,[1,2] which is caused by chemotherapy and the underling disease.[3] During the neutropenic episode, the risk of infection is high, and fever in these patients is an emergency condition. So, early diagnosis of infection is needed and intravenous antibiotic therapy should be considered immediately. Due to lack of clinical and microbiological findings, we need some paraclinical tests that are highly sensitive and specific to help physicians in making a decision. Some laboratory tests such as interleukin-6, C-reactive protein (CRP), and procalcitonin (PCT) have been suggested.[4,5]

CRP is an acute phase protein which is used as a biochemical inflammatory marker. CRP concentration level during the infection phase depends on tissue destruction, the extent of malignant disease, and the duration of fever, and it does not increase by a significant amount in the 24-48 h after the onset of inflammation.[3,6] Interleukin-6 is not useful due to its expensiveness and low specificity.[3]

PCT is a 116-amino acid polypeptide that is known as the pro-hormone of calcitonin.[3,7,8] PCT rises within 3 h after the onset of symptoms to a level which can be measured.[9] PCT serum concentration rises in infections such as meningitis and sepsis,[3,7] and this increase exists in immunocompromised patients as well.[2,10]

Carnino *et al*. showed that PCT level is higher in patients with bacterial and fungal infections as compared to viral infections, and is not increased in other inflammatory processes.[10] Delevax *et al*. demonstrated that PCT level more 1.2 mg/ml is a sign of bacterial infection and the cue for starting antibiotic treatment; they also determined the sensitivity as 65% and specificity as 96%.[8] In a study of this concentration, sensitivity of 80% and specificity of 64% were reported.[11] In fact, PCT was reported to be more sensitive and specific than other inflammatory markers.[12] Halimi Asl *et al*. evaluated the accuracy of this test in febrile neutropenic children with malignancy. The results of their study showed that the sensitivity and specificity of PCT were 90% and 80.4%, respectively.[13]

PCT level is higher in patients with hematologic malignancies compared to patients with solid tumor and in

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inpatients versus outpatients. Carnino *et al*. found that the highest level of PCT was seen in acute leukemia.[10]

Based on the necessity of early detection of infection in febrile neutropenic patients and the utility of PCT that has been demonstrated in recent studies, the aim of this study was to determine the sensitivity and specificity of PCT in detecting sepsis in febrile neutropenic patients, in comparison with CRP protein at a referral malignant care center in 2010-2011.

Materials and Methods

This study was approved by the ethical committee for research in Isfahan University of Medical Sciences (Grant No. 389327). In this cross-sectional study, 64 febrile neutropenic patients who were referred to a referral malignant care center from December 2010 to February 2011 were selected. Written informed consents were obtained from all patients.

According to the 1997 guidelines of the Infectious Disease Society of America (IDSA), febrile neutropenia is defined as oral temperature ≥38.3°C or ≥38°C for more than 1 h, when ANC is less than 500 cells/μl or the expected reduction of ANC is below 500 cells/μl in the next 24-48 h.

Febrile neutropenic patients who were above 14 years and had not received any empirical antibiotic therapy more than 12 h of their enrollment in the study were included. Sixty-four patients were enrolled in the study and were that divided into two groups as follows:

Group 1: Patients with sepsis (proven or suspected infection with systemic inflammatory response syndrome)

Group 2: Patients without sepsis (fever, neutropenia with negative blood cultures, and no sign of clinical sepsis syndrome).

Subjects were interviewed by a physician, and data including age, gender, underlying malignancy, vital signs, duration from diagnosis, duration of current hospital stay, and duration of fever before sending blood culture were collected.

After the diagnosis of febrile state, a phlebotomist who was trained to do the venipuncture obtained blood cultures in a sterile manner to avoid any contamination during the procedure. Blood samples were taken for analyzing white blood cell count, platelet count, ANC, CRP, and PCT. Serum CRP was measured by immunoturbidimetric method (COBAS Integra C reactive protein (Latex) test; Roche Diagnostics, Basel, Switzerland). Also, PCT levels in serum samples were determined using enzyme-linked immunoassay (ELISA) kit (VIDAS BRAHMS Procalcitonin; bioMérieux, Lyon, France). For blood cultures, the BACTEC 9050 blood culture instrument (Becton Dickinson, Baltimore, MD, USA) was used. By using the E-test from AB Biodisk (Solna, Sweden), the minimum inhibitory concentrations (MICs) of different antibiotics were determined. All tests were free and performed according to manufacturers' instructions and recommendations.

Data were analyzed with SPSS software version 19 (SPSS® Inc., Chicago) using Chi-square test and independent sample *t*-test for evaluating the relationship between bacterial infection and qualitative and quantitative variables, respectively. $P < 0.05$ was defined as significant for all tests.

Results

In this study, 64 patients with fever and neutropenia were evaluated. There were 37 patients (57.8%) in the non-sepsis group and 27 patients (42.2%) in the group with sepsis. Forty-two patients were males (65.6%) and 22 were females (34.4%).

The mean age of the patients was 46.29 ± 18.15 years. The mean ages of patients in the non-sepsis and sepsis groups were 48.24 ± 17.97 and 43.62 ± 18.40 years, respectively, and the difference was not significant ($P = 0.16$). A total of 18 microorganisms were isolated, of which 10 (55.5%) were gram-positive bacteria, 3 (16.7%) were gram-negative bacilli, 3 (16.7%) were other bacteria, and 2 (11.1%) were fungi.

Difference in the sex distribution of the two study groups was also not statistically significant ($P = 0.117$).

PCT and CRP levels in all subjects were measured. The mean PCT level in the sepsis group was 28.65 ± 2.68 and in the non-sepsis group was 2.48 ± 0.66, which was a statistically significant difference ($P = 0.000$).

The mean values of CRP in the sepsis and non-sepsis groups were 159.48 ± 9.73 and 125.17 ± 10.63, respectively. The *P* values calculated for these values showed statistically significant difference between the two groups ($P = 0.015$) [Table 1].

In this study, we measured the accuracy of PCT and CRP in differentiating between sepsis and non-sepsis groups. Using receiver operating characteristic (ROC) table, for each of these factors, the cut point (cut-off point) was calculated and then its sensitivity and specificity was calculated for each individual [Table 2].

Discussion

Neutropenia with fever is one of the most common syndromes in leukemic patients,[1,2] which is caused by chemotherapy and underling disease.[3] During the neutropenic episode, the risk of infection is higher, and an early diagnosis of infection is very important to reduce mortality. Due to lack of clinical and microbiological findings, we need some paraclinical tests that are highly sensitive and specific to help physicians in making a decision. According to the results of this study, PCT can serve as a diagnostic marker of sepsis in the febrile neutropenic patients, and in comparison with CRP, the level of PCT was higher and statistically significant.

Table 1: The mean of PCT and CRP in two groups

	Sepsis	Non-sepsis	*P* value
PCT	28.65±2.68	2.48±0.66	0.000
CRP	159.48±9.73	126.17±10.63	0.015

PCT=Procalcitonin, CRP=C-reactive protein

Table 2: Cut-off points, specificity, and sensitivity of PCT and CRP in the diagnosis of sepsis

	Cut-off point	Sepsis (*n*=27)		Non-sepsis (*n*=37)		Sensitivity, % TP/ (TP+FN)	Specificity, % TN/ (TN+FP)
		TP	FN	TN	FP		
	6.025	27	0	33	4	100	89.1
PCT	12.500	25	2	36	1	92.5	97.3
	22.100	18	9	37	0	66.6	100
	61.750	27	0	9	28	100	24.3
CRP	125.550	19	8	16	21	70.5	42.1
	203.200	4	23	35	2	14.8	92.1

TP=True positive, FN=False negative, TN=True negative, FP=False positive, PCT=Procalcitonin, CRP=C-reactive protein

Becker *et al*. introduced PCT as a diagnostic marker in infection. They found that the combination of PCT and CRP tests was the most useful in the diagnosis of infection.[14] Many studies have suggested that the combination of PCT and CRP tests is the most accurate diagnostic method.[15]

Much evidence implies that PCT and CRP could be useful in the diagnosis of infection in the febrile neutropenic patient. Different studies have mentioned sensitivity in the range of 40-83% and specificity in the range of 60-96% for PCT, and also, they noted that PCT is more specific in comparison to the CRP, and PCT was proposed to have a high value in the diagnosis of bacteremia.[16-19] Hausfater *et al*. evaluated the PCT level in 243 febrile neutropenic patients. The results of their study showed a sensitivity of 77% and a specificity of 59% for this marker.[20]

In the present study, we found a sensitivity of 92.5% and specificity of 97.3% for PCT, while CRP had a sensitivity of 70.5% and specificity of 42.5%. The results of our study were similar to a meta-analysis which also found that PCT was more accurate than CRP.[19]

In the present study, we assessed the relationship between the two groups with respect to age and gender, and there was no statistically significant difference in them between the two groups.

In the 70s, gram-negative pathogens were responsible for 70% of blood stream infections, while in mid 80s, gram-positive organisms began to predominate and in the late 90s, these pathogens accounted for almost 70% of cases of bacteremia.[21] In a multicenter study on febrile neutropenic patients in the USA, Wisplinghoff *et al*. reported that gram-positive microorganisms were the cause of 62% and 76% of blood stream infections in 1995 and 2000, respectively, while only 22% and 14% of all blood stream infections originated from gram-negative organisms at the same time.[22]

PCT is considered as a diagnostic marker for the severity of infections.[1] The results of our study showed that PCT is useful in the diagnosis of sepsis in febrile neutropenic patients and is highly sensitive and specific. But like any other study, we should also consider the clinical signs and symptoms of each patient.

One of the limitations of this study was the small number of the febrile neutropenic patients. We only evaluated 64 febrile neutropenic patients and we suggest to evaluate more patients in future studies.

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