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CLINICAL INVESTIGATION

Plasma Procalcitonin Levels in Chronic Haemodialysis Patients

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Abstract: The objective of our study was to assess procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations in end-stage renal disease (ESRD) patients undergoing haemodialysis sessions and the effect of intermittent haemodialysis on PCT levels. We measured plasma PCT and CRP levels in 43 ESRD patients without evidence of systemic infection at the beginning of haemodialysis and 4 hours later. Control group consisted of 40 volunteers with no complaints. Venous blood samples were collected from the patient before and after hemodialysis and the control groups. PCT was assayed by immunoluminometry. The mean plasma concentration of PCT (2.13 ± 0.7 ng/mL) and CRP (14.3 ± 2.9 mg/L) was elevated prior to the start of the patients hemodialysis compared to healthy controls (PCT; 0.18 ± 0.03 ng/mL, CRP; 4.5 ± 2.2 mg/L) ($P < 0.0001$). After 4 h of haemodialysis, the levels of PCT decreased significantly ($P > 0.05$). In addition, a weak correlation between PCT and CRP before dialysis was established. It was found that PCT levels significantly increased in haemodialysis patients without signs of infection. This confirms the presence of a chronic systemic inflammatory state in these patients. Although haemodialysis was associated with a significant decrease of serum PCT, haemodialysis had no significant effect on CRP levels.

Key Words: Procalcitonin, haemodialysis, C-reactive protein

Introduction

Systemic bacterial infections are a major clinical problem in patients with end-stage renal disease (ESRD) (1). The conventional laboratory variables such as white blood cell count and erythrocyte sedimentation rate (ESR) levels are often affected by the uremia or by the haemodialysis process (2). A specific marker of bacterial infection in renal patients should distinguish infection from noninfectious inflammatory disorders.

Procalcitonin (PCT), the main precursor of calcitonin hormone, is a polypeptide with 116 aminoacids. For the first time in 1993, it was found to increase significantly in serum in serious bacterial infections such as sepsis. Later many researchers observed that PCT levels increase in patients with trauma, burns and neutropenia as well as infections such as meningitis, pneumonia (3,4). The researches indicate that PCT can be an indicator of immune activation and used in the future as a mediator to monitor the continuity of this activation. However, it is emphasized that in order for it to be accepted as a potential tool for diagnosis and monitoring, studies must be performed comparing with other values of the inflammatory response in various groups of patients (3-5). C reactive protein (CRP) is an acute phase reactant that increases in inflammatory responses and is frequently used for follow-up (6,7).

In patients on haemodialysis, inflammation is stimulated by acute-phase responses triggered by various pathophysiological mechanisms such as exposure to bacteria, endotoxins or viruses, and immunological phenomenon that occur because of the biocompatibility of the dialysis procedure, or metabolic and immunological disorders due to chronic renal failure per se (8). Although PCT has been described as a new marker of inflammation, it has been extensively studied in dialysis patients. As some studies have reported, CRP and PCT

during haemodialysis has not been fully clarified. The aim of the study was to assess PCT and CRP plasma concentrations in ESRD patients undergoing haemodialysis session and the effect of intermittent haemodialysis on PCT levels.

Materials and Methods

The study involved 43 consecutive patients without evidence of systemic infection between 19 and 68 years age having chronic kidney disease and undergoing haemodialysis treatment in Firat University, Firat Medical Center. The control group included 40 volunteers, 20 male and 20 female, whose ages ranged between 18 and 60 (46.6 ± 14.8). The cases in the control group had CRP within normal limits and did not have any complaints. Table 1 shows the features of the patients included in the study, the method and period of haemodialysis treatment. None were treated with corticosteroid and erythropoietin. There was no clinical evidence of infection or major surgical procedures in the three weeks preceding the study and none of these patients had any immunologic or thromboembolic disorder or malignancy.

Haemodialysis treatment was performed for 4 hours 3 times a week using bicarbonate-buffered dialysate. In haemodialysis, polysulphone dialyser (Hemoflow F6, Fresenius, Germany), and low molecular weight heparin for anticoagulation (Fragmin 2000-5000 Ü) were used. Blood flow rate was in the range of 200-300 mL/min; ultrafiltration rate was between 300-1000 mL/hour. The water treatment system consisted of simple reverse osmosis. All dialysis generators were disinfected after each dialysis procedure. Regular microbiological tests showed no bacterial growth in any samples of the bicarbonate-buffered dialysate. Vascular access was via an arteriovenous fistula.

Table 1. Clinical characteristics of the 43 patients.

Sex ratio	18M / 25F
Age(years)	47.02+ 14.7
Time on dialysis (year)	3.76 + 0.3
Hemoglobin levels (g/dl)	9.3 + 0.4
Urea reduction rate (%)	68 ± 5
Kt/V (unit)	1.64 ± 0.32
Primary renal diseases	
Diabetes Mellitus	11 (% 25.6)
Glomerular disease	11 (% 25.6)
Hypertensive nephrosclerosis	4 (% 9.3)
Urolithiasis	4 (% 9.3)
Polycystic kidney disease	3 (% 6.9)
Amyloidosis	2 (% 4.7)
Vesicoureteral reflux	1 (% 2.3)
Unknown etiology	7 (%16.3)

The average age of patients in the study was 47 years and 58.1% were women. The mean urea reduction ratio was 68 ± 5%, mean Kt/V urea (Urea clearance x time/the volume of distribution of urea) value 1.64 ± 0.32, mean serum albumin concentration was 3.98 ± 0.47, and protein catabolism rate (PCR) 1.6 ± 0.2. The mean hemoglobin value of the patients was 9.3 ± 0.4g/dL. It was found that the most frequent cause of the chronic kidney disease was diabetes mellitus. From the 43 patients undergoing haemodialysis, venous blood samples were taken before and after the 4 hours of dialysis. Venous blood samples were also taken from those in the control group; blood samples were taken immediately centrifuged and kept at -80 ^{0}C until the day of research. Procalcitonin levels were determined by immunoluminometric assay using BRAHMS kits (Brahms Diagnostica, Berlin, Germany). CRP levels were measured by the immunonephelometric assay using Dade Behring kits.

Statistical analysis

Statistical evaluation was made in Windows 98, using SPSS software and Student T test and Wilcoxon tests for nonparametric data. For analysis of correlation between the values, Pearson correlation analyses were used. Data were expressed as mean ± SD. Differences at the level of $P < 0.05$ were considered statistically significant.

Results

In haemodialysis patients, mean PCT concentrations showed a mean of 2.13 ± 0.7 ng/mL and in the control group 0.18 ± 0.03 ng/mL ($P < 0.0001$, Table 2). The PCT levels were above 0.5 ng/mL in 30 patients (69.7%) at baseline versus 24 patients (55.8%) at the end of haemodialysis ($P > 0.05$). On average, the PCT levels decreased from 2.13 ± 0.7 ng/mL at baseline to 1.18 ± 0.3.ng/mL at the end of haemodialysis ($P < 0.05$). There was no difference in urea reduction ratio or Kt/V between patients with low or high PCT levels.

Table 2. Pre- and post-haemodialysis PCT and CRP values of patients.

	Control group	Pre-haemodialysis	Post-haemodialysis
PCT (ng/ml)	0.18 + 0.03	2.13 + 0.7*	1.18 + 0.3**
CRP (mg/l)	4.50 + 2.24	14.3 + 2.9***	13.4 + 3.18***

* $P < 0.0001$, vs. control
** $P < 0.05$, vs. pre-haemodialysis
*** $P < 0.05$, vs. control

Serum concentration of CRP was 14.3 ± 2.9 mg/L in haemodialysis patients. In the control group, CRP value was 4.5 ± 2.2 mg/L ($P < 0.05$). There was no significant difference in CRP plasma concentration with haemodialysis. In comparison with pre-haemodialysis PCT, it was found that PCT levels correlated only weakly with CRP levels ($r = 0.32$, $p = 0.02$). No correlation was found between post-haemodialysis PCT and CRP levels ($r = 0.07$, $p = 0.6$, Table 2).

Discussion

High level of serum or plasma PCT is an indicator of the magnitude of inflammation and the immune response given by the scurf. PCT is at very high levels in sepsis and serious infections, at medium levels in bacterial infections of organs, at low levels in some parasitic and fungal infections, and at normal levels in viral infections and small-scale surgical operations. Normally the reference value of PCT in the serum is below 0.5ng/ml (5). Sitter at al suggested that PCT proved superior to other markers of infection and might be a useful diagnostic marker in renal patients with bacterial infection (9). The aim of the present study was to evaluate PCT and CRP concentrations in haemodialysis patients without signs of infection. We demonstrated that PCT is high in haemodialysis patients, and is decreased moderately after haemodialysis session, and that PCT and CRP concentrations are weakly correlated before haemodialysis. Level C et al. found a relationship between PCT and other inflammatory parameters such as CRP or IL-6 (10). Although PCT is not produced by circulating blood cells, its synthesis is closely dependent on IL-6 and TNF α. Thus the presence of an elevated plasma PCT levels in prehaemodialysis indicates that uremia per se and not the dialysis process is the principle cause of increased plasma PCT either directly or possibly as a consequence of IL-6 and TNF α release (11).

In our study, PCT levels were decreased after haemodialysis. The cause of this may be PCT clearance by dialysis, because of its low molecular weight (12). Nishikura et al. emphasized that PCT was first absorbed by the filter membrane and then subjected to an ultradiafilter, the PCT clearance seems to become constant at 2.3 to 3.4 mL/min during a 5 h to 24 h haemodiafiltration session (13). In one study, it was demonstrated that high PCT levels were decreased by high-flux membranes, but not low-flux membranes (14). In fact increases in PCT levels by cytokine activation during the course of haemodialysis would be expected. However, Dandona et al. have shown that an initial release of PCT in serum can be detected at the earliest 4-6 h after stimulation of endotoxin(15). Therefore, it may be unlikely to observe an increase of PCT levels during haemodialysis. This decrease in serum PCT may reduce the sensitivity of PCT (11). We suggested that, in haemodialysis patients, PCT plasma concentrations may be altered independently of the presence, nature or activity of infection.

In patients undergoing chronic haemodialysis the immunoturbidimetry method revealed plasma CRP levels of 24 ± 4.2 mg/mL and in the control group it was 1.7 ± 0.67 mg/mL ($P < 0.001$) (7). The high level of CRP in inflammatory cases such as bacterial infection, trauma, collagen tissue disease is non-specific and even if the inflammation is removed the high level remains for some time. However, the in vivo PCT half time is defined to be about 25-30 hours. Dropping of high PCT levels is an indicator of recovery. If it remains high or decreases very slowly, there is no recovery (16, 17). Numerous studies have reported a strong association between inflammation, nutritional status, and mortality in dialysis patients (2, 18). In addition, PCT could be considered as an acute phase protein associated with the early phase of inflammatory processes before the occurrence of impaired nutritional status. In a research, 16 (44%) of

the 36 chronic haemodialysis patients had serum PCT levels of above 0.5 ng/ml whereas at post-dialysis, this figure decreased to nine (25%) at the 240th minute. The average pre-haemodialysis PCT level was 0.58 ± 0.35 ng/mL but it decreased to 0.44 ± 0.32 ng/mL in the post-dialysis period. On the other hand, the CRP level, which was 0.57 ± 0.44 mg/mL before haemodialysis, increased to 0.70 ± 0.51 mg/mL after the treatment (17).

In our research, the high levels of PCT observed at pre-dialysis in the chronic haemodialysis patients makes us suspect the existence of a slight inflammation that is not totally obvious and identifiable, and has a chronic character. The determined CRP levels also support this idea. CRP reference values are nephelometrically 0-5 mg/L. The CRP value we found is about twice the normal value. Lock of significant difference in the CRP levels after haemodialysis indicated that CRP was not eliminated with haemodialysis, and haemodialysis had no significant effect on CRP levels. CRP may be a useful marker of infection in these patients.

In conclusion, it was observed that PCT levels increased in patients on chronic haemodialysis. We conclude that PCT is a possible marker of chronic systemic inflammatory state in these patients, while CRP is a valid marker of chronic inflammation. Although haemodialysis was associated with a significant decrease of serum PCT, haemodialysis had no significant effect on CRP levels.

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