Dicle Tıp Dergisi / Dicle Medical Journal (2017) 44 (2) : 175-182

www.diclemedj.org

Özgün Araştırma / Original Article

Comparison of Procalcitonin and C-reactive Protein in Differential Diagnosis of Sepsis and Severe Sepsis in Emergency Department

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Received: 20.12.2016 Revised: 10.04.2017 Accepted: 05.05.2017

Abstract

Objective: Sepsis and severe sepsis (sepsis accompanied by acute organ dysfunction) are leading causes of death worldwide. In this study, our aim was to investigate utility of biomarkers commonly used in diagnosis of sepsis in discriminating these two entities.

Methods: Two-hundred and three patients involved were divided into 2 subgroups as sepsis and severe sepsis according to Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Then groups were compared according to clinical and laboratory (including C-reactive protein (CRP) and procalcitonin (PCT) levels) characteristics.

Results: Of 203 patients included into the study, 124 (61.1%) were male and 79 (38.9%) were female. The most common reason for sepsis was urinary tract infection (n=64, 31.5%), followed by catheter infection (n=16, 7.9%) and pneumonia (n=14, 6.9%). Escherichia coli was the most common agent in both blood and urinary cultures. Majority of the patients were treated with ceftriaxone (n=33, 16.3%), followed by meronem/dapson (n=25, 12.3%). In both groups, CRP and PCT levels were high, even higher in severe sepsis group. However, any statistical significance could not be determined between groups. Mortality rate in sepsis patients was 6.4%.

Conclusion: Plasma levels of both markers elevate in sepsis and severe sepsis. It was determined that CRP and PCT is higher in severe sepsis than in sepsis. However, the difference is not statistically significant. Plasma levels of CRP and PCT are not useful in differential diagnosis of sepsis and severe sepsis.

Keywords: C-reactive protein, procalcitonin, sepsis, severe sepsis, Emergency department

DOI: 10.5798/dicletip.319750

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Acil Serviste Sepsis ve Şiddetli Sepsisin Ayırıcı Tanısında Prokalsitonin ve C-reaktif Proteinin Karşılaştırılması

Özet

Amaç: Sepsis ve şiddetli sepsis (akut organ disfonksiyonunun eşlik ettiği sepsis) dünyada ölümlerin başlıca nedenlerindendir. Bu çalışmada amacımız, sepsis tanısında sıkça kullanılan biyobelirteçlerin bu iki durumun ayrımındaki yararlılıklarını araştırmaktır.

Yöntemler: Dahil edilen 203 hasta; Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 kılavuzuna göre sepsis ve şiddetli sepsis olmak üzere iki gruba ayrılmıştır. Daha sonra gruplar klinik ve laboratuar (C-reaktif protein (CRP) ve prokalsitonin (PCT) dahil olmak üzere) özelliklerine göre karşılaştırılmıştır.

Bulgular: Çalışmaya katılan 203 hastanın 124 (%61,1)'ü erkek, 79 (%38,9)'u kadındı. Sepsisin en sık nedeni üriner sistem enfeksiyonlarını (n=64, %31,5) takiben kateter enfeksiyonları (n=16, %7,9) ve pnömoni (n=14, %6,9) idi. Üriner ve kan kültürlerinde en sık ajan Escherichia coli olarak tespit edildi. Hastaların çoğu seftriakson (n=33, %16,3) ile tedavi edilirken bunu meronem/dapson (n=25, %12,3) tedavisi takip etti. Her iki grupta da CRP ve PCT düzeyleri yüksek iken şiddetli sepsis grubunda daha yüksek saptandı. Ne var ki, gruplar arasında istatistiksel olarak anlamlı fark tespit edilemedi. Sepsis hastalarında mortalite oranı %64 olarak saptandı.

Sonuç: Sepsis ve şiddetli sepsiste her iki beirtecin de plazma düzeyleri artmaktadır. Şiddetli sepsiste CRP ve PCT seviyelerinin sepsise kıyasla daha yüksek olduğu tespit edildi. Ne var ki, aradaki fark istatistiksel olarak anlamlı değildi. Sepsis ve şiddetli sepsisin ayırıcı tanısında CRP ve PCT'nin plazma düzeyleri faydalı bulunmamıştır.

Anahtar kelimeler: C- reaktif protein, prokalsitonin, sepsis, şiddetli sepsis, Acil Servis

INTRODUCTION

One of the most challenging tasks in critical care medicine is the treatment of serious infection related multiple organ dysfunction, termed in general as sepsis, severe sepsis, and septic shock. However, sepsis means a very heterogeneous patient population, which varies in etiology and severity; therefore, universally applicable diagnostic criteria and treatment algorhythms are difficult to be defined[1].

Sepsis still represents a major cause of morbidity and mortality in critically ill patients despite the use of modern antibiotics and resuscitation therapies[2]. There is a lack of early diagnosis and timely intervention for sepsis in the emergency department (ED), and recent interest has focused on biomarkers for early diagnosis, risk stratification, and evaluation of prognosis of sepsis[3].

C-reactive Protein (CRP) is a protein produced in response to infection and/or inflammation and it is widely used in clinical tests to diagnose and manage patients with sepsis. This biomarker is an acute phase reactant whose synthesis in the liver is upregulated by IL-6.The CRP's role during acute inflammation is not entirely clear and it may bind the phospholipid components of microorganisms, facilitating their removal by macrophages[4].

Procalcitonin (PCT) is a prohormone (peptide precursor) of calcitonin that is released by parenchymal cells, including liver cells, kidney cells, adipocytes, and muscle cells in response to bacterial toxins, leading to elevated serum levels (up to 5000-fold) within 2 to 4 hours; in contrast, procalcitonin is downregulated in patients with viral infections[5].

In this study, our aim was to investigate clinical and laboratory characteristics sepsis and severe sepsis patients and search for utility of CRP and PCT levels in differential diagnosis of sepsis and severe sepsis in ED.

METHODS

Between August 2014 and August 2015, 203 patients diagnosed as sepsis in ED were

involved into the study. According to clinical features, patients were divided into 2 subgroups as sepsis (Group I, n=175) and severe sepsis (Group II, n=28). Diagnoses of sepsis and severe sepsis were confirmed by specialists in infectious diseases based upon Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 by Dellinger et al. [6]. See table 1 and 2 for details.

Table 1. Diagnostic Criteria for Sepsis according to Surviving Sepsis Campaign Infection, documented or suspected, and some of the following:

General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two sd above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao2/Fio2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

Group I was composed of patients with presence (probable or documented) of infection together with systemic manifestations of infection. Patients with sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion constituted Group II.

Inclusion criteria for sepsis-induced hypotension was defined as a systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension. Blood cultures of the patients were studied via Vitek® automated system in order to identify the causative agents for sepsis.

Then, groups were compared according to their vital signs, clinical and laboratory findings.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 22.0. Descriptive data were given as arithmetic mean ±standard deviation, minimum-maxiumum and percentages. For statistical evaluation, Chi-square and Mann-Whitney U tests were used. $p<0,05$ was considered statistically significant.

Table 2: Definition of Severe Sepsis according to Surviving Sepsis Campaign

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao2/Fio2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao2/Fio2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (international normalized ratio > 1.5)

RESULTS

Of 203 patients included into the study, 124 (61.1%) were male and 79 (38.9%) were female. When medical histories of the patients were investigated, it was determined that 169 (83.3%) had hypertension (HT), 93 (45.8%) had coronary artery disease (CAD), 62 (30.5%) had Diabetes Mellitus (DM), 51 (25.1%) had chronic kidney disease, 26 (12.8%) had chronic obstructive pulmonary disease (COPD).

When etiologic factors of the patients were investigated, it was determined that the most common reason for sepsis was urinary tract infection (UTI) (n=64, 31.5%). It was followed by catheter infection (n=16, 7.9%) and pneumonia (n=14, 6.9%).

Positive blood culture was obtained in 131 patients (64.5%) and the most common agent was Escherichia coli (E coli) (n=18, 8.9%), followed by Metisilin-sensitive Staphylococcus aureus (MSSA) (n=7, 3.4%) and Klebsiella pneumonia (K. pneumonia) (n=5, 2.5%). In urinary cultures of the patients, the most common agent was found to be E. coli (n=34, 16.7%). In catheter cultures, E. coli and MSSA were the most common etiologic agents (n=5,2.5%).

Most of the patients were treated with ceftriaxone (n=33, 16.3%), followed by meropenem/dapsone (n=25, 12.3%).

Mean length of stay in the hospital was 10.8±7.5 days.

Despite treatment, 13 patients have died in study period. Mortality rate was found to be 6.4%.

Characteristics of all patients included in the study are summarized in table 3.

When groups were compared according to their vital signs, any statistical significance could not be determined. Our results revealed that severe sepsis was statistically significant among males (p=0.024).

When patients were compared according to co-morbidities, medical history, antibiotic use and response to antibiotherapy, any statistical significance could not be determined.

Additionally, comparison of groups according to agents in blood, urinary and catheter culture reproduction did not reveal any statistically significance.

Comparison of laboratory findings of groups did not reveal any statistical significance.

In sepsis and severe sepsis groups, mean values of CRP and PCT were found to be 134, 184 and 6.2, 19.7, respectively (normal range for CRP: 0-5 mg/dL and PCT: 0-046 ng/ml). Both CRP and PCT levels were found to be higher in severe sepsis group. However, when groups were compared, any statistical significance could not be determined. See table 4 for comparison of CRP and PCT between groups.

Table 3: Characteristics of patients with sepsis and severe sepsis

Sex n (%)	
Male	124 (61.1)
Female	79 (38.9)
Co-morbidities n (%)	
Chronic obstructive pulmonary disease	26 (12.8)
Malignity	24 (11.8)
Renal disease	51 (25.1)
Coronary artery disease	93 (45.8)
Hypertension	169 (83.3)
Diabetes Mellitus	62 (30.5)
Liver disease	2 (1)
Final diagnoses n (%)	
Urinary tract infection	64 (31.5)
Catheter infection	16 (7.9)
Pneumonia	14 (6.9)
Soft tissue infection	4 (2)
Blood culture results n (%)	
E. coli	18 (8.9)
Metisilin-sensitive *S. aureus*	7 (3.4)
K. pneumonia	5 (2.5)
E. feacalis	3 (1.5)
Metisilin-resistant *S. aureus*	3 (1.5)
S. hominis	3 (1.5)
Urinary culture results n (%)	
E. coli	34 (16.7)
K. pneumonia	4 (2)
E. faecalis	3 (1.5)
Catheter culture results n (%)	
E. coli	
Metisilin-sensitive *S. aureus*	5 (2.5)
Metisilin-resistant *S. aureus*	5 (2.5)
E. faecalis	2 (1)
	2 (1)
Antibiotherapy	
Ceftriaxone	33 (16.3)
Meronem	15 (7.4)
Imipenem	15 (7.4)
Meronem/dapson	25 (12.3)
Length of stay (days) in the hospital	10.8±7.5

Table 4: Comparison of CRP and PCT in sepsis and severe sepsis groups

	Sepsis	Severe sepsis
C-reactive protein (mg/dL)	134.6±117.4	184±139
Procalcitonin (ng/mL)	6.2±13	19.7±30.3

DISCUSSION

Results of our study revealed that neither CRP nor PCT may be used in differentiating sepsis from severe sepsis.

Female gender has been demonstrated to be protective against infection, whereas male gender may be deleterious due to a diminished cell-mediated immune response and cardiovascular functions. Male sex hormones, i.e., androgens, have been shown to be suppressive on cell-mediated immune responses. In contrast, female sex hormones exhibit protective effects which may contribute to the natural advantages of females under septic conditions[7]. Even though it is known that urinary tract infections are more common among females[8], our study revealed that majority of the patients with sepsis were male. This mechanism may be explained by the protective role of female sex hormones against infections.

It was previously reported that genitourinary infections are the third cause of infection[9]. In our study, genitourinary infections were found to be the most common reason for sepsis. This may be associated with the fact that our hospital serves as an advanced center and admits neglected elderly patients from other hospitals.

It was also reported that respiratory tract infection, particularly pneumonia, is the most common cause of sepsis, and associated with the highest mortality. However, the relative importance of pneumonia has decreased over time. Men and alcoholics are particularly prone to developing pneumonia, while genitourinary infections are more common among women. Other common sources of infection include abdominal, skin, and soft tissue, device-related, central nervous system, and endocarditis[9]. In our study, respiratory tract related sepsis was the third common cause of sepsis. Presence of an advance Chest Diseases Hospital in Çorum may be the reason of reduction in lung-related sepsis. High frequency of device related sepsis,

particularly dialysis catheter, may be related to lack of information of patients and their relatives about the importance of dressing at home. Also, there may be a negligence in early recognition of infections at the catheter site.

Staphylococcus aureus (20.5%), Pseudomonas species (19.9%), Enterobacteriacae (mainly E. coli, 16.0%), and fungi (19%) are known to be the most common microbial agents responsible for sepsis development[9]. Recently, it has been reported that main agent isolated from catheter induced UTIs is E. coli[10]. Since UTI was found to be the most common source of sepsis in our study, E. coli was the most common organism in urinary and blood cultures. Surprisingly, even in catheter culture, E. coli was the most common agent. Contamination of catheter site with urine in neglected patients may be the reason for this finding.

One of the most used assays in sepsis diagnosis is a positive blood culture. However, this diagnostic tool has its limitations because of the delay in the time for results and the issue that positive blood cultures are not present in a majority of cases[11]. We know that less than one half of the patients who have signs and symptoms of sepsis have positive blood culture or other microbiological proof of an infectious focus[12]. In our study, positive blood culture was obtained more than half of the patients with sepsis. Relatively high number of positive blood cultures may be associated with the fact that blood cultures have been obtained in the early stage before antibiotherapy. Additionally, lower contamination rates in our study may be the reason for accurate diagnosis.

Treatment of sepsis and severe sepsis includes broad-spectrum antibiotics, administration of 30 mL/kg crystalloid for hypotension or lactate >4 mm/L, and vasopressors[6]. The use of early and appropriate antibiotic therapy is crucial to improved survival rates in severe sepsis and septic shock. Early antimicrobial therapy along with other supportive resuscitation goals should be achieved to avoid the further development of cellular dysfunction, tissue injury, and overwhelming inflammatory response[13]. Low mortality rate in our study may be associated with rapid antibiotic and fluid therapy initiated in the ED.

Diagnosis and initiation of therapy remains a clinical decision by assessing the patient's history, possible symptoms of infection, and development of acute organ dysfunction. However, biomarkers can aid and shorten this decision process when taking into account the shortcomings of biomarkers. Procalcitonin is currently the most investigated biomarker for this purpose and the only biomarker which has been integrated into treatment algorithms[14]. Recently, the biomarkers used as diagnostic criteria for sepsis, plasma CRP or PCT levels more than 2 standard deviations (SD) above the normal value, are now part of the inflammatory variables which, together with infection, whether documented or suspected, constitute a definition of sepsis[6,15]. Even though importance of CRP and PCT tend to decrease in recent guidelines, they are being widely used for diagnosis of sepsis in clinical practice. Procalcitonin differentiates bacterial infections from systemic inflammatory response of other etiologies with higher sensitivity and specificity compared to CRP[16].

C-reactive Protein is a biomarker of inflammation, not of infection. C-reactive Protein is highly sensitive but lacks specificity. Moreover, there are few interventional studies evaluating its true added diagnostic value in the emergency unit, thus preventing the use of CRP as a biomarker of infection. Serum PCT dosage is more specific for diagnosis of bacterial infection. Procalcitonin levels do not increase or increase only slightly in non-bacterial inflammatory syndromes. Procalcitonin also provides prognostic information and risk stratification assessment in the emergency unit[17]. In our study, we determined that plasma levels of these two biomarkers elevate in both sepsis and severe sepsis. Additionally, plasma

levels of PCT were higher when compared to plasma levels of CRP. However, our results revealed that there was not a statistical significance between groups. Even though CRP and PCT are useful in diagnosis of sepsis and severe sepsis, it may not be used in differential diagnosis of these two clinical conditions. For differential diagnosis, following recent algorithms seems to be more useful.

Mean length of stay in our study was found to be 10.8 days. Some authors found improvement in secondary outcomes in septic patients, such as reduced infectious complications and length of hospital stay, but the relevance of these findings in the face of potential harm is unclear[6]. It was reported that hospital length of stay in sepsis has reduced without affecting mortality[18]. We suggest to reduce length of stay in hospital and duration of mechanical ventilation in patients with sepsis in order to prevent nasocomial infections.

There seems to be an increase in the incidence of sepsis, with mortality rates of 20–50%, and according to recent data from the United States, sepsis is the single most expensive reason for hospitalization at present[19,20]. In our study, mortality rate for sepsis was found to be lower probably due to advanced techniques and guidelines used for both diagnosis and treatment of sepsis.

Limitations of the study

Major limitation of our study is that we could not compare two groups according to other biomarkers of sepsis. Comparison of plasma levels of lactate and/or presepsin may be significantly different between groups. Another limitation of our study is inadequacy of all laboratory findings of the patients due to lack of appropriate patient records.

CONCLUSION

Differential diagnosis of sepsis, severe sepsis and septic shock remain to be a clinical challenge for both ED and Infectious diseases specialists. Differential diagnosis of these conditions are mainly based on updated guidelines. Search for an ideal biomarker for discriminating severe sepsis from sepsis still continue. Our results revealed that, even CRP and PCT are useful in diagnosis of sepsis, their utility in differentiating severity of sepsis is limited.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

Financial Disclosure: No financial support was received.

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