THE EVALUATION OF THE PROCALCITONIN LEVELS IN CHRONIC PROSTATITIS PATIENTS

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ABSTRACT

Objective: To explore the relationship between procalcitonin levels and non-bacterial chronic prostatitis and its place in follow ups.

Material and Method: From January, 2014 to August, 2014, 53 patients with symptomatic chronic prostatitis were included in this study. Before and after treatment, the United States National Institutes of Health chronic prostatitis symptom index (NIH-CPSI), pain scores, the International Prostate Symptom Score (IPSS), procalcitonin, leukocyte (WBC), mean platelet volume, hemoglobin (Hb), total prostate-specific antigen (PSA), C-Reactive Protein(CRP) levels, and erythrocyte sedimentation rate (ESR) were evaluated prospectively.

Results: In 47 of the 53 patients (89%) who participated in the study, the procalcitonin levels in the serum were over the threshold value of 0.05 ng/ml. After the treatment, 29 of these 47 patients beginning with high procalcitonin levels (62%) were found to have levels lower than the threshold value of 0.05 ng/ml. In which 18 patients with procalcitonin levels below the threshold, significant decreases in the levels (0.069±0.014, 0.053±0.005, p<0.001) were noted. In 6 patients who had chronic prostatitis with an initial value lower than the threshold, the value remained lower than 0.05 ng/ml.

Conclusion: Because chronic prostatitis is a recurring chronic disease, the detection of relapses, finding antibiotic treatment options, and determination of procalcitonin levels may be of importance. Further studies will improve our understanding of the chronic prostatitis dilemma.

Keywords: Chronic prostatitis, procalcitonin, mean platelet volume. **Nobel Med 2016; 12(2): 60-65**

KRONİK PROSTATİT GRUBUNDAKİ HASTALARIN PROKALSİTONİN SEVİYELERİNİN DEĞERLENDİRMESİ

ÖZET

Amaç: Kronik prostatit, her yaş grubunda görülebilen ve yaşam kalitesi üzerine olumsuz etkileri olan yüksek prevalanslı bir hastalık olmasına rağmen altında yatan etiyoloji ve fizyopatojenezi halen muammadır. Bu çalışmanın amacı, prokalsitoninin non-bakteriyel kronik prostatitlerle ilişkisi ve takipteki yerini irdelemektir.

Materyal ve Metot: Ocak 2014 ve Ağustos 2014 tarihleri arasında, kronik prostatit teşhisi konulan semptomatik 53 hastanın tedavi önce ve sonrası, Birleşik Devletler Ulusal Sağlık Enstitüleri kronik prostatit semptom indeksi (NHI-CPSI) ağrı skorları, uluslararası prostat semptom skoru (I-PSS), prokalsitonin, lökosit, ortalama trombosit hacmi, hemoglobin(Hb), total prostat spesifik antijen (PSA), C-reaktif protein (CRP) seviyeleri ve eritrosit sedimantasyon hızı prospektif olarak değerlendirildi.

Bulgular: Çalışmaya dâhil edilen kronik prostatitli 53 hastanın 47'sinde (%89), kan prokalsitonin düzeyleri eşik değer olan 0,05 ng/ml'nin üzerindeydi. Tedavi sonrası yüksek prokalsitonin düzeylerinin 29 hastada (29/47=%62) eşik değerin altına düştüğü ve 18 hastada eşik değerin üzerinde olmakla birlikte, tedavi öncesi değerlerden istatistiksel olarak çok anlamlı aşağıya düştüğü (0,069±0,014, 0,053±0.005, p<0,001) görüldü. Kronik prostatitli 6 hastada ise, tedavi öncesi ve sonrası değerler, 0,05ng/ml altında idi.

Sonuç: Rekürrenslerle giden kronik bir hastalık olarak kronik prostatitte relapsları saptamada ve antibiyotik tedavisi seçeneğinin belirlenmesinde prokalsitonin düzeylerinin belirlenmesinin önemli olabileceğini düşünüyoruz. Gelecekteki daha geniş çalışmalarda bu öznenin seçilmesi, konuyu aydınlatacaktır.

Anahtar kelimeler: Kronik prostatit, prokalsitonin, ortalama trombosit hacmi. **Nobel Med 2016; 12(2): 60-65**

INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common prostate disease seen in men under the age of 50. However, there is no established mechanism or specific medical treatment for it.[1] The global incidence is 9-14%.[2] The NIH classification of prostatitis syndromes divides them into 4 distinct types; type I: acute bacterial prostatitis, type 2: chronic bacterial prostatitis, type 3: chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CNP/CPPS), and type 4: asymptomatic inflammatory prostatitis.[3] In addition, type 3 prostatitis is classified by prostate massage fluids direct microscopy according to the leucocyte presence as IIIA or IIIB. CNP/CPPS is the most common type of prostatitis, and the pathophysiology, diagnosis, and treatment of this type have not yet become clear.

Procalcitonin (PCT), with a molecular weight of about 13 kilodaltons, is a polypeptide containing 116 amino acids.[4] This hormone, which is produced in the thyroid gland and contains 32 amino acids, was first discovered in 1989 as a precursor of calcitonin by Ghilliani *et al.* Active calcitonin is made from procalcitonin in the C cells of the thyroid gland through very specific proteolytic enzymes. PCT and calcitonin synthesis is initiated by translation of preprocalcitonin, a precursor peptide comprising 141 amino acids. This protein includes one signal sequence (amino acids 1-25), the N-terminal region of procalcitonin (N-ProCT), calcitonin sequence, and the C-terminal region of PCT called catacalsine.[5] In recent studies, it has been proven that PCT can cause significant inhibition in lymphocytes, in vitro prostaglandins, and thromboxane synthesis. Most likely, the responsible mechanism here is the inhibition of cyclooxygenase activity. The in vivo inhibition of eicosanoid occurs with serious bacterial inflammation and sepsis, in which the high serum concentration of PCT is reached.[6]

The aim of the present study is to examine the relationship between procalcitonin levels and non-bacterial chronic prostatitis and its role in follow up evaluations.

MATERIALS AND METHODS

Between January, 2014 and August, 2014, 53 male patients-whose symptoms were reoccurring despite medical treatments, who could not be relieved from their symptoms, or who had abnormal urination accompanied by symptoms of genital, perineal, suprapubic and/or pelvic pain despite treatment for over 6 months-were evaluated for a prospective study in order to examine possible steps for physiopathogenesis. This group was evaluated through medical history, urological examination, radiological evaluation, microbiological studies, complete blood count, procalcitonin, leukocyte (WBC), mean platelet volume (MPV), hemoglobin (Hb), total prostate-specific antigen (PSA), C-Reactive Protein (CRP) levels, and erythrocyte sedimentation rate (ESR), evaluations based on the I-PSS and NIH-CPSI form, and the U-POINT classification.

Because it would be included in the study, type III prostatitis patients (U-POINT organ specific ones) were asked questions to determine whether they would be included in the study. Patients were questioned about chronic genital-pelvic-perineal pain with differing frequency and degree of accompanying dysuria, pollakiuria, lower urinary tract symptoms such as urgency or incontinence, erectile dysfunction, changes in seminal fluid, hematospermia or painful ejaculation, and groin, thigh, back, and leg pain. These and any other complaints were recorded. Also, physical examinations (fever, digital rectal examination) and routine tests were performed. Additionally, possible underlying conditions-such as obstructive prostate disease or urethral stricture, erectile dysfunction (ED), interstitial cystitis, overactive bladder, bladder tumors or other bladder pathology, neurological and neuropathic pain, musculoskeletal pain, inguinal lymphadenitis, urethritis, bacterial prostatitis and all other urinary tract infections were eliminated with the use of ultrasonography (USG), uroflowmetry, residual urine, I-PSS, cystourethroscopy and urodynamics study, IIEF-5, or transrectal ultrasound when needed, and extensive microbiological examinations.

Patients with light and mild to moderate ED who did not have a significant psychological component and were taking pharmaceuticals for diseases such as diabetes, hypertension, and hypercholesterolemia were kept in the study. Even if the microbiological analyses were negative, these patients were kept in the relevant literature with antibiotics (fluoroquinolone) and non-steroidal anti-inflammatory treatment on the side, and these patients were called for a check-up after treatment.[7,8] There were 53 patients who completed treatments and came in for their check-ups.[7,8] Urologic examination was performed and the I-PSS and NIH-CPSI forms were completed. Additionally, a complete blood count (CBC), CRP, PSA, and procalcitonin tests were done. Parameters were compared before and after treatment.

Microbiological Evaluation

To localize lower urinary tract infections, the traditional 4-glass test was administered to each patient who likely had CP/CPPS. The 4-glass test samples were obtained in the following way: (1) VB1, approximately the first 10 ml were used to give information about urethral colonization; (2) VB2, middle and late urine for sampling; (3) EPS, express prostate secretion; (4) VB3, the first 10ml of urine taken after a prostate massage given to stimulate secretion. The 4 cup samples were analyzed with direct microscopes and standard microbiological methods (blood agar and MacConkey agar). Patients without any uropathogens, whether they had leukocytes in direct microscopy (n=41) or not (n=24), were included in the study. No matter what location it was

found in, if a positive culture was found, the patient was excluded from the study. All of the microbiological studies were performed under the care of a single expert in the same laboratory. This microbiologist was not given any information about the study.

Tests

The American National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) survey, is split into 3 parts-pain (location, intensity, and frequency), urinary symptoms, and quality of life-and consists of 9 questions (4+2+3), which require responses on a 45 point scale.[9] The maximum values are 21 for pain, 10 for urinary symptoms, and 12 for quality of life. A higher point value indicates a higher level of discomfort. To recognize the symptomatic patients in our study and decide whether to include or exclude each patient, the pain score was used.

To eliminate the obstructive patients, patients who had pelvic pain or who did not fit in a certain pattern and had micturition problems filled out the I-PSS form. Patients who had severe symptoms were redirected to get treatment for obstructive prostate disease and excluded from the study. Patients with an IIEF-5 score below 12 were excluded from the study.

U-POINT is a new classification system that is used to identify phenotypes in 6 different fields: urinary, psychosocial, organ-specific, infection, neurological, and sensitivity (skeletal muscle).[10] In contrast, for patients who have already been diagnosed, UPOINT should be seen as a guide to help classify patients and help them find appropriate treatment options. This rationality was used in our experiment to identify patients whose symptoms were organ specific. In this group, patients who were bladder specific were separated for detailed analysis of results as listed above. As with the patients from other areas, the bladder specific patients who were excluded from our study were directed towards appropriate treatment options.

PCT Measurement

For the purpose of determining PCT levels, a sample of 5 mL of blood was taken from each subject and stored at -20°C. Later, PCT levels were determined using the automated immunofluorescence method (BRAHMS).

Complete blood count test

Physical examination and body temperature measurements were performed on all patients before blood samples were taken. If the patient did not have a fever, their blood was taken. No preservatives were used on the blood, and the tests were completed within 3 hours.

Informed consent from the patients and ethical committee approval (Taksim Training and Research Hospital Local Ethical Committee: E.P.K.K/45793301-900) were obtained.

Statistical Evaluation

Data before and after the treatment were analyzed using the SPSS 14.0 statistics program (SPSS, Chicago, IL, USA). Because the variable was independent, the "paired samples t-test" was used to make comparisons. $p<0.05$ were considered statistically significant.

RESULTS

The mean age of the 53 patients who were included in the study was 37.1±8.3 (23-56). The duration of their complaints ranged from 6 to 72 months. The median and mean duration of their complaints were 24 months and 32±17 months, respectively. Chronic pelvic pain localizations in patients were as follows: lumbosacral (30), suprapubic (29), penile (27), perianal (21), testes (14), groin (7), and thigh (4). Patients with symptoms accompanying the pain, in order of frequency, were found to be as follows: dysuria (39), desire and need to urinate often during the painful period (37), nocturia (30), ED (20), fatigue, insomnia, depression and similar psychological symptoms (18), feeling of inability to empty bladder (14), painful ejaculation (6), difficulty in starting to urinate (6), and hematospermia (1). All patients underwent digital rectal examination. There were 5 patients who did not show characteristics in the digital rectal examination. The others experienced tenderness and pain, including a mild tenderness. Surface irregularities and soft nodule-like structures were palpated. Based on EPS inflammation, 39 of the patients were IIIA, and 14 of the patients were IIIB.

Pretreatment parameters (mean±SD) were found to be as follows: I-PSS 8.5±3.5 (2-21), NIH-CPSI pain score:16.3±8.3 (5-37), Hb (g/dL):15.2±1.0 (11.8-16.6), leukocytes (WBC (cell count/μL)):7.409±1.723 (3.270-13.102), sedimentation rate (mm/hour):8.7±5.1 (1-19), CRP:0.20±0.17 (0.02-0.8), PSA (ng/mL): 1.33±1.60 (0.29-8.70), and PCT (ng/mL):0.065±0.020 (0.02-0.12). The patients' symptoms were significantly decreased after the treatment. The difference in the post treatment mean I-PSS is 2.5±2.4 (0-9), and it is statistically highly significant ($p<0.001$). Similarly, the NIH-CPSI pain score mean was found to be 3.3±3.1 (0-13) ($p<0.001$). In contrast, the Hb (g/dL) values (15.1±0.7) ($p>0.05$) and CRP values (0.16±0.14) ($p>0.05$) showed no changes.

The post treatment value of PSA (ng/ml) was found to be 1.14±1.20 (p=0.015). Likewise, ESR scores were
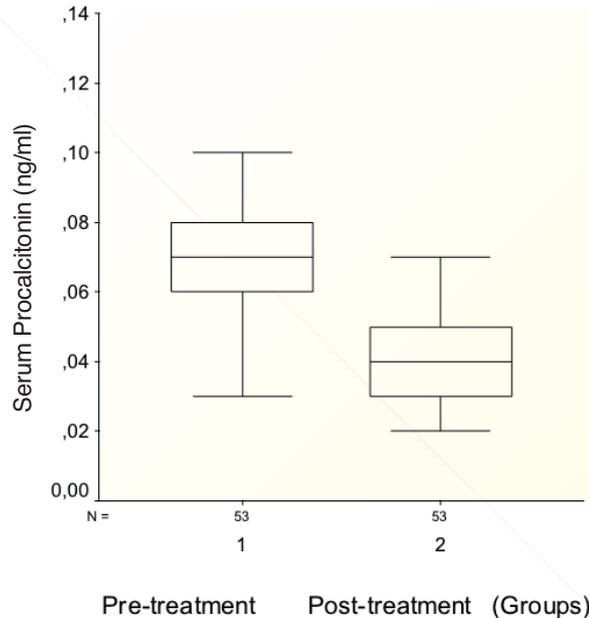

Figure 1. Box plots of serum procalcitonin levels in treatment of chronic prostatitis groups.

Table Laboratory data for 53 patients with chronic prostatitis					
	Pre-treatment		**Post-treatment**		
	Mean±SD	(Min–Max)	Mean±SD	Min–Max	p
Age (years)	37.1±8.3	(23–56)			
IPSS	8.5±3.5	(2–21)	2.5±2.4	(0–9)	<0.001
NIH-CPSI	16.3±8.3	(5–37)	3.3±3.1	(0–13)	<0.001
Hb (g/dL)	15.2±1.0	(11.8–16.6)	15.1±0.7	(13.2–16.4)	0.718
LC (cells/μL)	7.409±1.723	(3.270–13.102)	6.945±872	(4.508–8.410)	0.003
MPV (fL)	9.6±0.8	(7.7–11.9)	9.3±0.6	(8.0–10.4)	0.013
7.20-11,10-ESR (mm/hour)	8.7±5.1	(1–19)	6.9±2.1	(3–10)	0.021
CRP (mg/dL)	0.20±0.17	(0.02–0.8)	0.16±0.14	(0.02–0.9)	0.257
PSA(ng/mL)	1.33±1.60	(0.29–8.70)	1.14±1.20	(0.40–7.00)	0.015
PCT (ng/mL)	0.065±0.020	(0.02–0.12)	0.037±0.011	(0.02–0.07)	<0.001

IPSS: International prostate symptom score, **NIH-CPSI:** the national institute of health chronic prostatitis symptom index, **Hb:** hemoglobin, **LC:** leukocyte counts, **MPV:** mean platelet volume, **ESR:** erythrocyte sedimentation rate, **CRP:** C-reactive protein, **PSA:** prostate-specific antigen, **PCT:** procalcitonin, **Paired Samples Test:** significance p<0.05

reduced after treatment (6.9±2.1mm/hour) (*p*=0.021). WBC (number of cells/ml) was decreased after treatment (6,945±872) (*p*=0.003). Mean platelet values had showed little change between the before and after treatment scores (9.6±0.8 fl-9.3±0.6 fl) (*p*=0.013) (Table, Figure 1,2,3).

Before treatment, 47 out of 53 patients (89%) had blood procalcitonin levels over the threshold (0.05 ng/ml). Following treatment, 62% (29) of these patients were found to have levels that had fallen below the threshold. In the rest of the patients who remained above the threshold, there was still a statistically significant decrease in procalcitonin levels (0.069±0.014, 0.053±0.005,
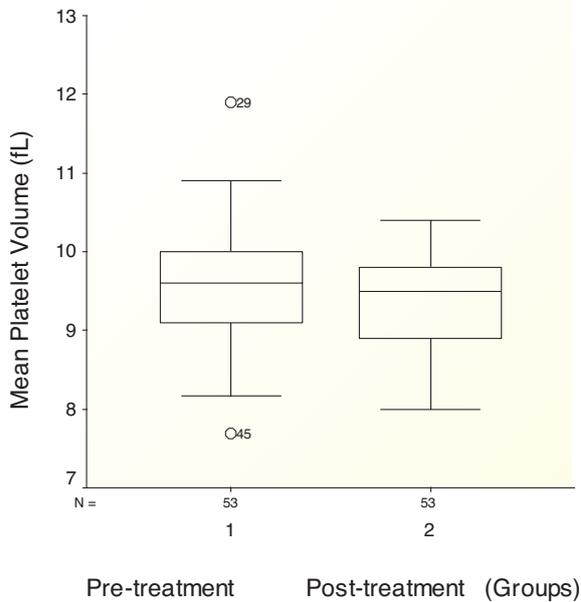
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Figure 2. Box plots of mean platelet volumes in treatment of chronic prostatitis groups.
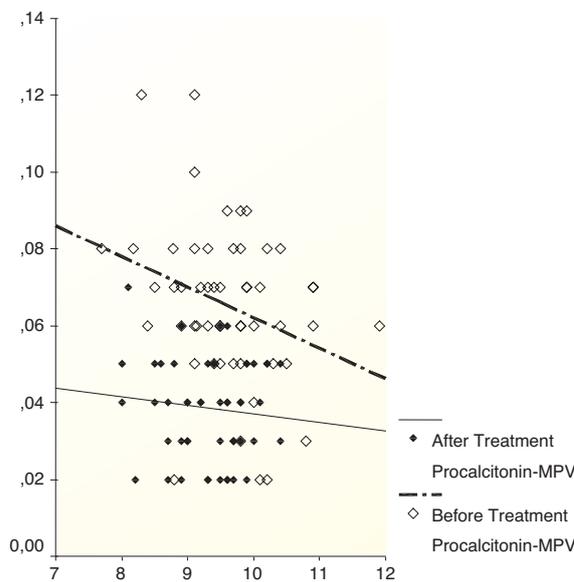

Figure 3. The correlation plots of the data incases of chronic prostatitis.

$p < 0.001$). In the remaining 6 patients, PCT levels were below 0.05 before and after treatment.

DISCUSSION

CPPS seems to encompass a large number of symptom groups. Despite ongoing efforts, there is still no gold standard for diagnosis and treatment. In the literature, antibiotics, alpha-blockers and/or gabapentin, pregabalin, tricyclic antidepressants, and memantine are being studied to solve the mystery of etiology and physiopathogenesis. Mostly used therapy for CPPS is antibiotics, although less than 10% of patients have any bacteria localized to the prostate.[7,8-11]

In the case of progress of the infection, many markers can be used as obvious indicators of the body's response to the infection. Of these, CRP inflammation is a very sensitive indicator, but CRP cannot always be used to distinguish between inflammation that is caused by bacteria and inflammation that is not. This is because CRP values also significantly increase after surgery, multi-trauma, infections, tumors, autoimmune diseases, and chronic inflammatory disease.[12] MPV, which was studied within the framework of new marker research efforts for CP, has also been scrutinized.[13] In recent years, procalcitonin in general has been studied as an acute phase reactant for acute bacterial diseases and sepsis.[14,15]

However, high PCT levels can be found in non-bacterial conditions, such as malaria, severe trauma, burns, and medullary thyroid carcinoma.[16] Under normal conditions, PCT, which is used as the precursor for calcitonin, is synthesized in C cells from the thyroid medulla and neuroendocrine cells from the lung, including leukocytes following proinflammatory simulation and is produced by many cells.[17] By modulating proinflammatory cytokines, PCT affects the immune response. Its half-life is about 25 hours. It acts as a chemokine in the inflammation field by pulling mono and parenchymal cells. The PCT value for healthy individuals is <0.05 ng/mL. It is significant that levels are higher than 0.05 ng/mL in lower respiratory tract infections. The fact that levels are above 2 ng in systemic infections and above 10 ng in sepsis further confirms the situation. Patients admitted to intensive care units due to sepsis or shock have no time to wait for blood cultures, so usage of this technique has been convenient.[4,18-20] It should be kept in mind that plasma levels will also increase with major abdominal surgery, trauma or major burns, liver damage, pancreatitis, fungal infections and multi-organ dysfunctions. PCT levels were significantly improved after the treatment of diabetic foot ulcers.[21]

There are not any publications in the PCT literature concerning chronic prostatitis patients. We did not encounter any considerable work on this subject. In the present study, we intended to provide new insights on the evaluation of PCT before and after treatment of CP patients. The pretreatment values for non-bacterial symptomatic prostatitis patients were found to be 0.065±0.020 ng/mL, whereas the post treatment values were 0.03±0.011 ng/mL. The decrease in the pain scores of these CP patients suggests that PCT was possibly related to the systematic periods.

CONCLUSION

Although many parameters have been studied as markers of chronic prostatitis, PCT remains the latest promising one. In addition, monitoring of PCT levels may be a promising marker to keep track of this chronic, periodically recurring disease in follow-up.

*The authors declare that there are no conflicts of interest.

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