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Antibiotics for elevated prostate specific antigen: Where do we stand?

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ABSTRACT

Objective: The empiric use of antibiotics for elevated prostate specific antigen (PSA) is practiced by many urologists worldwide. This study aims to investigate the effect of antibiotics on the degree of PSA change, linking it with histopathology results.

Materials and Methods: This is a prospective randomized study. Patients presenting with a high PSA were randomized into two groups. Group 1 received antibiotics for a period of 4 weeks, while Group 2 did not receive any antibiotics. Both groups had repeated samples of PSA measured 6 weeks from their initial presentation. All patients underwent transrectal ultrasound-guided biopsy of the prostate. Results of PSA measurements and the degree of change were correlated with results of histopathology.

Results: Eighty-four patients completed the study. Their mean age $\pm$ standard deviation was 66.8 ± 6.9 years. Group 1 included 44 patients, while Group 2 included 42 patients. Prostate cancer (PCa) was detected in 50% and 35.7% of Group 1 and Group 2 patients, respectively ($p = 0.52$). No statistically significant difference in the mean change in PSA level (Δ PSA) between both groups was noted ($p = 0.54$). In Group 1, a more significant lowering of PSA was documented in PCa than in non-PCa patients ($p = 0.008$). No statistically significant relationship between Δ PSA and Gleason score in both groups was present.

Conclusion: The empiric use of antibiotics does not hold any benefit for patients presenting with an elevated PSA. Also, the degree of change in PSA does not correlate with results of transrectal ultrasound-guided biopsy of the prostate.

1. Introduction

Prostate cancer (PCa) is a significant medical condition with an increasing incidence worldwide.[1] In addition to a pathologic diagnosis, prostate-specific antigen (PSA) measurement is considered an essential method for detecting PCa. Although PSA is prostate specific, it is not cancer specific, as such it can be elevated in nonmalignant conditions such as benign prostatic enlargement and prostatitis.[2] A serum PSA value of 4 ng/mL has long been used as a cut-off value for performing prostate biopsy; however, in recent years the threshold has been reduced to 2.5 ng/mL as a significant proportion of men harbor PCa at levels lower than what was previously recommended.[3]

In clinical practice, many urologists tend to administer empiric antibiotics for patients presenting with moderately elevated PSA

principally aiming at reducing unnecessary prostate biopsies. Few studies have been made to provide scientific evidence for this practice.[2–7] Although most of them did find a significant reduction in serum PSA after antibiotic treatment, they had one or more weaknesses in their methodology such as retrospective design,[7] absence of a control group,[4] or failure of obtaining pathologic results from all participants.[5,6]

In this randomized prospective study we aim to evaluate the effect of antibiotic therapy on patients presenting with an elevated serum PSA level and perform a prostate biopsy on all participants in an attempt to correlate histopathologic results with the degree of PSA change.

2. Materials and methods

This is a prospective randomized study conducted at the uro-oncology unit in a tertiary care center. Between March 2011 and December 2014, patients referred with an elevated serum PSA and meeting the inclusion and exclusion criteria were included in this study. The inclusion criteria were patients presenting with an

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elevated serum PSA level (PSA > 4 ng/dL). While the exclusion criteria were the presence of symptoms of urinary tract infection or prostatitis, history of prior prostate surgery, biopsy or radiotherapy, any abnormal finding on digital rectal examination (DRE), urinary catheterization during the previous 4 weeks, previous use of 5-α reductase inhibitors, hypersensitivity to any medical ingredient in the quinolone group, and presence of bacterial growth or pyuria in urine samples obtained from asymptomatic patients. All study participants signed an informed consent and the Internal Review Board (Hamad Medical Corporation) approved the study protocol carrying the Internal Review Board number 12144/12.

Prior to their enrollment in the study, all patients were primarily assessed with DRE, urinalysis, and culture. Using computer generated randomization tables, eligible patients were randomly divided into two groups. Group 1 patients received empiric antibiotic therapy with ciprofloxacin 500 mg twice daily for a total of 4 weeks, while Group 2 patients did not receive any antibiotic therapy. Six weeks after their initial presentation, a repeat serum PSA test was performed for all patients followed by transrectal ultrasound-guided biopsy of the prostate (TRUSBP).

PSA measurement was performed using the Architect i2000SR analyzer (Abbott Manufacturing Inc., Abilene, TX, USA). The total PSA assay is a two-step immunoassay to determine the presence of total PSA (both free PSA and PSA complexed to a1-antichymotrypsin) in human serum, using a chemiluminescent microparticle immunoassay with flexible assay protocols. This method of measurement is easy to use, accurate, precise, and suitable for a routine clinical laboratory.[8]

TRUSBP was performed according to the standards of care set by our institute. Prophylactic antibiotics included: oral ciprofoxacin 500mg and a single intravenous injection of 1.5 g cefuroxime given 30 minutes prior to the procedure. Patients were placed in the left lateral decubitus position, and a DRE was first performed using lidocaine hydrochloride 2% sterile gel (Rialocaine, Ryiadh Pharma, Saudi Arabia) anesthetic ointment. A 7.5-MHz transducer (Accuvix v10, Madison Ultrasound System, Samsung Town, Seoul, South Korea) was gently advanced into the rectum and 10 mL of lidocaine hydrochloride 2% (Xylocaine, Pharmaceutical Solutions Industry, Jeddah, Saudi Arabia) was injected locally on both prostate edges. After obtaining the measurements, an 18-G needle loaded in a spring-action biopsy device was used to obtain the specimens. A 12-core biopsy is the standard at our institution.

The 12-core TRUSBP specimens were assessed for adequacy and individually stored in different containers, each labeled with the patient's identification and with a number mapped according to their designated site. The containers were assessed in the histopathology department and examined by a qualified pathologist who reported the findings according to the College of American Pathologists guidelines.[9] If adenocarcinoma was diagnosed, the report usually included the length of each biopsy and the percentage of cancer involvement in each biopsy, the Gleason grade(s) and the extent of any high-grade (Gleason 4 or 5) component, the number of biopsy cores positive for cancer, and their location.

The first PSA result is denoted as PSA1, while the second PSA result as PSA2. The change in PSA (Δ PSA) is calculated by subtracting PSA2 from PSA1. A negative result indicates a reduction in PSA level, while a positive result indicates an elevation in PSA level.

The data was presented as the mean (standard deviation) for continuous variables, and the frequency and percentage for ordinal and nominal variables. Continuous and categorical variables were assessed using t test and Chi-square test, respectively. A p value < 0.05 was considered statistically significant. All data were analyzed using SPSS version 20 (IBM, Armonk, NY, USA).

3. Results

A total of 92 patients met the inclusion and exclusion criteria and were included in the study. Eight patients were lost to follow-up and did not attend for repeat PSA testing or TRUSBP and were excluded from the study. The mean age ± standard deviation of the study population was 66.8 ± 6.9 years. Prostate cancer was detected in 37 patients. A comparison between Group 1 and Group 2 patients is presented in Table 1. Group 1 included 44 patients, while Group 2 included 42 patients. PCa was detected in 50% and 35.7% of Group 1 and Group 2 patients, respectively ($p = 0.52$). A drop in PSA level was detected in 27 (61%) patients and 21 (50%) patients of Group 1 and Group 2, respectively ($p = 0.23$). No statistically significant differences in histopathology results were detected between patients with and without a drop in PSA (Figure 1).

Group 1 patients had a statistically significant Δ PSA between PCa (+PCa) and non-PCa (−PCa) patients, −1.02 ± 2.9 and 1.03 ± 2.4, respectively ($p = 0.008$). No statistically significant Δ PSA was noted in Group 2 patients ($p = 0.77$; Table 2). A correlation between Δ PSA and Gleason score of PCa patients in both groups is presented in Table 3. No statistically significant Δ PSA in relation to Gleason score was found between both groups ($p = 0.17$).

4. Discussion

Serum PSA is a nonspecific marker that can be elevated in noncancerous conditions. This prospective randomized study explores the common use of empiric antibiotic therapy for elevated PSA prior to TRUSBP and for the first time correlates prostate biopsy results, specifically Gleason score, to antibiotic use and the degree of change in PSA. Overall, empiric therapy with ciprofloxacin was not associated with statistically significant difference in mean Δ PSA before and after treatment. Paradoxically patients with PCa who received antibiotics had a significant reduction in their PSA level before biopsy (Δ PSA = −1.02 ± 2.9, $p = 0.008$).

An understanding of the motives behind the empiric use of antibiotics for high PSA is of great importance. Many urologists tend to use this management strategy principally because of the presence of numerous studies linking inflammation in the prostate to increased PSA levels.[5,10,11] The extent of disruption of epithelial integrity caused by inflammatory infiltrate is the main etiology behind this observation. Subclinical prostatitis was detected in up to 40% of patients with an elevated PSA in one study.[11] Carver et al[10] also reported 32% chronic prostatitis National Institute of Health type-4 cases in a randomly chosen group of 300 men. However, while antibiotics might be useful in bacterial prostatitis, almost all cases of asymptomatic prostatitis (National Institute of Health

Table 1
Comparison between study groups.

	Group 1 ($n = 44$)	Group 2 ($n = 42$)	p
Age (y)	65.4 ± 6.9	64.8 ± 7.2	0.98
PSA 1	7.7 ± 2.9	7.2 ± 3.4	0.45
PSA 2	7.6 ± 3.4	7.4 ± 3.4	0.85
Δ PSA	0.16 ± 2.8	−0.2 ± 2.4	0.54
PSA decline	27 (61)	21 (50)	0.23
Histopathology			
PCa	22 (50)	15 (35.7)	0.52
BPH	22 (50)	27 (64.2)	
Chronic inflammation	4 (9)	3 (7.1)	
ASAP	2 (4.5)	2 (4.7)	

Data are presented as n (%) or mean ± standard deviation.
ASAP = atypical small acinar proliferation of indeterminate significance; BPH = benign prostatic hyperplasia; Pca = prostate cancer; PSA = prostate specific antigen; Δ PSA = change in prostate specific antigen.
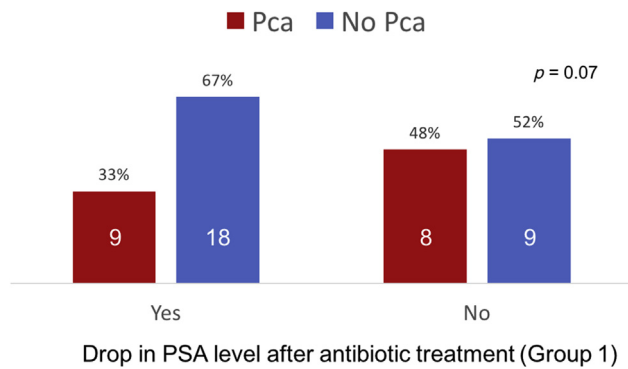
Figure 1. Correlation between the histopathology result and changes in serum prostate specific antigen (PSA) levels among Group 1 patients. Yes = percentage of patients with a PSA reduction; No = percentage of patients with no PSA reduction; PCa = prostate cancer.

Table 2
Correlation between change in prostate specific antigen (PSA) level and prostate cancer (PCa) in both groups.

	Group 1 ($n = 44$)			Group 2 ($n = 42$)		
	+Pca	−Pca	p	+Pca	−Pca	p
Δ PSA	−1.02 ± 2.9	1.03 ± 2.4	0.008	−0.08 ± 2.3	−0.32 ± 2.5	0.77

Data are presented as mean ± standard deviation.
Δ PSA = change in prostate specific antigen.

Table 3
Correlation between change in prostate specific antigen and Gleason score.

	Gleason 2−6	Gleason 7	Gleason 8−10	p
Total ($n = 37$)	0.4 ± 2.6	−1.3 ± 1.4	−1.7 ± 3.6	0.02
Group 1 ($n = 22$)	0.6 ± 2.7	−1.3 ± 1.6	−1.7 ± 3.6	0.06
Group 2 ($n = 15$)	0.03 ± 2.5	−1.4 ± 1.2	NA	0.18

Data are presented as mean ± standard deviation.
NA = not applicable.

Category 4) are not caused by bacteria,[12] thereby not requiring treatment. Additionally, other studies failed to find a correlation between PSA and prostate inflammation,[13–15] depicting prostate volume rather than inflammation as a major confounding factor causing PSA elevation.

Another reason that might support the use of antibiotics is to avoid unnecessary prostate biopsy. TRUSPB is the gold standard procedure for PCa diagnosis.[16] It is indicated in the context of serum PSA elevation with or without abnormal DRE. Although this procedure is irreplaceable, it is still associated with various unavoidable complications such as sepsis, hematuria, and rectal bleeding.[17,18] Fever and sepsis are perhaps the most influential causes of postbiopsy morbidity and the most common reason for hospitalization after TRUSBP. Severe infections were initially reported in < 1% of cases, but have increased as a consequence of antibiotic resistance.[19] In a study of 455 patients undergoing TRUSBP, Al Rumaihi et al[17] reported the occurrence of postbiopsy fever in 5.9% of cases. An obvious increase in the overall risk of postbiopsy infection has been noticed over the past decade. The principle reason for this observation is the unjustified use of antibiotics.[20] An increasing rate of quinolone resistance is present as a dramatic 22% of men were found to have quinolone-resistant flora on prebiopsy rectal swabs.[21] In a study by Song et al,[22] extended spectrum of beta lactase producing *Escherichia coli* were isolated from blood samples of 95.9% of patients with postbiopsy infections. All these reasons support against the use of empiric antibiotics for

high PSA, as such an act may increase the risk of postbiopsy infection with resistant organisms.

Few studies have specifically explored the use of antibiotics in patients with an elevated PSA level. Saribacak et al[2] compared 50 patients to whom fluoroquinolone was administered prior to TRUSBP with an equal control group. A significant PSA decrease was observed in the treatment group at repeat measurement and the drop was also more significant in patients without PCa than with PCa. In another study, 215 culture-positive prostatitis patients with a high PSA received 2-months treatment with levofloxacillin and were followed with another reading. A significant reduction in PSA level was noted to the extent that TRUSBP was not performed in 53 out of 215 patients. However, seven (4%) out of the remaining 162 patients who underwent TRUSBP had PCa.[23] Azab et al[4] conducted a prospective study on 142 patients with an elevated PSA and positive-expressed prostatic secretions. All patients received treatment with antibiotics for 6 weeks and were followed with another PSA reading. Despite finding a significant decrease in PSA level up to 41%, PCa was detected in patients with PSA levels less than 2.5 ng/mL.

Schtricker et al[7] failed to find any advantage for administration of antibacterial therapy. Out of 65 men who received antibiotics, and 70 men who did not receive antibiotics, PSA reduction was equally noticed in 40% of patients from both groups.[7] This study failed to find any statistically significant difference in PSA levels between patients receiving antibiotics and patients not receiving antibiotics (Table 1). Additionally, in patients receiving antibiotics, PSA reduction was statistically significant in those who were found to have PCa (Table 2). The significance of the latter finding suggests that the drop in PSA after antibiotic treatment, may not necessarily rule out cancer. In fact, a link between prostate inflammation and PCa has been established which may explain why PSA may respond to antibiotic therapy in PCa patients. A large, multiracial study reported an increased risk of PCa in patients having a history of prostatitis (relative risk = 1.3, 95% confidence interval: 1.10—1.54).[24] Furthermore, a recent study by Stark et al,[25] suggested that chronic inflammation may be associated with PCa progression. Unfortunately, inflammation is commonly underreported when cancer is detected in tissue samples, an obstacle that prevented us from confirming such an association in this study.

This is the first study to correlate PSA change with Gleason score. Although no statistically significant difference in Δ PSA was noticed between PCa patients from Groups 1 and 2, overall a significantly higher Gleason score was found in patients with the most reduction in PSA level (Table 3). This eerie result is not necessary uncommon. In a recent study by Izumi et al[26] evaluating 642 patients who underwent TRUSBP, although not statistically significant, the percentage of Gleason score 8—10 in patients with a PSA level of < 3.5 ng/mL was higher than that in patients with a PSA level between 3.5 ng/mL and 10 ng/mL. In another study evaluating outcomes of patients with Gleason score 8—10 PCa, patients with a PSA level ≤ 2.5 ng/mL had proportionately worse outcomes than their counterparts with higher PSA levels.[27]

One limitation to this study is not using a PSA range of 4—10 ng/mL as an inclusion criterion. However, this could also be considered a strength as it mimics routine practice exploring the value of empiric antibiotic therapy in such patients. Another limitation is not using a placebo group which could have made the study double blind.

5. Conclusion

The empiric use of antibiotics for PSA elevation is not justified as it can delay PCa diagnosis. Significant PSA reductions existed with PCa, and more importantly in patients with higher Gleason grades.

Conflicts of interest

Sources of funding

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