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Assessment of procalcitonin and other inflammatory markers in peritoneal dialysis-related peritonitis*

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Aim: It is demonstrated that in end-stage renal failure without an infectious pathology conventional laboratory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) or other acute-phase proteins increase non-specifically. We aimed to evaluate procalcitonin (PCT) and other inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in patients with continuous ambulatory peritoneal dialysis (CAPD)-related peritonitis.

Materials and methods: A case-control study was conducted in a 600-bed tertiary hospital. Fifty patients with CAPD-related peritonitis constituting the study group and 50 CAPD patients without infection as the control group were included in the study between February 2006 and July 2006. Baseline serum WBC count, PCT, ESR, and CRP levels were determined in all patients.

Results: Fifty-six peritonitis episodes were detected in 50 patients. The mean ESR and CRP levels were significantly higher in the study group ($P < 0.001$). PCT levels were >0.5 ng/mL in 21 of the 50 patients (42%) in the study group and 8 of the 50 patients (16%) in the control group. The positive predictive value was 100% for CRP levels higher than 5 mg/dL and PCT levels higher than 2 ng/mL. The sensitivities were calculated as 40% and 14% by the same cut-off levels for CRP and PCT, respectively.

Conclusion: Serum CRP level is a significant and valuable parameter for detecting inflammation, and determining a new cut-off point for CRP will increase its usefulness in patients with CAPD-related peritonitis. The sensitivity and specificity of PCT were not superior to CRP in peritoneal dialysis-related peritonitis.

Key words: Procalcitonin, C-reactive protein, peritonitis, inflammation markers

Peritoneal diyalizle ilişkili peritonitte prokalsitonin ve diğer inflamatuar parametrelerin değerlendirilmesi

Amaç: Kronik böbrek yetmezliği (KBY) tanılı hastalarda herhangi bir infeksiyöz patoloji olmadan da eritrosit sedimentasyon hızı, C-reaktif protein ve diğer akut faz proteinleri gibi sık kullanılan inflamatuar parametrelerde artış olduğu bildirilmiştir. Bu çalışmada peritoneal diyaliz ilişkili peritonit tanılı hastalarda prokalsitonin ile C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı (ESR) gibi diğer inflamatuar parametrelerin durumu incelendi.

Yöntem ve gereç: Çalışma 600 yataklı bir eğitim ve araştırma hastanesinde yapıldı. Şubat 2006 ile Temmuz 2006 tarihleri arasında süreli ayaktan periton diyalizi ile ilişkili peritonit tanısı alan 50 hasta çalışma grubu, sürekli ayaktan periton diyalizi uygulanan ve herhangi bir infeksiyon belirti ve bulgusu olmayan 50 olgu kontrol grubu olarak alındı. Tüm hastalarda serum beyaz küre sayısı, prokalsitonin, ESR ve CRP düzeyleri çalışıldı.

Bulgular: Çalışma grubundaki 50 hastada 56 peritonit atağı tespit edildi. Çalışma grubunda yer alan hastaların ortalama ESR ve CRP düzeyleri kontrol grubuna göre yüksek bulundu ($P < 0,001$). PKT düzeyi çalışma grubundaki 50 hastanın 21'inde (% 42), kontrol grubundaki 50 hastanın 8'inde (% 16) 0,5 ng/mL'nin üzerinde bulundu. Peritonitli hastalarda 5

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mg/dL'den daha yüksek CRP ve 2 ng/mL'den daha yüksek PKT düzeylerinin her ikisi için pozitif prediktif değerler % 100 olarak saptandı. CRP ve PKT'nin aynı cut-off değerleri için duyarlılıkları % 40 ve % 14 olarak bulundu.

Sonuç: CRP inflamasyonun tespitinde önemli ve yararlı bir parametredir. Peritoneal diyaliz uygulanan hastalarda CRP için 5 mg/dL değerinin cut-off olarak alınması, sürekli ayaktan periton diyalizine bağlı peritonitte bu parametrenin yararına katkı sağlayacaktır. Periton diyalizi hastalarında prokalsitoninin sensivite ve spesifitesinin CRP'ye bir üstünlüğü yoktur.

Anahtar sözcükler: Prokalsitonin, C-reaktif protein, peritonit, inflamasyon belirleyicileri

Introduction

It is demonstrated that in end-stage renal failure without an infectious pathology conventional laboratory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) or other acute-phase proteins increase non-specifically (1-3). Procalcitonin (PCT), a polypeptide of 116 aminoacids (MW 13 kDa), is the precursor of calcitonin (4,5). It has been recently investigated as a new alternative inflammatory parameter to distinguish infections and other inflammatory events in a number of studies. High serum levels of PCT have been demonstrated in sepsis, bacterial, and fungal infections (5,6). The literature reveals only a few studies evaluating PCT in peritoneal dialysis (PD) and PD-related peritonitis (7-10).

The present study aimed to determine the diagnostic value of PCT and other conventional inflammatory markers and whether PCT is related to CRP, ESR, and white blood cell (WBC) count in patients with continuous ambulatory peritoneal dialysis (CAPD)-related peritonitis.

Materials and methods

Setting and Design

A case-control study was conducted in the Infectious Diseases and Clinical Microbiology Department and PD Unit of Nephrology Department of the 600-bed Ankara Training and Research Hospital between February 2006 and July 2006.

Patients

Fifty patients with CAPD-related peritonitis treated in the Infectious Diseases and Clinical Microbiology Clinic were included in the study as the study group. During the study period 50 consecutive patients who were followed-up in the PD Unit of the Nephrology Department were included in the study as the control group. The exclusion criteria consisted of history of any infection in previous 4 weeks, immunosuppressive therapy, steroid use, and clinical, radiological, or microbiological evidence of any infection.

All patients had a standard Tenckhoff catheter and double bag connecting system. Peritoneal dialysis fluid was lactate-based dialysate with glucose concentrations ranging from 1.5 to 4.25 g/L. The patients performed 4 exchanges per day with 2 L.

Diagnosis of Peritonitis

Peritonitis was defined as the development of cloudy peritoneal dialysis with or without abdominal pain, fever, vomiting, or nausea and WBC count being higher than 100 WBC/mm^3 with more than 50% polymorphonuclear leukocytes, the presence of microorganism in Gram staining and/or positive culture (11).

Clinical and Microbiological Data

Age, gender, and duration of CAPD were recorded in both groups. The symptoms, physical examination findings, WBC counts, microscopy and culture results of peritoneal dialysates, and antibiotic sensitivity results of isolated microorganisms were recorded in patients with peritonitis. After peritoneal dialysate was obtained for microbiological investigation, intraperitoneal cefazolin and gentamicin were administered empirically. Treatment was modified according to the culture results. The patients were followed-up until the end of treatment.

Investigated Laboratory Parameters

ESR

The Westerngren method was used for ESR measurement and levels greater than 15 mm/h was regarded as high.

CRP

CRP was measured by the nephelometric assay (Beckman Coulter IMMAGE, Berkman, Marburg, Germany). The normal range was defined as 0.0-0.8 mg/dL.

PCT

PCT was measured using the Brahms PCT-Q rapid card test (Brahms, Henningsdorf, Germany). The results were given in 4 groups as follows: (1) lower than 0.5 ng/mL, (2) between 0.5 and 2 ng/mL, (3) between 2 and 10 ng/mL, and (4) higher than 10 mg/dL.

In the study group, CRP, ESR, PCT, and other laboratory parameters were assessed on the first day of peritonitis and the 14th day of treatment. CRP levels were also determined on the 2nd day of treatment.

Statistical analysis

All statistical analyses were performed using SPSS for Windows 13.0. All data were expressed as mean ± SD for normal distribution and median or range values were used for skewed data. Chi-square or Fisher's exact test was used in univariate analysis. Spearman's correlation coefficient was used for correlations.

The study was conducted in accordance with the ethical approval regulations of the hospital.

Results

Fifty patients (35 male, 15 female) with peritonitis were included in the study. During the study period, 56 peritonitis episodes were detected in 50 patients. Fifty CAPD patients without peritonitis were included in the study as the control group. Mean age of the patients in the study group was 49.0 ± 16.9 years and mean age of the patients of the control group was 44.8 ± 14.4 years. The demographic characteristics were not significantly different between the study and control groups (Table 1). The causative microorganisms are shown in Table 2. During follow-up, 2 patients died and in 3 of the 6 patients who developed a second peritonitis episode the treatment was switched to hemodialysis.

ESR

ESR levels were elevated in 47 of the 50 patients in the study group (94%) and 44 of the 50 patients in the control group (92%). ESR values ranged between 6 and 132 mm/h in the study group and between 6 and 120 mm/h in the control group. The mean ESR value was significantly higher in patients with peritonitis, when compared with the control group ($P < 0.01$) (Table 1). On the 1st day of peritonitis and on the 14th day of peritonitis, mean ESR values were 61.5 ± 29.1 and 57.6 ± 27.1 mm/h, respectively. The change in ESR values was statistically significant ($P = 0.013$).

CRP

CRP levels were elevated in 88% of the study group (44/50) and 26% of the control group (13/50). The highest CRP levels detected were 41.5 mg/dL in the study group and 4.9 mg/dL in the control group. The median CRP level was significantly higher in the patient group, when compared with the control group ($P < 0.001$) (Table 1). Mean CRP level decreased from

Table 1. Some demographic characteristics and laboratory parameters of the study and control groups on the day of admission.

Demographic characteristic/ laboratory parameter (n)	Study group n (%)	Control group n (%)	P
Age	49.0 ± 16.9	44.8±14.4	0.188
Gender (F/M)	15 (30)/ 35 (70)	25 (50)/ 25 (50)	0.06
Duration of renal failure (median, months)	24 (3-180)	33 (3-240)	0.196
Duration of CAPD (months)	20 ± 18	22 ± 17	0.632
Serum WBC $10^3/mm^3$	10.1 (3.8-24.5)	9.2 (4.7-23)	0.306
ESR mm/h	61.5 ± 29.1	46.1 ± 25.3	< 0.01
CRP mg/dL*	3.1 (0.27-41.5)	0.51 (0.1-4.9)	< 0.001

*median

Table 2. The causative microorganisms in the peritonitis episode.

Microorganism	Number	%
CNS[1]	23	39.6
S. aureus	4	6.9
E. coli	4	6.9
Klebsiella spp.	3	5.2
Pseudomanas spp.	3	5.2
Enterococcus spp.	3	5.2
Streptococcus spp.	1	1.7
C. albicans	1	1.7
Difteroid spp.	1	1.7
Culture negative	15	25.9
Total	58	100.0

[1]CNS: coagulase-negative *staphylococcus*

7.0 mg/dL on the 1st day of peritonitis to 5.7 mg/dL on the 2nd day of treatment. The change in CRP levels during treatment was statistically significant ($P < 0.05$). The mean CRP level decreased to 2.6 mg/dL on the 14th day of therapy ($P < 0.01$). CRP levels of patients who had normal CRP levels on the 1st day of peritonitis did not increase during follow-up. These patients were older, with lower ESR and normal PCT levels.

PCT

Plasma PCT levels were elevated in 42% of patients in the study group (21/50) and 16% of patients in the control group (8/50). PCT levels of 8 patients in the control group were lower than 2 ng/mL. When the cut-off level was taken as 0.5 ng/mL, PCT levels were elevated in 22 of 56 (39.3%) episodes: ≥0.5 - <2 ng/mL in 14 episodes, ≥2 - <10 ng/mL in 4 episodes, and ≥10 ng/mL in 4 episodes. PCT levels were found as <0.5 ng/mL in 13 episodes (60%) and as ≥0.5 -<2 ng/mL in 9 episodes on the 14th day of therapy (Table 3).

To evaluate the diagnostic values of CRP, ESR, and WBC, ROC plot analysis was performed (Figure). In the plots for ESR and CRP, the area under the curve was significantly associated with a diagnosis of peritonitis (Table 4).

The predictive values of inflammatory markers in the diagnosis of peritonitis were calculated according to the following criteria: 11.000/mm^3 for WBC, 15 mm/h for ESR, 0.8 mg/dL for CRP, and >2 ng/mL and >0.5 ng/mL for PCT. Cut-off values of WBC, ESR, and CRP were also calculated by ROC curves prepared for diagnosing peritonitis. These values were calculated as 11.800/mm^3 for WBC, 72 mm/h for ESR, and >4.915 mg/dL for CRP. The predictive values of inflammatory markers in the diagnosis of peritonitis were calculated by these values**.** The positive predictive value was found as 100% for both CRP, being higher than 5 mg/dL and PCT being higher than 2 ng/mL. The sensitivities were calculated as 40% and 14% by the same cut-off levels for CRP and PCT, respectively (Table 5).

The evaluation of the correlation between inflammatory parameters revealed that PCT was positively correlated with CRP, peripheral WBC count, and peritoneal fluid WBC count ($P < 0.05$). CRP was positively correlated with ESR ($r = 0.200$, $P < 0.05$) and peripheral WBC count ($r = 0.293$, $P < 0.01$) in addition to PCT ($r = 0.4472$, $P < 0.001$)**.**

Discussion

Peritonitis is one of the major complications of CAPD and it increases the morbidity and mortality

Table 3. PCT levels of patients in both groups.

PCT	Control group	Study group day 0	Study group on the 14th day of treatment
<0.5 ng/mL	42	34	47
≥0.5 and <2 ng/mL	8	14	9
≥2 and <10 ng/mL		4	
≥10 ng/mL		4	
Total	50	56	56

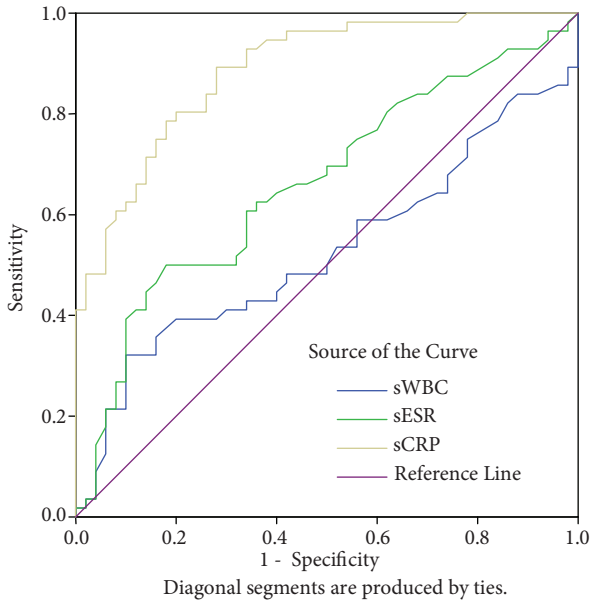

Figure. ROC curve.

Table 4. Area under the curve for WBC, ESR, and CRP.

Variable	AUROC	95% CI	P
WBC	0.526	0.414-0.638	0.644
ESR	0.662	0.558-0.766	< 0.01
CRP	0.887	0.827-0.948	< 0.001

Table 5. Sensitivity, specificity, positive and negative predictive values for WBC, ESR, CRP, and PCT.

Variable (cut-off)	Sensitivity	Specificity	PPV	NPV
WBC > 11800*	28	90	73.7	55.6
ESR >15	94	8	50.5	57.1
ESR > 72*	40	90	80	60
CRP >0.8	90	11.9	77.6	74
CRP > 5*	40	100	100	62.5
PCT > 2	14	100	100	53.8
PCT > 0.5	42	84	72	59.2

*Cut-off values according to the ROC curves.

rates in this patient group (12-15). Multiple peritonitis episodes can put an end to the CAPD program and more dependent treatment modalities like hemodialysis may be required (16-18). Thus, early diagnosis and treatment of peritonitis episodes are of critical importance. Conventional laboratory markers like white cell count, ESR, and CRP are usually affected by the underlying disease, uremia, and renal replacement therapy (3,19). In patients with end stage renal disease (ESRD), an ideal biochemical marker, which is going to be used for the early diagnosis of bacterial infection, should discriminate infection from other inflammatory events, should give some idea about the severity of infection, and should not be affected by the severity of renal failure and renal replacement treatments (20). This is why the value of procalcitonin (PCT), which was first identified by Assicot in 1993, is still under investigation in terms of diagnosing the infections seen in patients with ESRD (5). Most of these studies are performed on patients undergoing hemodialysis (HD) treatment (8,21,22). The literature reveals that in patients undergoing peritoneal dialysis (PD) and diagnosed with CAPD-related peritonitis only a few studies have investigated PCT (7-10).

As seen in HD patients, PD patients can also have high procalcitonin levels without an associating infectious pathology. In relevant studies, mean PCT levels of PD patients are reported to be higher than those in both healthy controls and patients not undergoing PD despite renal failure (7,10,23). However, only one of these studies reported the proportion of patients with high PCT levels, and other authors preferred to present their results in the form of mean PCT comparisons (7). In the above-mentioned study performed by Guz et al., 5.8% of PD patients had PCT levels higher than 0.5 ng/mL, being as high as 1.6 times the upper normal limit (7). This rate is higher in the present study, in which 16% of patients in the control group had PCT levels in the 0.5-2 ng/mL interval. In the study by Guz et al., it was reported that 44 patients out of 51 were undergoing CAPD treatment and other patients were undergoing automatized PD treatment, but the group in which these 3 patients with high PCT levels were included was not specified (7). In the present study all patients were undergoing CAPD treatment. In patients undergoing automatized PD and CAPD therapies, as data in the literature about baseline PCT levels are insufficient, we think that further investigations on

this subject are required. In the present study, the kit used for PCT measurements (Brahms PCT-Q rapid card test, Brahms, Henningsdorf, Germany) is different from the kit used in the study by Guz et al. (LUMItest PCT kit, B.R.A.H.M.S. Diagnostica, Germany) and the effect of this difference could be clarified with a study using different kits performed in the same patient group. One study found that PCT levels of PD patients were significantly high, when compared with HD patients and ESRD patients who were not undergoing renal replacement therapy, and thus it was suggested that PCT can be used in patients with renal failure but with exception of patients on CAPD (23). The reason for the increase in PCT levels of PD patients without signs of infection is explained by some hypotheses. These include the stimulation of PCT release depending on an inflammatory activity triggered by uremia or dialysis itself; renal failure leading to a decrease in PCT excretion and retention; and intra-abdominal fluid volume and/or dialysis catheter, which can lead to chronic endotoxemia (10,23,24). In the literature, various results about the decrease in PCT excretion with regard to renal failure have been reported (20,23). In a study comparing PCT levels of patients who were at different stages of renal failure, there was no significant difference between patient groups, and the slight increase in PCT levels was suggested to be related to uremia and extracorporeal treatment (20). Another study stated that a majority of PCT was excreted from the liver (23).

The cut-off level of PCT in patients without uremia was 0.5 ng/mL, while a level of 1.5 ng/mL was suggested for patients undergoing programmed HD in a regular fashion (8,21,22). However, in the study by Guz et al., as only 5.8% of PD patients had PCT levels higher than 0.5 ng/mL, this value was suggested as a cut-off (7). As mentioned earlier, in the present study, 16% of patients with PCT levels higher than 0.5 ng/mL did not have any sign of infection.

In the present study 42% of patients diagnosed with peritonitis and 39.3% of peritonitis episodes had PCT levels higher than 0.5 ng/mL. In the study by Guz et al., 62% of peritonitis episodes had PCT levels higher than 0.5 ng/mL (7). The rate in the present study being this low can arise from different kits used or be related to different intrinsic patient factors.

In the present study, 58% of patients diagnosed with peritonitis had normal PCT levels. It is known that PCT levels rise in severe infections and sepsis, while staying under the 0.5 ng/mL limit in viral infections, local infections, allergic states, and autoimmune diseases (5,6,25,26). We think that the reason why PCT levels did not increase in all episodes is that the majority of peritonitis episodes remained localized infections.

It is known that in PD patients about 90% have high ESR and 25%-60% have high CRP levels (7,27,28). In ESRD patients, most factors like anemia, which are supposed to affect ESR, have no influence on CRP values; nevertheless, the increase in CRP levels can be under the influence of inflammation and tissue damage, as well as infection (29). In the present study, when the parameters of subjects in the control group were evaluated, it was revealed that 92% had high ESR and 26% had high CRP levels.

In the present study, high CRP levels (for the kit used, the upper limit of normal range is 0.8 mg/dL) had a sensitivity of 90% and a specificity of 11.9%, the latter being especially low, when compared with the specificity of PCT levels being higher than the 0.5 ng/mL limit (84%). ROC curves were prepared for calculating cut-off values and, according to them, in diagnosing peritonitis the sensitivity of CRP levels higher than 5 mg/dL and PCT levels higher than 0.5 ng/mL were more or less similar (40% versus 42%), while the specificity of CRP was higher than PCT (100% versus 84%). On the other hand, while PCT levels higher than the 2 ng/mL limit had a specificity of 100%, this threshold could only determine 14% of cases of peritonitis. We think that, although PCT levels > 0.5 ng/mL have a lower specificity, taking them into consideration would be more appropriate because of sensitivity. When the cut-off value was reestablished as 5 mg/dL for CRP according to the ROC curve, the sensitivity and specificity of PCT were not superior to those of CRP. However, in our comparisons, the cut-off value of the CRP kit was taken as 0.8 mg/dL according to its manufacturer and the threshold for ESR was taken as 15 mm/h, thus demonstrating that PCT, despite its low sensitivity, had quite a high specificity. Similar results were reported in the study by Guz et al. (7). In the present study, the specificity of cut-off levels calculated

according to the ROC curve were higher in terms of diagnosing peritonitis, when compared with the cut-off values formerly used for the same conventional inflammatory markers. It was emphasized that PCT is more valuable than CRP in the diagnosis of bacterial infection, while the latter is still an important inflammatory parameter in clinical practice (30). As increased CRP can be related to non-infectious reasons, we advocate that in the practical approach the clinic signs of the patient being taken into consideration together with CRP and PCT would be more appropriate. A limitation of the present study was PCT measurements not being studied by the quantitative method. Thus, during calculations of PCT sensitivity and specificity, only > 0.5 and >2 ng/mL values were used as cut-off limits.

It was also suggested that, as half-life of CRP is longer, PCT could be more valuable in reflecting the treatment response, and thus should be followed-up on a daily basis (30-33). In the present study, levels of all parameters (ESR, CRP, and PCT) decreased significantly at the end of treatment. However, as PCT was not studied on a daily basis, no information could be provided with regard to its more rapid decrease when compared with CRP and ESR.

The evaluation of correlations between inflammatory parameters revealed that PCT was positively correlated with CRP, peripheral WBC count, and peritoneal fluid WBC count.

The present study investigated the diagnostic and prognostic value of an encouraging inflammatory parameter, namely PCT, in patients diagnosed with CAPD-related peritonitis. When the cut-off value of CRP was reestablished by ROC curves, it was observed that the sensitivity and specificity of PCT were not superior to CRP in terms of diagnosing peritonitis. However, we think that confirmation of this finding with further studies is necessary.

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