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Original Article

Prostate-specific antigen reduction after empiric antibiotic treatment does not rule out biopsy in patients with lower urinary tract symptoms: prospective, controlled, single-center study

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ABSTRACT

Background: To evaluate men, with lower urinary tract symptoms and newly elevated serum prostate specific antigen (PSA) to determine whether a three-week course of ciprofloxacin antibiotics lowers serum PSA levels and affects recommendations for prostate biopsy.

Methods: A prospective, controlled, single-center prospective trial of 177 men with a newly elevated PSA and lower urinary tract symptoms was conducted. Patients were randomized to three weeks of ciprofloxacin or observation. After three weeks, patients PSA levels and derivatives were repeated. At the end of 3 weeks, all patients underwent TRUS guided systematic 12-core prostate biopsies regardless of the final PSA value.

Results: Of 177 men who completed the study, 88 were in the treatment and 89 in the observation group. 46.5% of treatment and %18 of control groups patients PSA levels had decreased after 3 weeks and a significant PSA reduction was observed in the treatment group compare to control group (p: 0.035) but no significant prostate cancer detection rates were observed between the groups (p: 0.418). Also, in the treatment group prostate cancer detection rate was significantly higher in patients whom PSA levels were decreased (p: 0.011).

Conclusion: This study has shown that, use empirical antibiotic treatment decreased the PSA levels but did not have any effect on prostate cancer detection. In addition, prostate cancer detection rates were found to be higher in patients with reduced PSA levels after treatment. Therefore, it may not be safe to rule out biopsies in patients who achieve a satisfactory PSA response to antibiotics.

1. Introduction

The use of, prostate-specific antigen (PSA) as a serum marker has revolutionized prostate cancer (PCa) diagnosis[1] and has resulted in changes that include an increase in the number of prostate biopsies performed. However, screening for PCa is one of the most controversial topics in urological literature.[2] Some authors argue that the use of current American Urological Association guidelines may lead to a significant number of men with aggressive PCa being missed.[3] By contrast, a Cochrane review that was published in 2013 has determined that PSA screening is associated with an increased diagnosis of PCa, but no benefit was observed on overall survival.[4]

There is no consensus on how to manage high PSA levels that have occasionally been detected during PSA screening, because PSA levels can increase for several reasons, including trauma, ejaculation, and rectal and urethral procedures. In addition, numerous noncancerous etiologies can cause elevated PSA levels, such as benign prostatic hyperplasia, inflammation, and infection.[5,6] Most urologists make decisions on the basis of their training and experience. Some of them, in daily practice, use antibiotics to reduce high PSA values. After a course of antibiotics, the PSA measurement is repeated and if it remains elevated, biopsy is recommended. If it significantly decreases, a biopsy may be avoided.

Several studies have shown that receiving antibiotic treatment prior to deciding to have a biopsy can reduce PSA values to normal levels, and biopsy can be avoided.[7,8] However, empiric antibiotic use in this setting is associated with drug-related side effects[9],

Abbreviations: fPSA, free prostate-specific antigen; IPSS, International Prostate Symptom Score; Q_{max}, maximum flow rates; PCa, prostate cancer; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; TRUS, transrectal ultrasonography.

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promotion of microbial resistance,[10] and an increased rate of sepsis after prostate biopsy.[11] Furthermore, high occurrence of Gleason scores ≥7 PCa (17%) at low PSA levels (≤2 ng/mL) shows that, the decrease in PSA should not be undertaken.[12]

In this prospective and controlled study, we tried to investigate the effect of antibiotics on total PSA (tPSA) and free PSA (fPSA) levels in patients with high PSA levels. The PSA ratios during and at the end of antibiotic treatment were measured; the cancer detection rates were investigated and compared with the control group.

2. Patients and methods

The study was conducted between June 2014 and November 2016 on 177 patients who had been referred to Okmeydanı Training and Research Hospital outpatient department. The study was approved by the local ethics committee, and informed consent was obtained from all participants. Patients with lower urinary tract symptoms and shown to have a PSA level higher than 2.5 ng/mL and a palpably normal digital rectal examination were included in the study.

In all cases, detailed history was taken, and physical examinations were performed. International Prostate Symptom Score (IPSS) assessments were performed, and urine samples for urine analysis and urine culture were taken. Blood samples were taken for measurement of creatinine and blood urea nitrogen levels. Digital rectal examination was conducted, and KUB was taken for all patients. The urinary system was examined with urinary system ultrasound, and postvoid residual urine was measured. Prostate volume (PV) was measured with transrectal ultrasonography (TRUS) (GE Health_ Lociq 200 Pro). In addition, maximum flow rates (Q_{max}) of all cases were assessed with uroflowmetry.

Patients who had urinary infection, chronic kidney disease, bladder tumor, prostate tumor, neurogenic bladder, urethral stenosis, history of 5-alpha reductase inhibitor treatment, bladder calculi, having signs of acute or chronic prostatitis, and also patients who had a history of prostate surgery or prostate needle biopsy were excluded. In addition, those who had acute urinary system infection, hypersensitivity to quinolones, urinary retention, and who had recent digital examination history as well as cases with urethral catheter, which could have effects on serum PSA levels, were excluded.

Determination of tPSA and fPSA levels was repeated twice in each visit to prevent laboratory errors. The tPSA and fPSA analyses were conducted using the test “total and free prostate-specific antigen” (Roche Diagnostics, Cobas 6000) on a Modular E-Module of Roche Diagnostics, USA. All measurements were done in a central laboratory in blinded fashion and according to the manufacturer’s instructions in a central laboratory.

Patients were randomized systematically into two groups according to the order of admission. Those in the first group were given 500 mg oral ciprofloxacin twice a day for 21 days. The second control group received no treatment. Just after the termination of antibiotic treatment, all patients were reevaluated using the same parameters. At the end of 3 weeks, all patients underwent TRUS-guided systematic 12-core prostate biopsies regardless of the final PSA value.

TRUS-guided prostate biopsies were performed with the patient in the left decubitus position, using a biplanar 7.5-MHz transrectal ultrasound probe. Prior to the procedure, local anesthesia with periprostatic nerve blockade was done. With an 18-gauge needle, 12 core prostate biopsies were taken, and specimens were examined in the pathology department of our hospital.

Mean, standard deviation, median, and percentage values were used for descriptive statistics. The distribution of variables was checked with Kolmogorov–Smirnov test. Mann–Whitney *U* test was used for the comparison of quantitative data. Wilcoxon signed-rank test was used for the repeated measurement analysis. Chi-square test was used for the comparison of the comparison of qualitative data. SPSS 22.0 was used for statistical analysis. A p value less than 0.05 was considered statistically significant.

3. Results

A total of 177 patients participated in the study. The control group had a mean age of 58.9 ± 9.5 years, and the treatment group had a mean age of 60.2 ± 7.1 ($P = 0.255$). There were no differences between the two groups in terms of age, tPSA, fPSA, %f/t PSA (percent-free PSA), prostate-specific antigen density (PSAD), PV, Q_{max}, and IPSS (Table 1).

The mean ± standard deviation values of the initial PSA in the treatment and nontreatment groups were 6.1 ± 2.9 ng/mL and 6.4 ± 2.2 ng/mL, respectively ($P = 0.294$). After 3 weeks of antibiotic treatment, the mean of the final PSA in the treatment group decreased to 5.3 ± 2.6 ng/mL, and significant change was observed between initial versus final PSA levels ($P = 0.035$). In the control group after a 3-week period, the mean PSA level was measured (6.2 ± 1.9 ng/mL), and it was determined that the PSA reduction in the control group was not significant ($P = 0.118$). When comparing the mean PSA reductions between the two groups, PSA reduction was significant ($P = 0.022$). As for the mean change in PSA level from baseline to biopsy, antibiotic treatment decreased PSA levels in 46.5% of patients, whereas 15% of controls showed a decrease in PSA levels.

When we compared the patients prior to randomization, there were no significant differences in terms of PSAD levels ($P = 0.115$). PSAD levels decreased from 0.194 ng/mL^2 to 0.169 ng/mL^2 in the treatment group after the antibiotic treatment, and decreased from 0.246 ng/mL^2 to 0.238 ng/mL^2 in the control group ($P = 0.122$). The reduction in PSAD after 3 weeks in the treatment group was not significant ($P = 0.115$) (Fig. 1).

The comparison of initial and final levels of fPSA revealed a significant difference in control group patients; in the treatment group, no significant reduction was observed in percent fPSA values after 3 weeks ($P = 0.115$). There was no statistically significant improvement in IPSS and Q_{max} with the antibiotic treatment. No difference was observed in the control group, as expected (Table 2).

Overall, PCa was detected in 40 of 177 (22.5 %) patients who had PSA levels ≥2.5 ng/mL and 30 of 113 (26.5%) of patients who had PSA levels ≥4 ng/mL. In the control group, 22 of 89 (24%) men were diagnosed with PCa, whereas 18 of 88 patients (21.5%) in the antibiotic group were diagnosed with cancer ($P = 0.718$). In addition, as a result of pathologic examination, there was no difference between the two groups in terms of Gleason scores (Table 3).

Table 1
Comparison of groups at randomization

	Control group		Treatment group		*P*
	Mean ± SD	Median	Mean ± SD	Median	
No. of patients		89		88	
Age (yr)	58.9 ± 9.5	57.0	60.2 ± 7.1	58.4	0.255[a)]
Prostate volume (mL)	26.4 ± 5.8	26.0	31.3 ± 7.8	30.0	0.112[a)]
Q_{max} (mL/s)	10.3 ± 3.2	10.0	10.3 ± 3.2	12.0	0.164[a)]
IPSS	17.6 ± 3.6	18.0	17.0 ± 4.0	18.0	0.388[a)]
PSA (ng/mL)	6.4 ± 5.2	4.5	6.1 ± 2.9	4.7	0.294[a)]
fPSA (ng/mL)	1.2 ± 1.0	1.0	1.4 ± 0.8	1.2	0.154[a)]
Percent free PSA (%)	25.3 ± 22.9	18.3	25.4 ± 14.3	22.1	0.175[a)]
PSAD (ng/mL^2)	0.24 ± 0.03	0.23	0.16 ± 0.02	0.15	0.108[a)]

fPSA, free PSA; IPSS, International Prostate Symptom Score; percent free PSA, % f/t PSA; PSAD, prostate-specific antigen density; Q_{max}, maximum flow rate; SD, standard deviation.
[a)] Mann–Whitney *U* test.

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