

## PROCALCITONIN AS A MARKER FOR EARLY DIAGNOSIS OF SEPSIS

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### ABSTRACT

Sepsis is a critical condition often caused by bacterial infection and associated with death and mortality. The prognosis of this disease depends on early diagnosis and proper treatment. Definite diagnosis of sepsis is positive blood culture and this test needs a long time to perform, so other biochemical parameters such as procalcitonin serum level has been introduced. To determine sensitivity, specificity, positive and negative predictive value of procalcitonin serum level at first time and 72 h after admission and to compare it with blood culture test for diagnosis of sepsis. Blood sample for blood culture, peripheral blood smear at first time and procalcitonin serum level measuring by semi quantitative method at first and 72 h after admission were sampled. Nine patients had positive blood cultures. Peripheral blood smear was positive in 38 patients, (29 patients: gram stain positive, 6 patients: gram stain negative and 3 patients: both gram positive and gram negative). At first time 76.8% had positive procalcitonin ( $>0.5 \text{ ng mL}^{-1}$ ) and after 72 h 65% of patients had positive procalcitonin. Sensitivity, specificity, positive and negative predictive value of procalcitonin at the first time were 100, 16, 16 and 100% and for procalcitonin after 72 h respectively were 75, 35, 15 and 90%. This study showed that sensitivity of procalcitonin serum level can be used for diagnosis of sepsis. Procalcitonin increased as severity of sepsis and this study suggests high serum level of procalcitonin after 72 h might indicate poor outcome.

**Keywords:** Sepsis, Procalcitonin, Sensitivity, Specificity

### 1. INTRODUCTION

Sepsis is one of the main problems in most of health centers and it is life-threatening disease that causes wide spread mortality and morbidity in the world. Indeed, sepsis is the result of a reaction between infectious microorganisms and the host immune system. Rapid diagnosis in its early stages and treatment by appropriate antibiotics leads to reduce patients' mortality (Mandell *et al.*, 1995).

To define the word, "sepsis" has a complete association with SIRS concept (systemic

inflammatory response syndrome). SIRS is the body's inflammatory response. To define, it is when the following criteria are available:

- Temperature more than  $38^{\circ}\text{C}$  or less than  $36^{\circ}\text{C}$
- Heartbeat rate more than 90 beats per minute
- Respiratory rate more than 20 times per minute, or paco 2 less than 32 mmHg
- White blood cell count more than 12,000 or less than 4000, or bandemia more than 10% (Gidela *et al.*, 2008; Mandell *et al.*, 1995)

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In the presence of SIRS and probable or confirmed infectious focus, the sepsis may be occurred (Gidela *et al.*, 2008; Mandell *et al.*, 1995). These criteria have low sensitivity and specificity for detecting disease, in spite of the fact that the existing of non-infectious various disease and conditions, including trauma, pancreatitis, cardiac infarction, cardiac tapenade and cause to make false positive and negative results in diagnosis of SIRS (Canan *et al.*, 2003; Mandell *et al.*, 1995). At the present, diagnosis of sepsis is a controversial. Standard laboratory tests and the clinical signs have low sensitivity and specificity, since the most severely ill patients will reveal some degree of inflammatory response, while they may have sepsis or not (Arkader *et al.*, 2006).

Despite the fact that one of the key elements for diagnosis is blood cultures test, but it has some problems such as not being positive in the majority of cases and delay in obtaining positive results, all of which shows that an additional marker is required for diagnosis of sepsis (Kopterides and Tsangaris, 2012). In this regard, several biomarkers are being introduced. For example different types of cytokine, such as TNF-a, IL10 and CRP and also procalcitonin which are more suggested by the useful recent studies and have been able to become a head of other markers (Heper *et al.*, 2006; Charalampos and Vincent, 2010).

Regarding to this fact that early and proper diagnosis of sepsis is one of main strategies for reducing mortality, so, the importance of diagnosis and also the lack of strong standard criteria for diagnosis has directed the last sepsis international conference, in the presence of possible or absolute infection, toward check some of biochemical and hemodynamic markers. One of these markers is Procalcitonin (a prohormones which composed of 116 amino acids) which is very useful in sepsis diagnosis in cases that the blood culture test is negative and its level is associated with sepsis severity (Canan *et al.*, 2003). It seems that specificity of this marker is higher than CRP and WBC count and it tends to rise quickly as bacterial infections (but not viral infections) develop, increase with the severity of infection and decline with improvement (PCCM, 2013).

Few studies have been done on the distinguish value of procalcitonin serum levels and their results have been controversial (PCCM, 2013; Makoo *et al.*, 2010; Heper *et al.*, 2006).

Considering the importance of distinguishing sepsis, starting antibiotic therapy in and avoiding unnecessary

antibiotic therapy in non-sepsis cases this study was designed to determine sensitivity and specificity of this marker in the diagnosis of sepsis.

## 2. METERIALS AND METHODS

This study was done to determine the sensitivity, specificity and predictive values of procalcitonin on diagnosis of sepsis on 60 patients 59-68 years, whit sepsis criteria, including 35 men and 25 women, who admitted to emergency unit of Peymaniye hospital of Jahrom, Iran.

After being secure about the subjects had sepsis criteria, the serum level of procalcitonin was determined. The basis of positive clinical and lab tests  $0.5 \text{ ng mL}^{-1}$  of serum pricalcitonin was cut off point and the negative and positivity levels were considered as following:

- $0.5\text{-}2 \text{ ng mL}^{-1}$  weakly positive
- $2\text{-}10 \text{ ng mL}^{-1}$  positive
- $10 \text{ ng mL}^{-1}$  <strongly positive

In order to find the possible source of infection and organ dysfunction, disease details and checkup result for the patients were gathered and then serum level of procalcitonin was determined by semi quantitative immunochromatogrsaphy method by commercial kit, at the time of visiting and over a period of 72 h.

Other necessary examinations for sepsis diagnosis such as blood culture test was done during the first 24 hours of hospitalization and other tests, such as analysis test and urine culture, chest radiography, ESR, CRP, LFT and Lp (if it was necessary) was taken simultaneously.

In addition, at the same time, when the patient sample was given for blood culture, it was used to examine the smear for microbiological assessment to examine for the presence of gram-negative and gram-positive microorganisms. Finally, patients were arranged in to the following groups:

Group1: Patients with positive blood cultures

Group2: Patients with positive peripheral blood smear

Group3: Patients have negative blood culture and smear and positive inflammatory markers (in flammatory marker means ESR and CRP)

Group4: Patients with negative blood cultures and smears and also negative inflammatory markers

According to the degree of sepsis severity, patients are placed in one of the following groups:

- Group1: SIRS
- Group2: Sepsis
- Group3: Severe sepsis
- Group4: Shock sepsis

That is, for placement in a specific group, the patient must have the characteristics of that group. In group 2, the patients have the SIRS symptoms with the possible infection source; Group3 included patients who had at least one of the following criteria which in fact reveal the organ dysfunction:

- $Pao_2/FIO_2 < 300 < \text{urine output} / 0.5 \text{ mL/kg/hr}$
- Serum creatinine  $> 2 \text{ mg dL}^{-1}$
- $INR < 1.5$  or  $PT > 60$
- Platelet count  $< 100,000$
- Total bilirubin  $> 4 \text{ mg dL}^{-1}$
- $PH < 7.35$  Systolic Bp  $< 90$  OR Mean arterial Bp  $< 60$  OR less 50 mL Hg compare to last base blood pressure. It response to fluid therapy

Group 4 was the patients of this group whom suffered from blood pressure drop and this drop of blood pressure not response to therapeutic fluid and needs vasoconstrictive agent.

In these two divisions, the PCT was measured at the time of zero and 72 h then the results of the procalcitonin and gold standard tests compared to each other and the sensitivity, specificity, positive and negative predictive values were calculated.

### 3. RESULTS

The widest spread infection was of the lung infection by 58.3% (35 patients) and then, the urinary tract 16.7% (10 patients), digestive 11.7% (7 patients), skin and soft tissue 6.7% (4 patients) and infections with unknown origin 6.7% (4 patients). Of the whole study population, 9 patients were reported as positive blood culture and that was the most common microorganism was Streptococcus. The Peripheral blood smear and gram-stained for 38 patients turned out to be positive and of which 29 patients had gram-positive, 6 patients had gram-negative and 3 patients had peripheral blood smear, including gram-positive and gram-negative. In this study, 5 patients died and

their serum level of procalcitonin in zero times were as following:

- In 4 patients (19%), positive ( $2-10 \text{ ng mL}^{-1}$ )
- In one patient (5%), strongly positive (greater than  $10 \text{ ng mL}^{-1}$ )

There was not found any significant correlation between serum level of procalcitonin at times zero and 72 h with gender and age ( $p = 0.113$ ,  $p = 0.121$ , respectively). Blood culture was reported as positive in 15% (9 patients). Blood culture tests were negative in all patients who had negative procalcitonin serum level at time zero.

Also, there was not found any significant correlation between Procalcitonin amount of times zero and 72 and blood culture ( $p = 0.119$ ,  $p = 0.125$ , respectively).

The average serum level of Procalcitonin at time zero was reported of  $9.2 \text{ ng mL}^{-1}$  in patients with positive and negative blood culture tests, but after 72 h the average serum level of Procalcitonin was reduced in the both groups, while the group who had negative blood cultures, this reduction was more noticeable. Procalcitonin reduction was not significant in patients with blood culture positive ( $p = 0.070$ ), but these changes showed a significant statistical correlation in patients with negative blood cultures ( $p = 0.0001$ ).

In patients with positive blood culture, based on the type of microorganism, the most percentage was pertained to streptococci organism and then Staph, *E. coli* and Enterococcus, respectively. No significant correlation was seen in time zero and 72 h type microorganisms ( $p = 0.360$ ).

It was reported that 38 patients (63.3%) had positive smear. The proportion of gram-positive organisms were 29 smears and gram-negative were 6 smears and 3 smears were mixture of positive and negative. So, there were no significant correlation between procalcitonin amount and peripheral blood smear in any of them ( $P = 0.417$ ,  $p = 0.500$ , respectively).

In zero times, in positive smear patients, the average of serum level of procalcitonin was non-significantly more than patients with negative smear and after passing 72 h, it was seen that the mean serum level of procalcitonin reduced in the two groups, which in patients positive smear this reduction was more visible.

The serum level of procalcitonin changes, in positive smear and negative smear patients, were significant in the two groups ( $p = 0.000$ ).

Among the 13.3% of the population with a negative procalcitonin serum level at zero time, 87.5% were categorized in the sepsis group and 12.5% were placed in severe sepsis group. Which there was seen no significant correlation between the procalcitonin serum level and sepsis severity at times zero and 72 ( $p = 0.251$ ,  $p = 0.290$ , respectively).

Though, after passing 72 h, the procalcitonin serum level decreased in all three groups and this reduction was more visible in patients of shock sepsis group than other groups.

In sepsis and severe sepsis patients, the changes of procalcitonin serum level was significant ( $p = 0.000$ ), but this changes were not significant in those with sepsis shock ( $p = 0.180$ ).

The under studying patients were also examined on the site of infection. From the 13.3% of patients with a negative procalcitonin serum level at time zero, 62.5% had lung infection, 12.5% had urinary tract infections, 12.5% had skin and soft tissue infections and 12.5% had unknown local infection.

There was not observed a significant correlation between the procalcitonin serum level at time zero and infection place ( $p = 0.335$ ). But after passing 72 h and measuring the procalcitonin serum level, it was revealed that the procalcitonin serum level in 35% of the total population was positive.

Of this 35% with a negative procalcitonin in time 72 h, 52.4% patients had pulmonary infection, 28.6% had urinary tract infection, 4.8% had digestive infection, 9.5% had skin and soft tissue infections and 4.8% were infected with an unknown location.

There was a significant correlation between the procalcitonin serum level, at the time 72 h the place of infection ( $p = 0.033$ ).

This significant correlation was 58.3% for patients with lung origin, 16/7% for urinary tracts origin, 11.7% for digestive origin, 6.7% for skin origin and 6.7% for patients with unknown origin.

The patients were examined to find that whether they have positive or negative inflammatory markers and finally the statistically correlation was not significant.

In group of patients with negative blood culture, negative peripheral blood smear and negative inflammatory marker, the relation of different variables such as age, gender, severity of sepsis and place of infection, in times zero and 72, was not seen a significant statistically correlation except in case of gender and in time 72 ( $p = 0.010$ ).

In this study, 8.3% (5 patients) had died. It was reported that all patients who died have positive procalcitonin serum level but correlation was not significant ( $p = 0.159$ ).

The serum level of procalcitonin in time 72 h as compared to 0, in patients who had died, had been fallen down and this was not significant ( $p = 0.590$ ).

The sensitivity, specificity, positive and negative predictive values for procalcitonin serum level were examined in zero and 72 h which its result was obtained, in case of time zero, as 100, 16, 16 and 100% respectively and in case of 72 h it was 75, 35, 15 and 90% respectively.

#### 4. DISCUSSION

Through various studies, procalcitonin was one of the markers which have been suggested for more rapid diagnosis of sepsis (Canan *et al.*, 2003).

In our study, we examined the sensitivity, specificity, positive and negative predictive values for procalcitonin at time zero and 72 h which its result was reported, in case of time zero, as 100, 16, 16 and 100% respectively; and in case of 72 h it was 75, 35, 15 and 90% respectively (**Table 1**).

Other studies that have been conducted show similar sensitivity but lower specificity. Of these studies, Canan *et al.* (2003) have stated that the procalcitonin sensitivity and specificity for differentiating SIRS from sepsis, is 85 and 91% respectively.

Another study which was conducted by Zahra Ahmadinejad *et al.* (2009) presents that the sensitivity and specificity for procalcitonin ( $0.5 \text{ ng mL}^{-1}$ ) are respectively, 89.2 and 82.9%. Another study by Heper *et al.* (2006) expressed the sensitivity and specificity for procalcitonin by 88 and 70% respectively.

In a study conducted by Wanner *et al.* (2005), it is expressed that the procalcitonin sensitivity and specificity is low in diagnosis of sepsis. Brunkest *et al.* (2000) and in a meta-analysis showed 77 and 85% for sensitivity and specificity respectively (Wacker *et al.*, 2013).

**Table 1.** Sensitivity, specificity, positive and negative predictive values for PCT serum level at time zero and 72 h after admission

PCT serum level	Sensitivity%	Specificity%	NPV%	PPV%
Zero time	100	16	100	16
72 h	75	35	90	15

NPV: Negative Predictive Value; PPV: Positive Predictive Value

However, in present study there was not a significant correlation between procalcitonin serum level sat zero and 72 h times with gender; which these results are in agreement with other studies (Heper *et al.*, 2006; PCCM, 2013; Makoo *et al.*, 2010; Ahmadinejad *et al.*, 2009). Although, in present study, in a group of patients who have a negative blood cultures, negative peripheral blood smears and negative inflammatory marker, there was a significant correlation between procalcitonin amount of 72 h and gender and it was 75% for female and 25% for male gender, but it should be noted that there were 8 patients in this group and most of them, 6 patients, were female.

But there was a significant correlation between procalcitonin amount, in time 72 h and the place of infection; which this relation was about 58.3% with lung origin and this result was in contrast to Heper results, because they did not find any significant correlation between procalcitonin serum level, in time 24, 48 and 72 h and place of infection (Heper *et al.*, 2006).

In the study that we carried out most of the patients had pulmonaryorigin (58.3%), the procalcitonin serum level, in time 72 h compared to time zero, had been decreased in all the population and this was significant, so it can be concluded that there was a relationship with the place of infection.

In the study we have done, in connection with the procalcitonin serum level at the times zero and 72 h and blood cultures, there was found no significant correlation; which it was in harmony with Heper studies (Angeletti *et al.*, 2012). But it was in contrast to the study by Ghorbani (2009) which it was concluded that there exist a significant correlation between the procalcitonin serum level and patients with positive blood cultures.

In the present study there is not a significant correlation between the procalcitonin amount in time zero and 72 h and type of microorganisms. This result is in parallel with the result of a study which was done on patients with infective endocarditic, which showed a significant correlation between the procalcitonin amount and Staphylococcus aurous in the infective endocarditic factor (Cuculi *et al.*, 2008).

In present study, it was realized that procalcitonin cannot discern between patients with different levels of sepsis (sepsis, severe sepsis and sepsis shock). Here, the findings of Ghorbani (2009) are in agreement with mentioned results, but in the study was done by Brunkorst *et al.* (2000) about the value of determining of PCT level in early diagnosis of SIRS patients, sepsis, severe sepsis and septic shock, compared

with WBC, CRP, platelet counting and AP-IL, it revealed this result that procalcitonin can distinguish between severe sepsis and sepsis shock groups.

It is worthy to mention that in Brunkhorst study, 21% of patients were belonged to septic shock group, while in our study only 3.3% of population had septic shock (Brunkorst *et al.*, 2000).

In present study the patients were categorized into two groups: sepsis and severe sepsis (severe sepsis and septic shock) and here it was seen that also in these patients the procalcitonin, in times zero and 72 h, cannot make a difference between these two groups and this result is in contradiction with (Heper *et al.*, 2006) thus, here it can be pointed that there is the probability of using antibiotics by patients before they hospitalized in hospital.

In present study the procalcitonin serum level, in the two times of zero and 72 h, in patients who died had higher procalcitonin serum level than patients survived; that is, in this case the result is in accordance with Heper results (Heper *et al.*, 2006).

And also in present study there was not seen any significant correlation between procalcitonin serum level changes in time zero and 72 h in patients who died, but it was significant for patients who survived similar result showed in the study that was done by (Ikeda *et al.*, 2012).

The last no table point is that in patients who had precaution awareness, procalcitonin serum level changes had less reduction in time 72 h than time 0 it can be stated that the procalcitonin serum level highness in time 72 h is useful for patients with precaution awareness.

## 5. CONCLUSION

In this study it was shown that procalcitonin serum levels have a high sensitivity in sepsis diagnosis and therefore, accompanying with other patient's clinical symptoms, are a suitable marker in sepsis diagnosis.

In time 72 h, the features of this substance had been higher than time zero, it is recommended more studies for more reliable results.

Since there is not a significant difference between the procalcitonin serum level, in time 72 h compared to time zero, in positive blood culture patients than negative ones and in sepsis shock patients than sepsis and severe sepsis, it can be expressed that the procalcitonin serum level decreases in a lower rate in sicker patients.

In this study the procalcitonin serum level had been decreased significantly in patients who died than whom

they are survived, so the richness of this marker comes with terrible precaution in patients.

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