THE ROLE OF PROCALCITONIN, C-REACTIVE PROTEIN, INTERLEUKIN-6, INTERLEUKIN-8 AND ENDOTOXIN IN THE EARLY DIAGNOSIS AND FOLLOW-UP OF LOCAL INFECTIONS

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ABSTRACT

Objective: *Infectious diseases are one of the leading cause of mortality and morbitidy in developed as well as in developing countries. Local infections, uriner tract and wound infections are most frequently seen. In this study the role of procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8) ve endotoxin is investigated in the early diagnosis and follow-up of local infections.*

Material and Method: *A total of 67 patients (33/34 patients with urinary tract and wound infections) between May 2006-June 2007 at various departments and intensive care units of Selçuk University Meram Medical School Hospital were evaluated. The control group consisted of 20 healthy individuals. The patients over the age of 18, with no history of antibiotic therapy were included in the urinary tract infection group if they were symptomatic and had a positive urine test.*

The patients who were monitored with the diagnosis of decubitus / diabetic foot ulcers or surgical zone infection who had positive wound culture tests were included in the wound infection group. The patients with negative culture results were excluded regardless of data indicating infection.

Results: *In the wound infection group changes of PCT, CRP, IL-6, IL-8 and endotoxin levels were from baseline to day 7 respectively 0.12/4.74–0.05/0.94 ng/ml, 11.3/203–4.17/200 mg/dl, 2.70/22.79–1.07/10.25 pg/ml, 0.19/5–0.1/4.8 pg/ml, 0.01/6.25–0.01/0.86 pg/ml ($p \leq 0.001$). In the urinary tract infection group changes of CRP, IL-6, IL-8 and endotoxin levels were detected from baseline to day 7 respectively 3.17/200–2.1/126 mg/dl, 1.26/14.25–0.8/6.85 pg/ml, 0.49/4.6–0.07/3.2 pg/ml, 0.07/9.65–0.01/3.65 pg/ml ($p \leq 0.001$). Changes in PCT level was statistically significant in the wound infection group ($p \leq 0.001$) but was not statistically significant in the urinary tract infection group ($p=0.004$).*

Conclusion: *PCT, CRP and endotoxin levels are useful tools for clinicians to differantiate local infections from the healthy people. CRP, IL-6, IL-8 and endotoxin levels are useful tools for follow-up urinary tract and wound infections.*

Key Words: *Urinary tract infections, wound infections, procalcitonin, c-reactive protein, interleukin, endotoxin*

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LOKALİZE ENFEKSİYONLARIN ERKEN TANISI VE TAKİBİNDE PROKALSİTONİN, C-REAKTİF PROTEİN, İNTERLÖKİN-6, İNTERLÖKİN-8 VE ENDOTOKSİNİN ROLÜ

ÖZET

Amaç: Enfeksiyon hastalıkları, gelişmiş ve gelişmekte olan ülkelerde morbidite ve mortalitenin önde gelen nedenlerindendir. En sık karşımıza çıkan lokalize enfeksiyonlar, üriner sistem enfeksiyonları ve yara yeri enfeksiyonlarıdır. Bu çalışmada, lokalize enfeksiyonların erken tanı ve takibinde prokalsitonin (PCT), C-reaktif protein (CRP), interlökin-6 (IL-6), interlökin-8 (IL-8) ve endotoksinin rolü araştırılmıştır.

Materyal ve Metod: Mayıs 2006-Haziran 2007 tarihleri arasında Selçuk Üniversitesi Meram Tıp Fakültesi servis ve yoğun bakımlarında izlenen, 33'ü üriner sistem enfeksiyonu ve 34'ü yara yeri enfeksiyonu tanısı alan toplam 67 hasta değerlendirilmiştir. Kontrol grubu 20 sağlıklı kişiden oluşmuştur. 18 yaş üzerinde, antibiyotik tedavisi almamış idrar kültüründe üremesi olan semptomatik hastalar idrar yolu enfeksiyonu grubuna, dekübit ülseri, diyabetik ayak enfeksiyonu veya cerrahi alan enfeksiyonu tanısıyla izlenen, yara kültüründe üremesi olan hastalar yara yeri enfeksiyonu grubuna alınmıştır. Enfeksiyon bulgusu olmasına rağmen, kültürlerinde üremesi olmayan hastalar çalışmaya dahil edilmemiştir.

Bulgular: Yara yeri enfeksiyonu grubunda PCT, CRP, IL-6, IL-8 ve endotoksin düzeylerinin bazal değere göre 7.gün değişimi sırasıyla 0.12/4.74-0.05/0.94 ng/ml, 11.3/203-4.17/200 mg/dl, 2.70/22.79-1.07/10.25 pg/ml, 0.19/5-0.1/4.8 pg/ml, 0.01/6.25-0.01/0.86 pg/ml idi ($p \leq 0.001$). Üriner sistem enfeksiyonu grubunda ise CRP, IL-6, IL-8 ve endotoksin düzeylerinin bazal değere göre 7.gün değişimi sırasıyla 3.17/200-2.1/126 mg/dl, 1.26/14.25-0.8/6.85 pg/ml, 0.49/4.6-0.07/3.2 pg/ml, 0.07/9.65-0.01/3.65 pg/ml olarak saptandı ($p \leq 0.001$). PCT düzeyindeki değişim yara yeri enfeksiyonu grubunda istatistiksel olarak anlamlı ($p \leq 0.001$) iken, üriner sistem enfeksiyonu grubunda istatistiksel olarak anlamlı bulunmadı ($p=0.004$).

Sonuç: Lokalize enfeksiyonları sağlıklı kişilerden ayırmada PCT, CRP ve endotoksin düzeyleri klinisyene yol gösterici bulunmuştur. İdrar yolu enfeksiyonlarının takibinde CRP, IL-6, IL-8 ve endotoksin düzeylerinden, yara yeri enfeksiyonlarının takibinde ise bu parametrelerin hepsinden faydalanılabilir.

Anahtar Kelimeler: Üriner sistem enfeksiyonu, yara yeri enfeksiyonu, prokalsitonin, c-reaktif protein, interlökin, endotoksin **Nobel Med 2012; 8(1): 61-66**

INTRODUCTION

Infectious diseases are one of the leading causes of morbidity and mortality in industrialized and developing countries. Infections are accountable for 40% of all deaths in the world.[1] Mortality and morbidity as a result of infectious diseases can be decreased significantly by establishing the correct diagnosis and providing appropriate therapy.[2, 3]

The most common local infections are urinary tract and wound infections. Bacteria are the frequent cause of such infections.[1] Culture testing is a very valuable tool, but results cannot be obtained promptly.[4, 5] Therefore, investigators have been trying to institute other markers that can be used for early diagnosis.

Sensitive and specific laboratory tests are needed to guide clinicians in diagnosing infections promptly and correctly, monitoring therapy response, avoiding irrelevant therapy and terminating therapy at the correct time. It is essential that such tests reveal the severity of infections, have high sensitivity in differentiating infectious and non-infectious cases, as well as being practical, inexpensive and accessible.

C-reactive protein (CRP) is one of the markers currently used to serve this end and procalcitonin (PCT) as specific markers used in the diagnosis and follow-up of bacterial infections. The effectiveness of interleukin-6 (IL-6), interleukin-8 (IL-8) and endotoxin are still being investigated in terms of early diagnosis and follow-up of infections.

This present study investigated the significance of PCT, CRP, IL-6, IL-8 and endotoxin in the early diagnosis and follow-up of localized infections. We aimed to determine the most effective indicators that can be used in the diagnosis and follow-up of localized infections.

MATERIAL and METHOD

A total of 67 patients (33 patients diagnosed with urinary tract infection and 34 patients diagnosed with wound infections) between May 2006 and June 2007 at various departments and intensive care units of Selçuk University Meram Medical School Hospital were evaluated. The control group consisted of 20 healthy individuals. Both the patients' and the controls' characteristics (age, gender, risk factors, laboratory and blood culture results) were →

recorded in patient follow-up forms. The patients over the age of 18, with no history of antibiotic therapy were included in the urinary tract infection group if they were symptomatic and had a positive urine test. On the other hand, the patients monitored with the diagnosis of decubitus ulcer, diabetic foot ulcers or surgical zone infection who had positive wound culture tests were included in the wound infection group. The patients with negative culture results were excluded regardless of data indicating infection.

The study was approved by the ethics committee of Selçuk University Meram Medical School.

Blood samples were collected from the enrolled patients and healthy controls at Day 0 and day 7. CRP and PCT levels were evaluated at Selçuk University Meram Medical School Central Laboratory.

The blood samples drawn from the patients and the controls on days 0 and 7 were centrifuged at 5,000 rpm for three minutes for obtaining the serum to be used for IL-6, IL-8 and endotoxin evaluation. Serum samples were stored at –80 °C and were evaluated at Sarayönü State Hospital Central Laboratory. CRP levels were analyzed nephelometrically (Dade Behring, Marburg-Germany). A CRP level of ≤ 5 mg/dl was considered as normal.

Immunoluminometric assay was used for determination of PCT levels (BRAHMS-Diagnostica, Berlin-Germany). A PCT value of 0.1 ng/ml or lower was considered to be normal. IL-6 (Human IL-6 Biosource Immunoassay Kit, California-USA), IL-8 (Human IL-8/NAP-1 Biosource Immunoassay Kit, California-USA) and endotoxin (LAL Chromogenic Endpoint Assay, Hycult Biotechnology, Uden-Netherlands) levels were determined by using Enzyme Linked Immunosorbent Assay (ELISA). ELISA washer (ELX50 Auto Strip Washer, Bio-Tek Instruments Inc., Vermont-USA) and ELISA reader (ELX800 Reader, Bio-Tek Instruments Inc., Vermont-USA) were used. IL-6 and IL-8 levels were considered to be normal at ≤7.8 pg/ml and ≤15.6 pg/ml, respectively. Limit value for endotoxin level was established specifically for the study. Statistical analyses were performed with SPSS 13.0 for Windows (Real State Corporation, England) by using t-test for dependent groups. $p<0.05$ was accepted as the level of significance.

RESULTS

A total of 87 subjects (67 patients and 20 healthy controls) were evaluated. Of the patients, 33 had urinary tract infection (19 women and 14 men, age range 25-82 years) and 34 had wound infection (11 women and 23 men, age range 22-85 years). The controls consisted of 7 women and 13 men. Their age range was 25-52 (Table 1). The

Table 1: Ages of the patients and controls

	n	Gender Female/Male	Age Median value (min/max)
Urinary tract infection	33	19/14	59.00 (25–82)
Wound infection	34	11/23	60.00 (22–85)
Control group	20	7/13	31.00 (25–52)

Table 2: Changes in PCT, CRP, IL-6, IL-8 and endotoxin levels for the urinary tract infection group from baseline to day 7.

Urinary tract infection group (n:33)	Min-Max value	Mean value	Median value	Standard deviation	p value
PCT (ng/ml)					
Day 0	0.04-0.56	0.15	0.08	0.14	0.004
Day 7	0.02-0.30	0.09	0.07	0.05	
CRP (mg/dl)					
Day 0	3.17-200.00	44.67	21.20	55.99	0.001
Day 7	2.10-126.00	17.67	9.49	26.19	
IL 6 (pg/ml)					
Day 0	1.26-14.25	6.09	6.25	2.86	‹ 0.001
Day 7	0.80-6.85	3.45	2.95	1.84	
IL 8 (pg/ml)					
Day 0	0.49-4.60	1.89	1.75	1.09	‹ 0.001
Day 7	0.07-3.20	1.15	0.98	0.84	
Endotoxin (pg/ml)					
Day 0	0.07-9.65	2.48	1.60	2.70	‹ 0.001
Day 7	0.01-3.65	0.59	0.18	0.89	

changes from baseline to day 7 in the markers evaluated for the urinary tract infection group consisting of 33 patients are shown in Table 2. PCT were not significant. On the other hand, the changes in CRP, IL-6, IL-8 and endotoxin levels were statistically significant ($p\leq0.001$). The changes from baseline to day 7 in the markers evaluated for the wound infection group consisting of 34 patients are given in Table 3. The changes in the levels of all parameters observed were statistically significant ($p\leq0.001$). The changes from baseline to day 7 for PCT, CRP, IL-6, IL-8 and endotoxin levels for the 20 subjects in the control group are presented in Table 4. The changes in the levels of any of the parameters observed were not statistically significant ($p\leq0.001$). Table 5 shows PCT, CRP, IL-6, IL-8 and endotoxin median values of the study groups.

The subjects in this study were categorized into three groups. Inter-group comparisons were made in terms of p values. When urinary tract infection and wound infection groups were compared, the changes in PCT and CRP levels were significant ($p<0.001$). However, significant changes were observed in PCT, CRP and endotoxin levels in the comparison between the urinary tract infection group and the controls ($p<0.001$). →

Table 3: Changes in PCT, CRP, IL-6, IL-8 and endotoxin levels for the wound infection group from baseline to day 7.

Wound infection group (n:34)	Min-Max value	Mean value	Median value	Standard deviation	p value
PCT (ng/ml)					
Day 0	0.12-4.74	1.67	1.33	1.35	‹ 0.001
Day 7	0.05-0.94	0.27	0.19	0.21	
CRP (mg/dl)					
Day 0	11.30-203.00	82.43	81.30	46.80	‹ 0.001
Day 7	4.17-200.00	44.27	35.00	44.19	
IL 6 (pg/ml)					
Day 0	2.70-22.79	6.25	5.55	3.63	‹ 0.001
Day 7	1.07-10.25	4.17	3.77	2.29	
IL 8 (pg/ml)					
Day 0	0.19-5.00	1.60	1.22	1.26	‹ 0.001
Day 7	0.10-4.80	0.99	0.78	0.99	
Endotoxin (pg/ml)					
Day 0	0.01-6.25	1.38	0.55	1.72	‹ 0.001
Day 7	0.01-0.86	0.21	0.16	0.23	

Similarly, significant changes were observed only in PCT, CRP and endotoxin levels in the comparison between the wound infection group and the controls ($p<0.001$).

DISCUSSION

Infectious diseases are one of the leading causes of morbidity and mortality in industrialized and developing countries. Infections are accountable for 40% of all deaths in the world.[1]

The incidence and prognosis of infectious diseases are determined by host, effective microorganisms and the conditions of that particular country where the patient lives. Mortality and morbidity as a result of infectious diseases can be decreased significantly by establishing the correct diagnosis and providing appropriate therapy.[2,3]

The most common local infections are urinary tract and wound infections, and they are frequently caused by bacteria.[1] Urinary tract infections are the most widespread bacterial infections in the world.[6,7] The golden standard of diagnosis is urine culture.[8]

Wound infections are often seen in the senior population, diabetics and immunosuppressive individuals, and include skin, soft tissue and surgical site infections. Wound infections become apparent with the development of drainage, redness, and increased warmth in the lesion area. Culture test is required for confirming the diagnosis.[9] Although culture tests are critical in establishing the definite diagnosis, results cannot be obtained promptly.[4,5] Therefore, investigators have been trying to find other markers that can be used for early diagnosis. Sensitive and specific laboratory tests are needed to guide clinicians in diagnosing infections promptly and correctly, monitoring therapy response, avoiding irrelevant therapy and terminating therapy at the correct time. It is essential that such tests reveal the severity of infections, have high sensitivity in differentiating infectious and non-infectious cases, as well as being practical, inexpensive and accessible.

PCT, a polypeptide and a precursor of the hormone calcitonin, is another marker which has gained popularity in recent years for the diagnosis and follow-up of bacterial infections.[10,11] Despite the inexistent PCT production in patients with thyroidectomy, PCT level is found to be elevated in the presence of infection, which suggests non-thyroid production of this marker. Although its source is not known plainly, PCT is thought to be released from neuroendocrinal cells in the liver, lungs or intestines. However, it has not been clearly elucidated exactly where and through which mechanism its production occurs.[10-12] Oberhoffer et al. demonstrated PCT expression in several leukocyte types (monocytes, granulocytes, B and T lymphocytes) by intracellular antibody staining.[13] Plasma PCT levels are elevated as a result of direct endotoxin stimulation or the impact of cytoxins.[14] PCT appears to be a more sensitive marker than acute phase proteins to bacterial stimuli due to its direct response to endotoxin stimulation.[15]

PCT plasma levels are very low in healthy individuals, but they are significantly elevated in patients with severe infections. While significant elevations are observed in severe infections, PCT levels are not seen to significantly increase during local and restricted infections.[10,12] Normal PCT level for healthy individuals are under 0.1ng/ml but it rises to values over 0.5 ng/ml during an infection. A serum PCT value of over 1.0 ng/ml may be observed in patients with bacterial, parasitic or fungal infections, accompanied by systemic data. The level can reach the 1,000 ng/ml mark for severe sepsis.[16]

Contrary to bacterial infections, PCT values change minimally in localized infections.[17] Tunçbilek et al. carried out a comparative study including patients with sepsis and with localized infections.[18] The median PCT value for patients with localized infection was between 1.43 and 0.31 ng/ml. Similarly, Enguix et al. reported median PCT values of 0.81 ng/ml and 0.41 ng/ml in neonates and in children with infections other than sepsis, respectively.[19] A multi-center study conducted by Aikawa et al. determined a median PCT value of 0.94-0.16 ng/ml in infections other than sepsis.[5] In this present study, a slight increase in PCT levels were observed in patients with urinary tract infection and wound infections. The baseline PCT values of patients with urinary tract infection were in the range of 0.04 and 0.56 ng/ml, with the median value of 0.08 ng/ml. →

The baseline PCT values of the patients with wound infection were in the range of 0.12 and 4.74 ng/ml, with the median value of 1.33 ng/ml. While PCT values of the control group were very low, there were no significant changes in PCT values at day 7 compared to baseline in the urinary tract infection group. The change in PCT levels from baseline was noted to be significant in the wound infection group as a result of therapy. This can be attributed to the worse prognosis of wound infections when compared to urinary tract infections in terms of clinical and laboratory data.

CRP is released during the acute phase response stage from hepatic cells. It is the most commonly used acute phase reactant in the diagnosis and follow-up of infections. CRP response is not specific to infection and has to be considered along with a through clinical evaluation.[20] CRP values in this present study were 3.17-200 mg/dl for the urinary tract infection group and 11.3-203 mg/dl for the wound infection group. There were no statistically significant differences between the groups in terms of providing guidance in the diagnosis or the severity of the infection. This can be attributed to non-specific characteristics of CRP and to its elevation in response to inflammation. CRP has a wide range of utilities. Determining infection severity is its most common use.[17] CRP levels rise in almost all inflammatory events, except for bacterial infections. Therefore, CRP has low sensitivity and specificity as a marker.[17] Hatherill et al. determined the median value of CRP to be 20 mg/dl in localized bacterial infections, and 12 mg/dl for viral infections in their study conducted on 175 pediatric patients.[21] The median CRP values in this study were 21.1 mg/dl for the urinary tract infection group and 81.3 mg/dl for the wound infection group. In their multi-center study, Aikawa et al. categorized the subjects into sepsis, localized bacterial infections, non-bacterial infections, suspected bacterial infections and non-infectious diseases groups.[5] They concluded that the differences in CRP levels were statistically significant in terms of differentiating localized infections and healthy individuals. In agreement with the results from the study conducted by Aikawa et al. we found that CRP was statistically significant in terms of differentiating patients with localized infections from healthy individuals.[5]

CRP is a marker commonly consulted in evaluating therapy response.[17] Both groups revealed significant drops in CRP levels as a result of therapy. This can be attributed to CRP's long half-life, resulting in a delayed drop in CRP level in response to therapy, when compared with the more prompt decrease observed in PCT levels.

Another marker investigated in terms of its sensitivity to early diagnosis and follow-up of infections is IL-6, an important acute phase reactant. Aikawa et al. reported a median IL-6 value of 199.5 pg/ml for their patients with systemic bacterial infections.[5] The median values of IL-6 were 141.2 pg/ml in the localized bacterial infection group and 152.6 pg/ml in the non-bacterial infection group. When groups were compared, IL-6 was observed to be of significance in differentiating healthy individuals from patients with systemic bacterial infections or localized infections. Inter-group comparison demonstrated that IL-6 was not of significance in differentiating patients with localized infections from healthy individuals. Patient follow-up on day 0 and day 7 revealed significantly improved IL-6 levels in both groups.

Another cytokine whose sensitivity has been investigated in terms of early diagnosis and follow-up of patients with infections is IL-8, a chemotactic and activating molecule for neutrophils.[22] Patient follow-up for therapy response on day 0 and day 7 revealed that the changes in IL-8 levels in both of the groups were statistically significant. Inter-group comparisons demonstrated that IL-8 levels were not statistically significant in terms of diagnosing →

Table 4: Changes in PCT, CRP, IL-6, IL-8 and endotoxin levels for the control group from baseline to day 7.

Control group (n:20)	Min-Max value	Mean value	Median value	Standard deviation	p value
PCT (ng/ml)					
Day 0	0.02-0.08	0.05	0.04	0.02	0.681
Day 7	0.02-0.09	0.05	0.05	0.02	
CRP (mg/dl)					
Day 0	3.17-4.13	3.25	3.17	0.26	0.350
Day 7	3.17-4.50	3.30	3.17	0.37	
IL 6 (pg/ml)					
Day 0	0.61-7.6	4.12	3.85	1.95	0.091
Day 7	0.69-7.1	3.38	3.45	1.81	
IL 8 (pg/ml)					
Day 0	0.21-7.6	1.41	0.77	1.71	0.326
Day 7	0.15-4.65	1.77	1.18	1.52	
Endotoxin (pg/ml)					
Day 0	0.01-0.09	0.04	0.05	0.03	0.391
Day 7	0.01-0.09	0.05	0.05	0.02	

Table 5: PCT, CRP, IL-6, IL-8 and endotoxin serum concentrations for the study groups

	n	PCT (ng/ml) Median value	CRP (mg/dl) Median value	IL-6 (pg/ml) Median value	IL-8 (pg/ml) Median value	Endotoxin (pg/ml) Median value
Urinary tract infection group	33	0.08	21.20	6.25	1.75	1.60
Wound infection group	34	1.33	81.30	5.55	1.22	0.55
Control group	20	0.04	3.17	3.85	0.77	0.05

localized bacterial infections and differentiating healthy individuals.

The molecule endotoxin is responsible for triggering infection induced systemic inflammatory response in gram-negative bacteria. Dandona et al. observed healthy volunteers following an injection of *Escherichia coli* endotoxin.[12] The subjects developed chills, rigors, fever and myalgia between 1-3 hours. TNF-alpha levels increased at the first hour and peaked within the second hour, returning to baseline concentration at the 6th hour. IL-6 levels peaked at the third hour, returning to baseline values at the 8th hour. PCT reached a detectable level at the 4th hour, peaking at the 6th and remaining elevated for at least 24 hours. Hugh et al. carried out a similar study to that of Dandona et al. and injected healthy individuals with *E.coli* endotoxin.[23] They reported systemic inflammation 1-2 hours following endotoxin injection.

Aikawa et al. evaluated endotoxin levels in a multi-center study conducted to investigate infection markers in their patients categorized into five groups.[5] They reported a median endotoxin value of zero for all five of the groups. Comparisons between the groups revealed that endotoxin levels were statistically significant only in terms of differentiating patients with bacterial infections from healthy individuals. Comparisons between the groups revealed that endotoxin levels were statistically significant in terms of differentiating patients with localized infections from healthy individuals.

In our study, which investigated the significance of PCT, CRP, IL-6, IL-8 and endotoxin in the early diagnosis and follow-up of localized infections, it was demonstrated that PCT and CRP levels have a diagnostic value for clinicians. All these markers can be utilized in monitoring therapy response in localized infections.

CONCLUSION

In conclusion, the markers whose significance in the early diagnosis and follow-up of infections was investigated can be valuable to establish infection severity and the correct therapy, as well as to overcome antibiotic resistance, monitor therapy response and consequently, decrease mortality and morbidity.

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