

Can Procalcitonin Help The Diagnosis of Osteomyelitis in Adults?: A Prospective Study

Prokalsitonin Yetiřkinlerde Osteomyelit Tanısına Yardımcı Olabilir mi?: Prospektif Bir alıřma

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SUMMARY

Purpose: The aim of this study was to evaluate the sensitivity, specificity and predictive values of procalcitonin in adults patients with osteomyelitis.

Material and Methods: A total of 30 consecutive patients with osteomyelitis and 30 healthy controls were enrolled in this study. The white blood cell count, erythrocyte sedimentation rate, C-reactive protein and procalcitonin (PCT) levels of the patients and controls were detected. Procalcitonin was measured by an Enzyme-Linked Immunosorbent Assay (Ray Bio® Human Procalcitonin ELISA Kit, Norcross GA, USA). Values of PCT levels >0,5 ng/ml were considered as high than normal.

Results: Among 30 patients included in the study 4 of them were subacute osteomyelitis while 26 of them were chronic osteomyelitis. The ratio of the female to male both in patients and the control group was 10/20. The mean age of the patients was 31,16 ±15,32 years, while in control group 32,22±14.32 years. 26 (86,7%) of the patients had clinical signs and symptoms of osteomyelitis. White blood cell count detected high in 5 (16.6%) of them, erythrocyte sedimentation rate was high in 20 (66.6%) of them and C-reactive protein was positive in 15 (50%) patients, but PCT levels found to be higher in all 30 (100%) patients (PCT>0.5 ng/mL). In our study, the PCT test, with a 0.5 ng/mL cut-off value, had a sensitivity of 100%, a specificity of 56% and a positive predictive value of 100%. The PCT test, with a 0.57 ng/mL cut-off value, had a sensitivity of 87%, a specificity of 86% and a positive predictive value of 87%. This cut-off value (0.57 ng/mL) is quite suitable in osteomyelitis patients.

Conclusion: The sensitivity, specificity, and positive predictive values of PCT test are more discriminative than the other acute phase reactants in the patients with osteomyelitis. Therefore, the PCT test can be used as a useful marker in the diagnosis of osteomyelitis.

Keywords: Procalcitonin, osteomyelitis

ÖZET

Ama: Bu alıřmanın amacı osteomyelit tanısı alan eriřkin hastalarda prokalsitoninin duyarlılık, zgllk ve prediktif deęerini lmektir.

Materyal ve Metot: alıřmaya osteomyelitli 30 hasta ve 30 saęlıklı kontrol grubu alındı. Her iki grubun lkosit sayısı, eritrosit sedimantasyon hızı, C-reaktif protein ve prokalsitonin (PCT) dzeyleri saptandı. Prokalsitonin, Enzyme-Linked Immunosorbent Assay (Ray Bio® Human Procalcitonin LISA Kit, Norcross GA, USA) yntemi ile lld. PCT'nin 0,5 ng/ml'nin zerinde olan deęeri, normalden yksek olarak kabul edildi.

Bulgular: alıřmaya dahil edilen 30 hastanın 4' subakut osteomyelit iken; 26'sı kronik osteomyelitli. Hastaların ve kontrol grubundaki toplam kadınların erkeklere oranı 10/20'di. Hastaların yař ortalaması 31,16 ± 15,32 iken, kontrol grubunda ise 32,22 ± 14,32 idi. Hastaların 26'sında (% 86,7) klinik bulgular ve osteomyelit semptomları vardı. 5 (% 16.6) hastada lkosit sayısı yksek, 20 (% 66.6) hastada eritrosit sedimantasyon hızı yksek, 15 (% 50) hastada C-reaktif protein pozitif iken 30 (% 100) hastanın tmnde PCT dzeyleri (PCT> 0.5 ng / mL) yksek bulundu. alıřmamızda, PCT testinin cut-off deęeri 0.5 ng/mL olarak deęerlendirildięinde, duyarlılıęı % 100, zgllę % 56 ve pozitif prediktif deęeri ise % 100 idi. PCT'nin cut-off deęeri 0.57 ng/mL deęerlendirildięinde, duyarlılıęı % 87, zgllę % 86 ve pozitif prediktif deęeri ise % 87 idi. Bu cut-off deęeri (0.57 ng/mL), osteomyelit hastaları iin daha uygun grld.

Sonu: Osteomyelitli hastalarda, PCT testinin duyarlılıęı, zgllę ve pozitif prediktif deęeri dięer akut faz reaktanlarına gre daha iyi ayırıcı tanıya gtrebilmektedir. Bu nedenle PCT testi, osteomyelitin teřhisinde yararlı bir belirte olarak kullanılabilir.

Anahtar kelimeler: Prokalsitonin, osteomyelit

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INTRODUCTION

Osteomyelitis is an infectious disease, which causes functional loss, psychiatric illness, paralysis and seldom mortality, despite the advent of effective antimicrobial therapy and recent advances in the operation techniques.¹ No specific laboratory test exists for the diagnosis of bone infections, with the exception of isolation of an organism from the bone which is considered the gold standard, but its sensitivity ranges are low.^{2,3} Laboratory markers, such as elevated white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels may be helpful but are not specific.⁴ For these reasons there is a need of a laboratory test that can be used in the diagnosis and the follow up of these patients. It is known that procalcitonin (PCT) levels are raised in the serum of patients with bacterial infections.⁵ In a meta analysis study of various bacterial infections, PCT was considered a sensitive marker than CRP.⁶ To our knowledge, there are no data concerning the serum PCT levels in adult patients with osteomyelitis. Therefore the aim of our study was to evaluate the sensitivity, specificity and predictive values of PCT in adults patients with osteomyelitis.

MATERIALS and METHODS

A total of 30 consecutive patients with osteomyelitis (4 subacute and 26 chronic osteomyelitis) and 30 healthy controls were enrolled in this study between 2008-2010. The study protocol was carried out in approved by the local research committee for ethics. The diagnosis of osteomyelitis was based on at least 2 of the following findings: 1) pus on aspiration from the affected bone 2) presence of classic signs and symptoms of osteomyelitis, 3) a positive imaging study, either on radiography or magnetic resonance imaging (MRI). It was accepted that acute osteomyelitis <2 weeks, subacute osteomyelitis 2-4 weeks and chronic osteomyelitis >4 weeks.

The infection was suspected on clinical conditions, laboratory markers and imaging study. Clinical conditions were defined as pain during passive movements, failure to move an extremity, pain, tenderness, warmth, and erythema of the involved bone. Patients and controls; a) who are between 18-65 years of age b) patients without having any chronic diseases exception osteomyelitis c) healthy adults without having any diseases d) no history of alcohol consumption and smoking were included in the study.

Primary osteomyelitis was diagnosed in 5 of the patients while 25 of them was secondary to a contiguous foci (post injury wound in 11,

post accident wound in 7, post operative in 3, gunshot wound in 2, electric shock injury in one and post injection wound in one patient). Laboratory markers (WBC, ESR and CRP) were obtained on admission, before initiation of intravenous antibiotic, when the osteomyelitis was suspected. Venous blood samples of the patients before antibiotic therapy were taken and stored at -80°C until the analysis of PCT. Also the blood samples of the control group were stored. Bone aspiration cultures were taken from 20 patients. Plain X-ray was taken to all patients but 2 of them were lost. Because of some problems about the patients, Magnetic Resonance Imaging (MRI) was taken to 18 patients. The levels of PCT for both groups were measured by an Enzyme-Linked Immunosorbent Assay (Ray Bio® Human Procalcitonin ELISA Kit, Norcross GA, USA). Values of PCT levels >0,5 ng/ml were considered as high than normal.

Statistical Analysis

Data are expressed as the mean ± SD. Statistical significance was determined using Bonferroni adjusted Mann Whitney-U test. All P values are 2- tailed. Receiver-operating characteristic (ROC) curve analysis was performed to find cut-off value of PCT for osteomyelitis. The level of statistical significance was defined as P < 0.05. The SPSS 11.5 commercial software package was used for statistical analysis.

RESULTS

Among 30 patients included in the study 4 of them were subacute osteomyelitis while 26 of them were chronic osteomyelitis. The ratio of the female to male both in patients and the control group was 10/20. The mean age of the patients was 31,16 ±15,32 years, while in control group 32,22±14.32 years. When compared for age and gender, no statistically significant difference was observed between the groups (for both P>0.05). The laboratory results (mean±SD) of both patients and controls are shown in Table 1.

White blood cell count detected normal in 25 (83.3%) of the patients, CRP was normal in 15 (50.%) patients and ESR was normal in 10 (33.3%) patients. The laboratory results were abnormal in 20 (66.6%) of the patients. 26 (86,7%) of the patients had clinical signs and symptoms of osteomyelitis (local pain, pain with motion, pain after touching, humor and function loss etc.). No clinical symptoms were detected in 4 (13.3%) of the patients. Aspiration specimen culture yielded 2 *Staphylococcus aureus* and 2 *Staphylococcus epidermidis*. There were positive sings with plain x-ray in 4 (%14,3)

| Laboratory parameters | Osteomyelit (n=30) | Control (n=30) | P value |
|-------------------------|--------------------|-----------------|---------|
| PCT (ng/mL) | 0,66±0,08 | 0,49±0,06 | <0.001 |
| CRP (mg/dL) | 3,26±4,19 | 0,13±0,35 | <0.001 |
| ESR (mm/h) | 47,06±37,72 | 9,86±5,26 | <0.001 |
| WBC (/mm ³) | 7892,30±2068,17 | 6572,75±1252,35 | 0,005 |

Table 1. Laboratory data of the patients with osteomyelitis and controls

patients, while no abnormal signs were found in 24 (%85,7) of the patients. MRI findings were positive in 18 patients. Because of the metallic implants, claustrophobia and the patients who not to comply with it, MRI could not taken to 12 patients. The comparison of the levels of PCT and other acute phase reactants (CRP, ESR, WBC) with sensitivity, specificity and positive predictive levels are shown in Table 2. The receiver-operating characteristic (ROC) curve analysis was performed to find cut-off value of PCT test. Area under curve (AUC) for PCT was found as 0,944, while it was found as 0,859 for ESR, 0, 813 for CRP and 0,712 for WBC (figure 1).

DISCUSSION

The diagnosis and management of osteomyelitis have still been a problem for the clinicians. Physical examination, WBC, CRP, ESR and X-ray imaging have been used routinely for this aim, however, they are not enough specific and descriptive.⁷ Bone culture is considered to be the gold standard; however, a decrease down to 30% in its sensitivity and mainly being used in diagnosis rather than follow-up, restricts its use as a routine procedure.⁸⁻¹⁰ In a study analysing radiological imaging methods, it was shown that the sensitivity and specificity of MRI was high in diagnosing osteomyelitis, however, its high cost is a disadvantage.¹¹ In our study, all of the 18 patients with an MRI scan had positive signs. However, in the remaining 12 patients (40 %) MRI scan was unavailable because of several reasons (metallic implants, unsuitable patient, claustrophobia), in addition to that, its high-cost, local artifacts and scar tissue on the healing area were all factors which lowered the significance and sensitivity of the MRI scan.¹¹ Because of the above-mentioned reasons, MRI scan on its own doesn't seem to be satisfactorily effective. This condition comes up with a need for sensitive tests which can be used in diagnosis and follow-up. A meta-analysis of the studies in various bacterial infections showed that PCT level was more sensitive than CRP.⁶ Another study

reported that blood culture positivity was correlated with PCT level and accordingly, PCT test might lessen the need for blood culture.⁷ However, as far as we know, while there have been two studies in children with osteomyelitis,^{10,12} there is no study which is done in the adult patient population. In this study, we found for the first time that PCT test was an important diagnostic marker in adult patients with osteomyelitis. P was significant with a value of <0.001 as shown in Table 1. Although P value was significant with the other acute phase reactants (ESR, CRP, WBC), their levels might be affected by many infectious and non-infectious factors. Consequently, they cannot be the considered as the only indicators of an infection.¹³⁻¹⁸ On the contrary, it is reported that PCT on its own can be used in the differential diagnosis and follow-up of bacterial and non-bacterial inflammation.^{5, 6, 19} The level of increase in PCT concentration is correlated with the severity of inflammatory reaction.^{20,21} In infection, increasing PCT levels show bad prognosis while decreasing PCT levels show good prognosis. PCT shows a rapid kinetic process, it begins to rise two hours following the infection, reaching to its peak value in 12 to 24 hours. Following the termination of infection, PCT turns to its normal levels. The studies of bacterial infections other than osteomyelitis showed that PCT test can be used in infection follow-up and the therapy duration might be individualized with the PCT level.^{22,23} Furthermore, with the use of PCT test, a contribution to solving the antibiotic resistance problem might be realized by preventing inappropriate use of antibiotics.⁶ PCT test seems to be a good alternative for individualized the therapy duration in osteomyelitis with long or indefinite therapy duration. Therefore, there is a need for studies showing the significance of PCT test in osteomyelitis follow-up.

| Laboratory Value | Sensitivity (%) | Specificity (%) | Positive Predictive Value |
|--------------------------------|-----------------|-----------------|---------------------------|
| PCT =0,5 ng/mL | 100 | 56 | 100 |
| PCT =0,62 ng/mL | 73 | 100 | 73 |
| PCT =0,57 ng/mL | 87 | 86 | 87 |
| CRP =5 mg/dL | 70 | 86 | 77 |
| CRP =15 mg/dL | 53 | 100 | 47 |
| ESR =20,5 mm/h | 70 | 69 | 80 |
| ESR =39,5 mm/h | 43 | 100 | 53 |
| WBC =6945 ×10 ⁹ /L | 60 | 66 | 73 |
| WBC =8845 ×10 ⁹ /L | 30 | 100 | 17 |
| WBC =10560 ×10 ⁹ /L | 1 | 100 | 3 |

Table 2. Sensitivity, Specificity, and Positive Predictive Value of PCT, CRP, ESR, and WBC

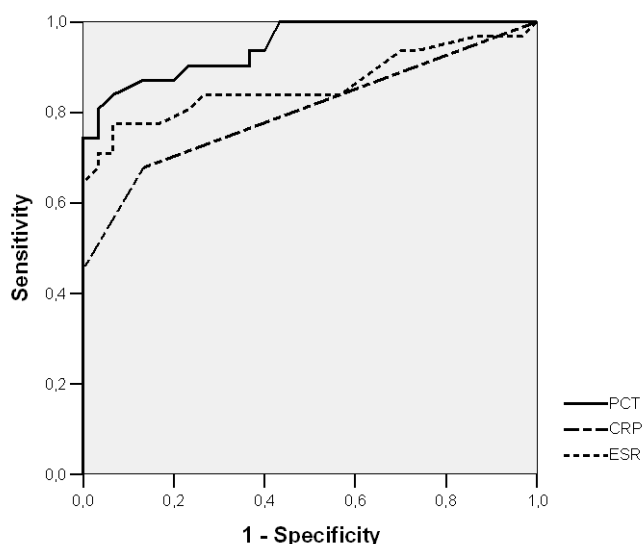


Figure 1. The receiver-operating characteristic (ROC) analysis curve for PCT, CRP and ESR in osteomyelitis

Physical examination showed positive signs in 26 (86,7%) patients while CRP was positive in 15 (50%) patients. However, PCT level was above normal (>0.5 ng/mL) in all of the patients (100%). Uncured osteomyelitis might cause disability and death while inappropriate antibiotic use might give rise to bacterial resistance and additional burden such as long therapy duration, patient incomppliance and long hospital stay. From this point of view, PCT test seems to be a promising method in diagnosing osteomyelitis.

Butbul-Aviel Y et al. reported that WBC, ESR, and CRP is not useful in differentiation between osteomyelitis and non-bacterial inflammatory conditions whereas PCT discriminates the two groups with success showing a specificity of 100% and sensitivity of 58,3%.⁸ As shown in Table 2, we reached to similar results in our study. When PCT and other acute phase reactants are compared, AUC seems to be more significant for PCT (figure 1).

Although Eberhard OK, et al. found a cutoff point for PCT value of 1 ng/mL as a sign for serious infection, Shin KC et al. have shown that PCT levels of 0.5 ng/mL or greater have a good specificity and a high positive predictive value for the differentiation between inflammation and bacterial infection.^{24, 25} In our study when we considered the PCT cut-off value as 0,57, we found that sensitivity was 87%, specificity was 86% and positive predictive value was 87%. We think that the suitable cut-off value for osteomyelitis is 0,57 ng/mL. Declining PCT level immediately after effective antibiotherapy, its sensitivity in the differentiation between non-bacterial and bacterial inflammation,^{19, 21} its high sensitivity,

specificity and positive predictive value, its cost-effectiveness, its being an easy to use test and providing immediate results make PCT level useful in the diagnosis of osteomyelitis. Faesch S et al., in their study with 18 osteomyelitis patients, reported that PCT test doesn't seem to be a good diagnostic test for osteomyelitis; however, studies with larger series are needed to be done for a decisive explanation.¹² Butbul-Aviel Y et al. in their study with 12 osteomyelitis patients reported that PCT test is a beneficial marker in the diagnosis of osteomyelitis.¹⁰ When we compared our study with the above-mentioned two, our study was conducted in a larger series and we found higher sensitivity, specificity, and positive predictive value.

The sensitivity, specificity and positive predictive value of PCT test for diagnosis of osteomyelitis are higher than other acute phase reactants. Therefore, PCT test can be used as a useful marker in diagnosis of osteomyelitis. Our work is the first study in adult patients with osteomyelitis and we hope it to be the initiator of larger series researches.

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