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Investigating the Relationship between Procalcitonin Serum Level and Response to Treatment in Urosepsis Patients

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ABSTRACT

Background and Aim: Urinary tract infection is a common and painful disease in humans. Rapid and timely diagnosis of sepsis and its differentiation from non-infectious causes that manifest with similar symptoms is very important because timely antibiotic treatment onset in patients with sepsis is very vital in reducing mortality and improving the final outcome of patients. This study was performed aiming to investigate the relationship between procalcitonin serum level changes and response to treatment in patients in 2016. Materials and Methods: In this study 15 women and 15 men of the patients over 18 years of age who were admitted to Yasouj Shahid Beheshti Hospital were selected. Then, urine culture and blood sample were taken simultaneously from the patients on day 5 and day 10 and two weeks after the start of treatment, and in case of negative urine culture in each one of the cultures, the procalcitonin serum level was measured. To analyze the data SPSS software was used. Findings: The mean and standard deviation of procalcitonin serum level before and after treatment were 8.88 ± 1.24 and 0.05 ± 0.01, respectively (p = 0.001). The mean and standard deviation of procalcitonin serum level before and after treatment in patients with complicated and uncomplicated urinary tract infection were 10.97 ± 1.46 and 0.54 ± 0.08, respectively (p = 0.001). Conclusion: Procalcitonin biomarker can be used in patients with urinary tract infection to evaluate the response to treatment and the duration of admission in the hospital and the duration of antibiotic therapy.

Key words: Urosepsis, Procalcitonin, Sepsis, SIRS.

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INTRODUCTION

Urinary infection is one of the most common diseases and also the most common complaint related to the urinary system, which means the presence of microbe in the urinary tract. The urinary tract includes the kidneys, bladder and urethra. The most common cause of urinary infection is infection with fecal microbes and it is 4 times more common in women than men [1], in a way that its prevalence has been reported up to 3% [2]. Urinary tract infections include cystitis (bladder infection) and pyelonephritis (kidney infection) and prostatitis (prostate infection) and urethritis (urethra infection) [3]. Following a urinary tract infection, the patient may have septicemia and septic shock. The incidence of disease complications is clearly associated with an increase in mortality [4].

Many studies have been carried out in the last decade to access markers that can be used to diagnose early sepsis [5]. Procalcitonin is produced during sepsis by macrophages and monocytes of various organs and released into the bloodstream [6, 7]. One of these studies has been conducted on the procalcitonin serum level in patients with sepsis, the results of which indicate an increase in the procalcitonin serum level in this group of patients [8]. Procalcitonin has a half-life of 15 to 20 hours in the blood and its concentration is related to the severity of infection in patients admitted to Intensive Care Unit (ICU) [9, 10]. Diagnosis of urinary tract infection begins

with taking the biography and a physical examination including measuring body temperature, costovertebral angle tenderness and examination of the abdomen and pelvis [11]. In recent years, the use of broad-spectrum antibiotics, which are often expensive drugs, has been widely used in the treatment of urinary tract infection, which, in addition to imposing more complications and heavier cost to the patient, gradually leads to resistance of microorganisms to new antibiotics and the reduction of their efficacy [12].

The aim of performing this study was to measure the procalcitonin serum level in patients with urosepsis before and after treatment, and to investigate the relationship between procalcitonin serum level changes and response to treatment in patients with urosepsis. Considering the increased resistance to antibiotics and increased costs due to hospitalization for patient and hospital, reducing the length of hospitalization of patients with urinary tract infection and choosing the correct antibiotic for treating and evaluating the patient's response to treatment, was the reason for the repetition of study and the necessity to perform it. The study was performed aiming to investigate the relationship between procalcitonin serum level changes and response to treatment in patients with urosepsis.

MATERIALS AND METHODS

This study is a laboratory study. The statistical population of patients over the age of 18 who had fever and at least one of the symptoms of burning and frequent urination, sides pain and tenderness and penile secretion, had urinary tract infection by primary diagnosis. This study was conducted in Shahid Beheshti Hospital of Yasuj in 2016. Of these, 30 people were selected for performing the study. After explaining the goals of study, if people had willingness to cooperate, after obtaining written informed consent, the middle urinary sample was collected in a sterile container and cultured on an blood agar culture medium, and after 48 hours those patients whose urinary culture had more than 100,000 colon bacteria per ml were considered as having urinary tract infection (UTI), and among these patients, those who had two or more of the SIRS criteria were included in the study as patients with urosepsis. Before starting antibiotic treatment, 2 ml of venous blood sample was taken, and after centrifugation and separating the serum, the sample was transferred to a freezer and stored at a temperature of minus 40°C and were kept under the same conditions until all samples were completed. Urinal culture and blood samples were taken simultaneously from patients on day 5 and day 10 and two weeks after the start of treatment, and if urine culture in each of the cultures was negative, the serum sample of the same day was selected to measure the procalcitonin serum level.

Exit criteria in this study are mechanical trauma, heat stroke, recent surgery operation, age less than 18 years old, getting cancer, burn, recent hospital admission, permanent urinary catheter, pregnancy, antibiotic use for more than 48 hours, patients who have a negative urine culture after two weeks of antibiotic treatment. Thirty patients with urosepsis who did not have exit criteria were included in the study. From all patients by getting the written consent a 2-cc blood sample was taken in the Clat test tube before the start of antibiotic treatment, and was transferred to the laboratory. Samples were centrifuged at 3000 round for 5 minutes, and the serum sample was separated to measure the procalcitonin serum level. After sampling, an appropriate antibiotic treatment was started based on the culture response and antibiogram, and the patients were followed up in respect of clinical symptoms improvement and the time of fever stop after the start of treatment. The type of bacteria grown in urine culture, the time of fever stop, and the SIRS criteria were entered in the pre-prepared forms in which the demographic characteristics of the individuals entered in to the study was recorded. From patients on day 5 and day 10 and two weeks after the start of treatment, urinal culture and blood samples were simultaneously taken again, and in case that the culture was negative in each one of the cultures, procalcitonin serum level was measured. Frozen serum samples were de-frozen at room temperature after completion of the sampling, and the procalcitonin serum level titre was measured by ELEXIS device through Electrochemiluminescence method designed based on the electrons velocity in the circuit. Data was collected and analyzed by SPSS software. To investigate the parametric tests of independent-t, paired-t, one-way ANOVA and Pearson correlation were used provided that variables were normal. In all statistical tests, the significance level was less than 5%.

RESULTS

There were 15 women and 15 men equally in this study, with the highest and the lowest age; the highest was higher than 50 years (40%) old and the lowest was 31 to 35 years [6.7] old respectively. Based on the experimental range of the kit used in the study, patients with procalcitonin serum level were considered to be less than and equal to 0.05 ng / ml. Patients with procalcitonin serum level between 0.05 and 0.5 ng / ml were located in low-risk range for severe sepsis, patients with procalcitonin serum level ranged from 0.5 to 2 ng / ml were located in the medium-risk range for severe sepsis and patients with procalcitonin serum level more than or equal to 2 ng / ml were located in the medium-risk range for severe sepsis. The frequency and frequency percentages have been reported in Table 1.

Table 1: Frequency and Frequency Percentages of Variables

Variable	-	Frequency	Frequency Percentages
Gender	Male	15	50
	Female	15	50
Age	Under 30 years	4	13.3
	31 to 35 years	2	6.7
	36 to 40 years	4	13.3
	41 to 45 years	5	16.7
	46 to 50 years	3	10.0
	More than 50 years	12	40.0
Procalcitonin Serum Level	Normal	3	10.0
	Low risk for severe sepsis	3	10.0
	Medium risk for severe sepsis	3	10.0

By using Kolmogorov-Smirnov (KS) test, procalcitonin serum level was normal before and after treatment ($p > 0.05$). By using paired t-test the procalcitonin serum level before and after treatment in patients with urosepsis was considerably significant ($p = 0.001$) (Table 2).

Table 2: Procalcitonin Serum Level before and after Treatment

Variable Statistical Index		Mean	Significance Level of Paired T-Test
Procalcitonin serum level before and after treatment	Procalcitonin serum level before treatment	8.88	P=0.01
	Procalcitonin serum level after treatment	0.05	

Between the procalcitonin serum level before and after treatment and the number of positive SIRS criteria in patients with urosepsis, the mean and standard deviation (21.78 ± 9.93) compared to other two groups are higher. Regarding the mean (according to the ANOVA test) of all three levels, the number of SIRS criteria with regard to procalcitonin serum level before treatment is not at the same level. Also, the mean of procalcitonin serum level before treatment in patients with 7 days admission [21.15] was higher than other levels. Regarding the mean (according to the ANOVA test) of all five levels, the number of hospitalization day with regard to procalcitonin serum level before treatment is not at one level (Table 3).

Table 3: Comparison Table of Mean and Standard Deviation of Procalcitonin Serum Level before Treatment with the Number of Positive SIRS Criteria in Patients with Urosepsis and Procalcitonin Serum Level before Treatment with the Number of Hospitalization Day in Patients with Urosepsis.

Levels of the number of SIR criteria and the number of hospitalization day	Statistical Index		
	Number	Mean (Procalcitonin Serum before Treatment)	Standard Deviation (Procalcitonin Serum before Treatment)
Number of positive criteria 2	15	1.75	1.84
Number of positive criteria 3	7	9.44	5.87
Number of positive criteria 4	8	21.78	9.93
Total	30	8.88	1.87
2 days	13	1.45	1.06
3 days	2	4.72	2.36
4 days	7	11.18	5.01
5 days	6	20.28	8.22
6 days	2	21.15	24.54
Total	30	8.88	1.24

The procalcitonin serum level before treatment with the number of positive SIRS criteria was compared by one-way ANOVA test, which with regard to the significance level of less than 0.05, there was a significant difference between procalcitonin serum levels before treatment with the number of positive SIRS criteria. Also, the procalcitonin serum level before treatment with the number of hospitalization day in patients with urosepsis with a significant level of less than 0.05

shows a significant difference between the procalcitonin serum level before treatment and the number of hospitalization day in patients with urosepsis.

Then, with regard to the significance of the variance test, to determine which of the levels of the number of SIRS criteria (two criteria, three criteria and four criteria) and which of the levels of the number of hospitalization day have significant difference, the Tukey post hoc test was used. The results showed that there was a significant difference between the number of positive SIRS criteria with regard to the procalcitonin serum level before treatment, and significant difference has been shown between various levels for the number of positive SIRS criteria separately and two by two, and between the levels of days 2, 3, and 4 there was no significant difference with regard to procalcitonin serum level before treatment, and also there was no significant difference between the levels of days 4, 5, and 7 with each other with regard to the procalcitonin serum level before treatment, and then in the other two by two comparisons, there was significant difference between the number of admission day according to the procalcitonin serum level before treatment (Table 4).

Table 4: Tukey Post Hoc Test to Compare Procalcitonin Serum Level before Treatment with the Number of Positive SIRS Criteria in Patients with Urosepsis and Comparison of Procalcitonin Serum Level before Treatment with the Number of Hospitalization Days in Patients with Urosepsis.

Various levels for the number of positive SIRS criteria	Number of patients	Sub-sets at significance level of 0.05		
		1	2	3
Number of criteria 2	15	1.75		
Number of criteria 3	7		9.44	
Number of criteria 4	8			21.78
significance level		0.001	0.001	0.001
Various levels based on the number of patients' hospitalization day	Number	Sub-sets at significance level of 0.05		
		1		2
2 days	13	1.45		11.18
3 days	2	2.72		20.28
4 days	7	11.18		21.15
5 days	6			
7 days	2			
Significance level		0.001		0.001

Also, there was a significant relationship between procalcitonin serum level before treatment and the number of positive SIRS criteria and since the correlation coefficient value was positive, it was concluded that there is a direct relationship between the procalcitonin serum level before treatment and the number of positive SIRS criteria.

There was a significant relationship between procalcitonin serum level before treatment and the number of hospitalization day, and since the correlation coefficient value was positive, hence there was a direct relationship between the procalcitonin serum level before treatment and the number of hospitalization day.

The mean of procalcitonin serum level before treatment in patients with negative urine culture is higher on day 14 (21.15) than other levels. Also, the mean of procalcitonin serum level before treatment in acinetobacteria microbe (22.70) is higher than other microbes. Regarding the mean (according to the ANOVA test) of all three levels, the negativity of urinary culture with regard to procalcitonin serum level before treatment are not at one level; also all four types of microbe grown in urine culture with regard to procalcitonin serum level before treatment are at one level.

Regarding that the significance level of less than 0.05 shows that there was a significant difference between the procalcitonin serum level before treatment with negativity time of urine culture in patients with urosepsis, there was no significant difference between procalcitonin serum level before treatment and the type of microbe grown in urine culture either ($p = 0.65$).

To determine which of the levels of negativity time of urine culture has significant difference, Tukey post hoc test was used (Table 5).

Table 5: Tukey's Post Hoc Test to Compare the Mean of Procalcitonin Serum Level before Treatment with Negativity Time of Urine Culture in Patients with Urosepsis.

Various levels for the number of the negativity time of urine culture	Number	Sub-sets at significance level of 0.05	
		1	2
Day 5	18	3.72	
Day 10	10	15.74	15.74
Day 14	2		21.15
Significance level		0.001	0.001

Among the 30 patients under study, 24 patients had complicated pyelonephritis, 15 of them were male, 6 of them were diabetic, 2 had chronic renal failure, and 1 had a history of urinary tract infection in the past year. The procalcitonin serum level before treatment was investigated in patients with complicated and uncomplicated urinary tract infection. The procalcitonin serum level before treatment in patients with complicated and uncomplicated urinary tract infection was observed by using independent t-test, that the significance level value of this test was equal to 0.023 and this value is less than 0.05 (Table 6).

Table 6: Independent T Test to Compare Procalcitonin Serum Level before Treatment in Patients with Complicated and Uncomplicated Urinary Tract Infection.

Variable Statistical Index	Mean		T value	Degree of freedom	Significance level sig.
Procalcitonin serum level before treatment in patients with urinary tract infection	Complicated	10.97	2.409	28	0.023
	Uncomplicated	0.54			

DISCUSSION

The results of this study showed that procalcitonin serum level has relationship with response to treatment in patients with urosepsis, and with the onset of antibiotic therapy and negativity of urine culture, its level is significantly reduced. These results are consistent with the study of Mobin et al. performed on the relationship between procalcitonin serum level and response to treatment in 38 patients with bacterial sepsis admitted to the ICU, and showed that procalcitonin serum level significantly reduces following the response to treatment [13]. Patients with a higher procalcitonin serum level before treatment, have a higher number of positive SIRS criteria. In a study performed by Fardin Asadi et al. it was showed that the procalcitonin serum level and CRP levels in patients with septic shock were significantly higher than patients with SIRS and sepsis, and procalcitonin serum level has more sensitivity in differentiating them from each other [14].

The procalcitonin serum level before treatment has significant relationship with the number of admission day in patients with urosepsis, and patients with higher procalcitonin serum level before treatment will be hospitalized for more number of day in hospitel. In the study of Sugimoto et al., it has been shown that patients with high procalcitonin serum level (higher than 10 ng/ml) had more severe complications than other patients [15], and also Ahmadinejad et al., showed that there is a significant relationship between procalcitonin serum level (higher than 10 ng/ml) with the death of patients with infectious sepsis [16] and other studies in this field have been performed and are consistent with the current study. It can be concluded from the findings and the results of previous studies that patients with urosepsis whose procalcitonin serum level is higher, will have higher duration of hospitalization [17-21]. Findings showed that the urine culture of patients with higher procalcitonin serum level before treatment will become negative later, which is consistent with other studies [22, 23]. In patients with urosepsis, the procalcitonin can be used as a biomarker for rapid assessment of response to treatment, and antibiotic treatment can be discontinued earlier in patients with low procalcitonin serum level. This point can reduce the long-term prescription of antibiotic and results in reducing the growing trend of microbial resistance to antibiotics. It is suggested that future studies are performed separately for each infectious disease and with a larger sample size and the results are compared. In patients with complicated urinary tract infection, procalcitonin serum level before treatment is higher than patients with uncomplicated acute pyelonephritis. Therefore, the duration of antibiotic treatment and the

duration of hospitalization should be performed more carefully for these patients.

CONCLUSION

The obtained results of this research are:
1. Procalcitonin serum level before treatment has a direct relationship with the number of hospitalization day in patients with urosepsis.
2. There was a relationship between the positive SIRS criteria number with regard to procalcitonin serum level before treatment.
3. There was a direct relationship between the procalcitonin serum level before treatment and the positive SIRS criteria number.
4. As the number of hospitalization day increases, the procalcitonin serum level before treatment increases.
5. The procalcitonin biomarker can be used in patients with urinary tract infection to assess the response to treatment and the duration of hospitalization in hospital and the duration of antibiotic therapy.

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