

Can procalcitonin be used for the diagnosis and follow-up of postoperative complications after fracture surgery?

Kırık cerrahisi sonrasında gelişen komplikasyonların tanı ve takibi için prokalsitonin kullanılabilir mi?

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Amaç: Bu çalışmada kırık cerrahisinin prokalsitonin düzeylerine etkisi ve prokalsitoninin kırık cerrahisinin yaratmış olduğu enflamatuvar reaksiyonla enfektif komplikasyonları ayırt etmedeki değeri araştırıldı.

Çalışma planı: Çalışmaya, pertrokanterik kalça kırığı nedeniyle tedavi edilen 21 hasta (8 kadın, 13 erkek; ort. yaş 72.5; dağılım 50-105) alındı. Hastalar, osteosentez ve parsiyel artroplastisi uygulananlar olmak üzere iki grupta incelendi. Ameliyat öncesinde ve ameliyattan sonra beş gün boyunca, prokalsitonin (PCT), C-reaktif protein (CRP), beyaz küre sayısı (WBC) ve ateş değerlerindeki değişimler incelendi.

Sonuçlar: Hiçbir hastada ameliyattan sonra yara enfeksiyonuna rastlanmadı. Yedi hastada komplikasyon gelişti. C-reaktif proteinin ameliyat öncesi değeri normalin yaklaşık beş katı idi; ameliyat sonrası ikinci günde pik yaparak azalmaya başladı, ancak beşinci günde ameliyat öncesi değerinin dört katı kadar yüksek bulundu. Ameliyat öncesinde PCT değeri tüm hastalarda normal sınırların altındaydı. Birinci günde pik yaptı; ancak, normal sınırları aşmadı; beşinci günde ameliyat öncesi değerlerine döndü. Komplikasyon gelişen grupta ortalama PCT değerleri normalin üzerinde bulunurken, CRP'nin tüm değerleri normalin üzerinde idi. Prokalsitonin için "cut-off" değeri ≥ 0.5 ng/ml alındığında, sistemik komplikasyonları belirlemede birinci günde %100 duyarlı ve %100 seçici, ikinci günde ise %100 duyarlı, %50 seçici bulundu.

Çıkarımlar: Prokalsitoninin kırık cerrahisi sonrası erken dönemde sistemik komplikasyonları saptamada kullanılabilir bir parametre olduğu sonucuna varıldı.

Anahtar sözcükler: Akut faz reaksiyonu/tanı; biyolojik belirteç/kan; C-reaktif protein/analiz; kalsitonin/kan; kalça kırığı/cerrahi; ameliyat sonrası komplikasyon/kan.

Objectives: We investigated the effect of fracture surgery on serum procalcitonin levels and the value of procalcitonin in differentiating inflammatory reaction caused by fracture surgery from postoperative infective complications.

Methods: Twenty-one patients (8 women, 13 men; mean age 72.5 years; range 50 to 105 years) who underwent surgery for pertrochanteric hip fractures were evaluated according to the procedures employed, namely osteosynthesis, and hemiarthroplasty. Procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WBC), and body temperature were measured before surgery and for five days postoperatively.

Results: No postoperative wound infections occurred. Seven patients developed complications. The mean preoperative CRP level was five times above the normal. It made a peak on the second day and then began to decrease, but still was four times higher than the preoperative level on the fifth day. Preoperatively, the mean PCT level was lower than the normal in all the patients. It made a peak on the first postoperative day without exceeding the normal range and returned to the preoperative level on the fifth day. In contrast to CRP levels which were above the normal in all the patients, PCT levels were higher than the normal only in patients who developed complications. Taking the cut-off value as ≥ 0.5 ng/ml, the sensitivity and specificity of PCT to determine systemic complications were 100% and 100% on the first day, and 100% and 50% on the second day, respectively.

Conclusion: Procalcitonin may prove to be a useful parameter to identify early postoperative systemic complications after fracture surgery.

Key words: Acute-phase reaction/diagnosis; biological markers/blood; C-reactive protein/analysis; calcitonin/blood; hip fractures/surgery; postoperative complications/blood.

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Procalcitonin is a glycopeptide consisting of 116 amino acids, and a precursor of the calcitonin hormone as well.^[1] Recently, it has become more interesting with its characteristics as a novel marker for infections, being not affected by specific bacterial infections, viral infections and SIRS (systemic inflammatory response syndrome) rather than with its prehormone characteristics.^[2]

The present study evaluated the effect of fracture surgery on the serum procalcitonin levels and the sensitivity and selectivity of procalcitonin in differentiating inflammatory reaction caused by fracture surgery from postoperative infective complications.

Patients and method

Twenty-one patients over 50 years of age (8 women, 13 men; mean age 72.5 years; range 50 to 105 years) who were treated in our clinic for pertrochanteric hip fractures between March 2004 and October 2004 were included in the study. The patients were divided into two groups depending on the surgical procedure applied; osteosynthesis and partial arthroplasty. The osteosynthesis group included 12 patients (8 women, 4 men; mean age 70 years; range 50 to 84 years) and, the partial prosthesis group consisted of nine patients (5 men, 4 women; mean age 75.8 years; range 53 to 105 years). Eleven patients (52.4%) had femoral neck fractures, and 10 (47.6%) had intertrochanteric fractures. The mean period to surgery was six days.

Any patient who was under 50 years old of age, and who had chronic organ failure, malignancy at terminal stage or pathological fractures, who received frequent blood transfusion, who had multiple trauma or fractures in multiple locations (due to triggering of the systemic inflammatory response), who underwent surgery within the last three months, and who had urinary, respiratory, and skin infections or chronic rheumatic disease (systemic lupus erythematosus, rheumatoid arthritis, Familial Mediterranean Fever, etc.) was excluded from the study. Patients who were over 50 years of age were selected because the surgical standardization is difficult due to diverse surgical treatment of hip fractures in patients who are under or over 50 years old, and the resistance to infection is reduced in advanced ages as well.

In the osteosynthesis group, the fracture fixation was achieved with a 135° angle Richards DHS (dynamic hip screw) plate in 11 patients, and with a second-generation intramedullary nail in one patient. In the partial prosthesis group, Thompson type of partial endoprosthesis was administered in eight patients, and bipolar type of partial endoprosthesis in one patient following the removal of femoral head. The prosthesis was fixed with bone cement CMV-1. Ten patients (47.6%) underwent spinal anaesthesia, and 11 patients (52.4%) had general anaesthesia. Eight patients (38.1%) required postoperative blood supply, and 13 patients (61.9%) received no blood transfusion.

In both groups, changes in procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WBC) and body temperature were assessed before the surgery and for five days following the surgery. Blood samples were collected at the same hour in the morning for each patient, and body temperature was measured four times a day at the same time of the day. Blood samples for procalcitonin and CRP tests were collected into dry tubes, and centrifuged at 4000 rpm for 10 minutes, and then the serums were separated.

Serum samples for C-reactive protein were processed by the Nephelometric Method (Dade Behring, BN II device, Germany) at the same day in the microbiology laboratory. During the analysis of blood samples, Sysmex XT 2000-i (Roche Diagnostics, Mannheim, Germany) was used for WBC. Serum samples for procalcitonin were stored at -20 °C until analysis. For procalcitonin assay, Kriptor (BRAHMS Diagnostica-Berlin, Germany) method was used.

For data analysis, SPSS 11.5 software was used. Non-parametric methods were employed, taking the sampling size into consideration; for frequency summary, median and 1st and 3rd quartile values, and for comparisons, Mann-Whitney U-test and Kruskal-Wallis variance analysis were used. Furthermore, Fischer's exact chi-square test was used for assessing the relation between categorical values. For evaluations, $p < 0.05$ was considered significant.

Results

None of the patients had postoperative wound infection. Seven patients developed septic or aseptic

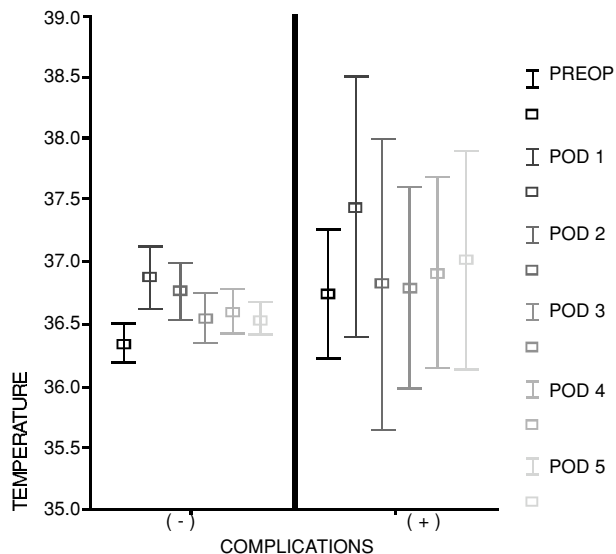


Figure 1. Change in body temperatures depending on the status of the complication.

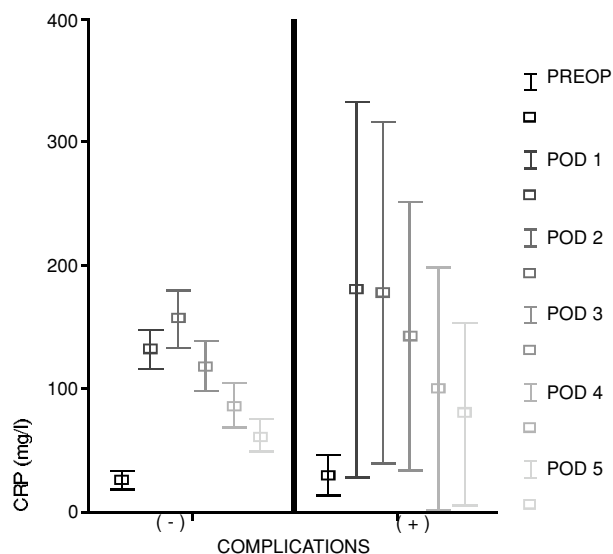


Figure 2. C-reactive protein values depending on the status of the complication.

complications, including decubite in three patients, upper respiratory infection (URI) plus decubite in one patient, URI in one patient, urinary tract infection in one patient, and bilateral pneumothorax in one patient.

A significant increase was found in fever in all of the patients at the postoperative day 1 compared to the preoperative levels ($p=0.001$; Figure 1).

The mean preoperative value for C-reactive protein was five times higher than the normal level (26.9 ± 13.8 mg/l). It made a peak at the postoperative day 2, and then showed a regularly decreasing

kinetic course. The CRP levels were still four times higher than the preoperative values at the postoperative day 5 (Figure 2).

No significant difference was observed between the osteosynthesis and partial arthroplasty groups and between the groups with and without complications for CRP levels (Figures 2, 3).

White blood cell count was also increased following the surgery, similar to CRP; but, it had a wavy kinetic curve. The peak values were reached at the postoperative day 1 in the osteosynthesis group, and at the postoperative day 2 in the partial arthro-

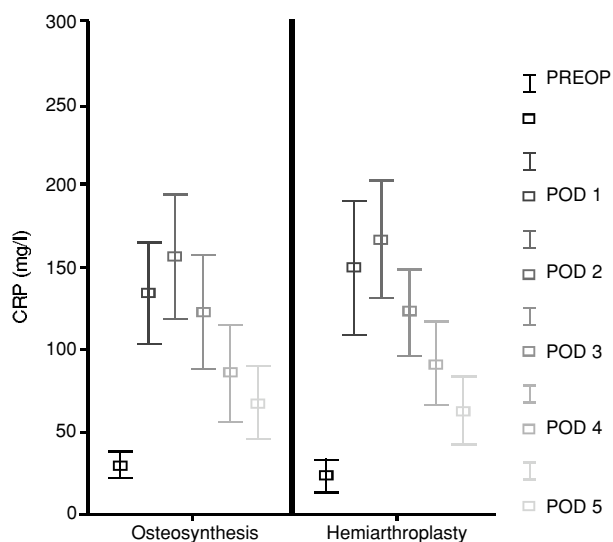


Figure 3. The kinetics of C-reactive protein (CRP) in the two surgical procedures applied.

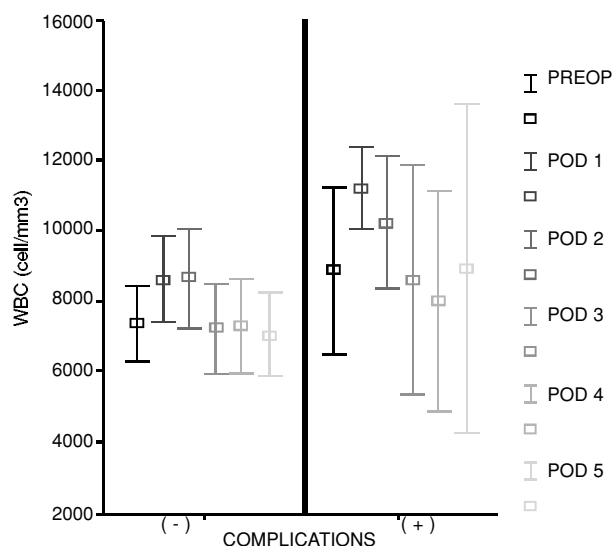


Figure 4. Change in the white blood cell (WBC) count depending on the status of the complication.

plasty group. It was within the normal limits in patients without postoperative complications while pathologic WBC values were observed in patients who developed complication (Figure 4).

All preoperative procalcitonin values were under the normal limits (mean 0.088 ± 0.078 ng/ml). It made a peak at the postoperative day 1, but remained within the normal limits. Unlike C-reactive protein, PCT returned to preoperative values at the postoperative day 5. The PCT values were not significantly different in patients with decubite ulcers (local wound complication) whereas they were significantly higher in patients with systemic complications ($p=0.000$; Figure 5).

No significant difference was found between the two treatment groups for PCT values (Figure 6).

When the cut-off value was taken as ≥ 0.5 ng/ml, the sensitivity and specificity of PCT to determine systemic complications were 100% and 100% at the postoperative day 1, and 100% and 50% at the postoperative day 2, respectively. Gender, type of fracture, surgical procedure, type of anesthesia, blood transfusion and time to surgery had no effect on the preoperative and postoperative PCT, CRP and WBC values.

Discussion

While it differs from center to center, the infection rate following the endoprosthesis surgery has been reported to be around 1 to 5 % at present.^[3]

Although it seems to be a lower rate, it is, in fact, very important because of its potential resistance to treatment, recurrence, interference with the surgical intervention, heavy economic burden, and death. Early diagnosis of infections and introduction of an appropriate treatment following the orthopedic surgery is critical in the prognosis and prevention of potential economic burden.

At present, there are many laboratory parameters used in the early diagnosis of infections. However, parameters like WBC, erythrocyte sedimentation rate (ESR) and CRP, which are mostly preferred for orthopedics and fracture surgery are not specific to the infection factors. Furthermore, both the fracture itself and the inflammatory reaction caused by the surgery have serious impacts on these parameters.^[4-6]

Based on this, we evaluated if procalcitonin, which has been widely used in recent years, particularly having high selectivity for bacterial infections, can be used in determining the infective complications following the fracture surgery. No previous clinical study was found in the literature related to it.

The objective of our study was to obtain the answers to the following five basic questions: (i) Is procalcitonin affected from the fracture and surgical trauma? (ii) If so, how can be normal values distinguished from the values related with the surgical trauma? (iii) What is the kinetics of PCT when a postoperative complication develops? (iv) Can procalcitonin assist in the diagnosis of a developing

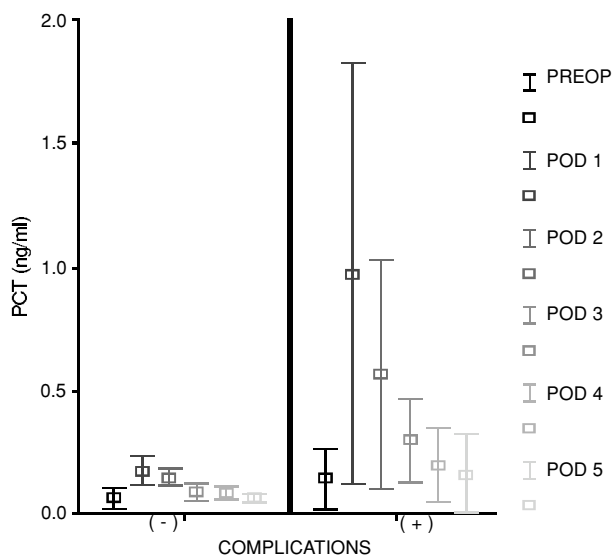


Figure 5. The kinetics of procalcitonin (PCT) depending on the status of the complication.

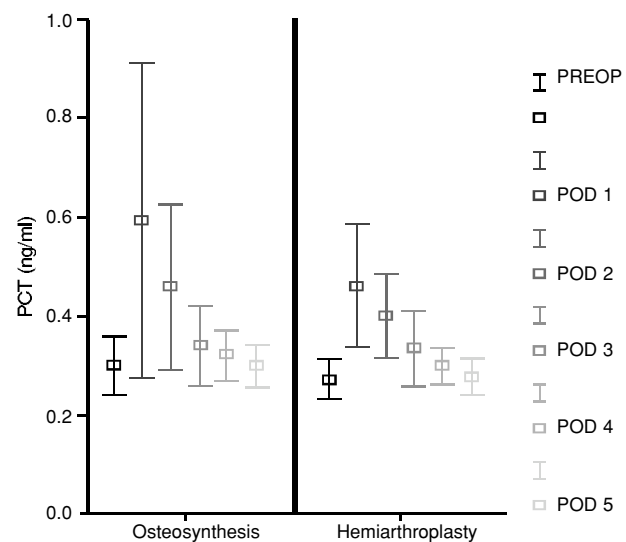


Figure 6. The kinetics of procalcitonin (PCT) in the two surgical procedures applied.

complication? (v) Does procalcitonin have any superiority to the other markers of infection?

The main problem was the procalcitonin itself at the beginning of the study. As already known, procalcitonin is the prohormone of calcitonin, which is one of the major hormones in the balance of bone formation/resorption. Animal experiments have shown that calcitonin was increased after the fracture and remained at higher levels nearly for a period of three weeks.^[7] Therefore, if calcitonin is increased after the fracture, then should the procalcitonin. Although it has been reported that the increased PCT is independent of the calcitonin during the infections,^[8] no clinical study is available on whether the PCT levels are increased or not after the fracture.

The mean preoperative PCT levels for 21 patients who participated in the study were 0.088 ± 0.078 ng/ml. All values were under the normal limit (0.5 ng/ml), which indicates that procalcitonin, like in the infection, also acts independent of the calcitonin after the fracture. The inflammatory reaction resulting from the fracture leads to a slight increase in PCT levels; but it is still within the normal limits.

Of the other parameters, the mean preoperative value for CRP was 26.9 ± 13.8 mg/l. Scherer et al.^[6] also found higher preoperative CRP values (11 mg/l). The systemic inflammatory reaction resulting from the fracture has an impact on the CRP, leading it to exceed the normal limits. Monitoring of the postoperative kinetics of the C-reactive protein showed that the peak was reached at the postoperative day 2 for majority of the cases (mean 161.6 ± 53.9 mg/l; Figure 2), which is also similar to previous studies. Kock-Jensen et al.^[9] reported that CRP increased rapidly following the surgery and made a peak at day 2 in 50 patients who underwent lumbar disc surgery. Yoon et al.^[10] indicated that peak CRP levels were reached at days 2 – 3 following the surgery in the long bone fractures. Similarly, Scherer et al.^[6] suggested that peak CRP levels were reached at the postoperative day 2, and they were affected by the region of the trauma. For example, the peak CRP value was 154 mg/l in femoral fractures while it was 35 mg/l in the ankle fractures.^[6] Milcan et al.^[11] indicated that the surgical technique administered has also an impact on the CRP levels. In a study of 51 patients, where some patients were

treated with soft tissue surgery, some with open reduction and internal fixation (ORIF), and some with amputation, peak CRP levels were reached at the postoperative day 2 in the groups who underwent soft tissue surgery and ORIF, and at the postoperative day 4 in the amputation group. In our study, patients underwent two diverse surgical procedures; partial endoprosthesis and osteosynthesis. No difference was found between the two groups regarding the kinetics of CRP and PCT (Figures 3, 6).

Based on our findings and previous studies, it seems that unlike PCT, CRP is affected by the trauma from the surgery to a greater extent, and it rises up to 30 times than its normal level regardless of the infection. At the same time, CRP response to inflammatory reaction is slower than procalcitonin.

Another parameter assessed in the present study was WBC. Unlike procalcitonin, WBC didn't have a standard kinetic course following the surgery. Peak levels were reached at the postoperative day 2 in the partial arthroplasty group and at the postoperative day 1 in the osteosynthesis group. However, unlike CRP, the mean peak levels of WBC were within the normal limits (mean 9139.5 ± 2371.5) similar to PCT. The white blood cell count provided differential responses to diverse surgical procedures in the same region. It had a tendency to decline after reaching the peak level, but with a wavy course (Figure 4).

Procalcitonin showed an immediate decline after reaching the peak level, and returned to preoperative levels at the postoperative day 5. No difference was found between the two surgical groups for PCT (Figure 6), which is similar to the results obtained in previous studies. Meisner,^[2] similarly, reported that PCT returned to normal preoperative levels at day 5 following minor surgeries. Aouifi et al.^[12] studied the effect of cardiopulmonary bypass on the serum PCT and CRP concentrations, and found out that PCT levels were neutralized at day 5 after the cardiopulmonary bypass. Baykut et al.^[13] reported that PCT levels were reduced to normal levels at the postoperative day 6 in patients without any complications following the cardiac surgery. Reith et al.^[14] showed that in 70 patients who were treated with colon or aortic surgery, PCT levels returned to normal values at the postoperative day 5 in the groups without complication for both surgical procedures.

These findings indicate that PCT returns to its normal level after removal of the factor leading to the inflammatory response in the absence of other stimulants. In our study, CRP had an immediate tendency to decline after reaching to the peak level. No significant difference was found between the two surgical groups in terms of immediate tendency to decline. Although the levels at postoperative day 5 were significantly lower than the peak levels, it appears that it was 13 times higher than the normal levels in the average (66.2 ± 31.6 mg/l; Figure 3). With a longer follow-up period on this subject, Larsson et al.^[5] reported that CRP was reduced to normal levels at day 21 in non-complicated patients following the elective orthopedic surgical interventions.

None of our patients had surgical wound infection, and seven patients developed septic or aseptic complications. In patients who developed complications, PCT had a kinetic course similar to the ones without any complications. After reaching to the peak level at the postoperative day 1, an immediate decline was observed, returning to normal levels at day 5. However, it seems that PCT levels were above the normal levels in patients with complications (Figure 5). While PCT levels were normal in patients with decubite, they were above the normal levels in four patients with systemic complications at the postoperative day 1. The difference between the non-complicated patients and the patients with systemic complications in terms of PCT levels at the postoperative day 1 was statistically significant ($p=0.0000$).

When the cut-off value of procalcitonin was taken as 0.5 ng/ml, the sensitivity and specificity of PCT to determine systemic complications were 100% and 100% respectively at the postoperative day 1 while the sensitivity and specificity were 100% and 50%, respectively at the postoperative day 2. Staehler et al.^[15] reported that the sensitivity and specificity of PCT to determine infections at the postoperative period in patients who were treated with heart transplantation were 77%, and 100%, respectively. Murray et al.^[16] found that the sensitivity and specificity of PCT to determine acute respiratory insufficiency in patients who underwent heart surgery with extracorporeal circulation were 100% and 100%, respectively; while the sensitivity and specificity of CRP were found 44% and 13%,

respectively in the same study. Eberhard et al.^[17] found that in 57 patients who underwent renal transplantation, the sensitivity and specificity of PCT to distinguish acute transplant rejection and post-transplant bacterial infection were 70% and 87%, respectively when the cut-off value was taken as 0.5 ng/ml; and the sensitivity and specificity of CRP were 43% and 100%, respectively when the cut-off value was taken as 5 ng/ml.

In our study, CRP levels were above the normal values in all patients with and without complications ($CRP \leq 5$ mg/L). Therefore, no statistical analysis was performed for sensitivity and specificity. The same problem was also addressed by Scherer et al.^[6] They defined a best cut-off value for CRP as it was severely affected by the inflammatory reaction resulting from the surgery. So, they stated that deep wound infection may develop in patients with a CRP level over 140 mg/l at the postoperative day 2. In our study, the CRP levels were over 140 mg/l in three patients with complications, and in five patients without complications after the postoperative day 2.

Meisner^[2] indicated that any patient with a PCT level above 1 ng/ml following the septic and minor surgeries must be carefully monitored; on the other hand, PCT levels above 10 ng/ml in patients without any complications following the abdominal surgery must be examined for complications such as postoperative infections and anastomosis failure as such levels are very rare. Reith et al.^[14] reported that patients with a PCT level over 1.5 ng/ml at the postoperative days 1 and 2 are likely to develop complications. Staehler et al.^[15] suggested that a PCT level over 10 ng/ml following the heart transplantation indicates a systemic infection, and a PCT level smaller than 10 ng/ml is an indication of a moderate infection. Aouifi et al.^[12] proposed that a PCT level above 5 ng/ml following the cardiopulmonary bypass surgery is an indication of the postoperative complication.

Our findings support the findings in the literature. The PCT levels were above 0.5 ng/ml in all of the patients with systemic complications. Based on our study and previous studies, it can be suggested that PCT follows a differential kinetics in diverse surgical procedures and it has different peak levels, which should lead the non-aseptic surgical branches to adopt a standard best cut-off value for themselves.

It has been also indicated that PCT levels, even though rarely, can rise over the normal values following the aseptic and minor surgeries.^[2] Orthopedic surgery is an aseptic surgery as well. In our study, PCT levels were under the normal limits in all of the patients without complications. However, a best cut-off value is required in order to foresee on what PCT levels the infective complications may develop. No best cut-off value was defined for PCT levels following the fracture surgery. In our study, no best cut-off value was calculated for fracture surgery as the number of patients was very limited. Yet, any patient with a PCT level over 0.5 ng/ml at the postoperative days 1 and 2 must be carefully monitored.

The present study was carried out on a limited type of fracture of orthopedic surgery with a limited number of patients due to economical restrictions. Therefore, our results may be insufficient in terms of both statistical data and scope of the orthopedic surgery. However, it is a basic study as it evaluates what kind of a kinetics PCT has, as an innovative infection parameter, following the fracture surgery, and its superiority to the other parameters employed routinely.

In conclusion, procalcitonin is much superior to other infection parameters based on the fact that it is not affected by the inflammatory response resulting from the surgery; it provides a faster response to the orthopedic surgical trauma compared to other parameters routinely used; it declines more rapidly after removal of the factor leading to the inflammatory response (day 5 for PCT, day 21 for CRP and day 43 for ESR); it follows a standard postoperative kinetics; and it has a 100% sensitivity and 100% specificity in determining the systemic complications at the postoperative day 1. We believe that results of any future studies including larger number of patients and diverse types of fractures would make PCT a serious and reliable parameter in determination and follow-up of the systemic complications following the orthopedic surgery.

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