Can Antibiotic Therapy avoid Unnecessary Biopsy in Males with Marginally Elevated PSA Levels?

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ABSTRACT

Introduction: Prostate specific antigen (PSA) is widely used for screening and early detection of prostate cancer. However, PSA is not a cancer specific tumor marker and the levels would be influenced by coexistent diseases particularly prostatic infections, which are common in third world countries. We evaluated the effects of antibiotic treatment on serum total prostate specific antigen, free prostate specific antigen and percent free prostate specific antigen in men with prostate specific antigen between 4 and 10 ng/ml with no hard areas on digital rectal examination (DRE).

Materials and Methods: 142 men with PSA levels between 4 and 10 ng/dl, were enrolled in this prospective study. Exclusion criteria were patients with urinary tract infection as evidenced by pyuria and documented history of prostatitis. Basal total-PSA (t-PSA) and free-PSA (f-PSA) were determined using immunometric assay technique based on chemiluminescence method. Ofloxacin (200mg twice a day was given orally for 1 week followed by 100mg at bedtime for three weeks) was given in these patients. t-PSA and f-PSA levels were repeated 4 weeks after therapy. Patients with persistently raised PSA (>4 ng/ml) after a course of antibiotic therapy underwent prostate biopsy whereas patients with PSA reductions were followed up with regular PSA assays to note for any increase in values.

Results: The mean age of the patients was 67 ± 6.7 years. The patients were randomly divided into 2 groups. Group A consisted for men who were given antibiotic therapy for a period of 4 weeks. Men followed up with repeat PSA levels without antibiotics were categorized as Group B. Mean t-PSA was 6.09 ± 1.34 and 3.84 ± 1.25 ng/ml before and after treatment, respectively (mean change -2.25 ± 0.52, $p < 0.001$) in Group A. 47 out of 102 (46.07%) in Group A had a reduction in PSA levels < 4 ng/ml after antibiotic therapy. Group B included 40 patients, out of which 10 patients (25 %) had reduction in PSA levels during one month of follow up. Out of the 55 patients in Group A, where the PSA levels did not decline with antibiotic therapy, who underwent prostate biopsy, 30 (54.54%) patients did not harbor malignancy. 19 out of these patients had chronic prostatitis on histological examination. There was an increase in %f-PSA by 7.19% in patients on antibiotic therapy and 9.49% in patients without antibiotics.

Conclusions: Antibiotic therapy significantly reduced PSA levels in males with borderline elevated PSA. Empirical antibiotic treatment in asymptomatic patients with a PSA level 4-10 ng/ml and a normal DRE could be used to select candidates for prostate biopsy, especially in third world countries where incidence of subclinical prostatitis is more prevalent. % f-PSA seemed to be a better tool to evaluate patients after a course of antibiotics.

Keywords: PSA Levels, Prostatic Biopsy, Unnecessary Biopsies, Antibiotic Therapy

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INTRODUCTION

PSA has been widely used for screening and early detection of prostate cancer. However, PSA is not a cancer specific tumor marker. Other physiological and benign conditions such as benign prostatic enlargement and prostatitis in addition to cancer can increase serum PSA and lead to potentially unnecessary biopsy procedures. Studies revealed that only 20% to 30% of men with PSA between 4 and 10 ng/ml will actually have prostate cancer, meaning that the remaining 70% to 80% will undergo unnecessary biopsies.[1] In these patients Benign Prostatic Hyperplasia (BPH), prostatitis and UTI are often given as the more common benign reasons for a high serum PSA level. A combination of history, a Digital Rectal Examination (DRE) and serum PSA level helps to differentiate many of these conditions, but a significant proportion remain indistinguishable. Such men do present clinicians with a difficult diagnostic dilemma; who needs a biopsy?

It is known that disruption of the natural anatomic and

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physiologic barriers between the prostatic milieu and the bloodstream is an important factor determining increased serum prostate-specific antigen (PSA) levels. Inflammation alters prostatic duct integrity causing PSA leakage from the acini and ductal lumina.[2]

In 1989, Dalton was the first to report total PSA elevation in acute prostatitis.[2] Many experimental and clinical studies suggested a correlation between acute and chronic prostatitis with increased serum PSA levels.[3,4] Subclinical inflammation of the prostate could elevate serum PSA in asymptomatic patients without clinically detectable prostate cancer. The prevalence of chronic prostatitis in the Indian population has not been well studied, though it is presumed that the condition may be prevalent.

Although prostatitis may cause PSA elevation, asymptomatic patients are not routinely screened for this disease before Transrectal biopsy. Prostate biopsy can be a painful procedure with potentially significant morbidity. A valid goal in management must therefore be to minimize the rate of negative biopsy. Much effort has been directed at differentiating between benign and malignant causes of an elevated serum PSA. The most important of these approaches include PSA density, PSA velocity, free to total PSA ratio and age-specific reference PSA ranges.

The aim of our study was to investigate the possibility of reducing the number of prostate biopsies in patients with borderline PSA elevation by administering a course of antibiotics. We evaluated the effects of antibiotic treatment on serum total prostate specific antigen, free prostate specific antigen and percent free prostate specific antigen in men with prostate specific antigen between 4 and 10 ng/ml and normal digital rectal examination (DRE).

MATERIALS AND METHODS

During a period of 2 years healthy men attending the urology clinics of our hospital having PSA values between 4 and 10 ng/dl, were enrolled. The same qualified Urologist performed DREs and it was considered normal if there was no palpable induration, nodule or any suspicion of malignancy.

Exclusion criteria were patients with urinalysis evidence of acute urinary tract infection (pyuria/ >5 Pus cells/ HPF in centrifuged samples and bacteriuria), those with a prior diagnosis of prostate cancer and acute prostatitis, presence of an indwelling catheter or previous prostatic surgery of any nature, recent instrumentation of the genitourinary tract (in the last 3 months), any form of hormonal manipulation or a history of allergy to Ofloxacin. A total of 152 men were included in the study. The patients were randomly divided into 2 groups. Group A included 102 patients were given Ofloxacin (200 mg twice a day orally for 1 week followed by 100mg at bedtime for further three weeks). PSA levels were repeated after 4 weeks. 40 patients with elevated PSA were followed up with repeat levels for 4 weeks without antibiotic therapy (Group B). Basal total-PSA (t-PSA) and free-PSA (f-PSA) were also determined in the two groups. Percent free PSA was calculated as the ratio of free PSA-to-total PSA. Samples were assayed in streptavidin coated tubes by using immunometric assay technique (COBAS® INTEGRA 6000, Roche Diagnostics, Switzerland) based on chemiluminescence method. All samples were analysed in the same laboratory to prevent the variations in measurement. A comprehensive internal quality control programme was followed and results were released after calibrating values between mean ±1SD. This internal quality control analysis was performed daily.

Patients with raised PSA (>4 ng/ml) after a course of antibiotics in Group A underwent prostate biopsy whereas patients with PSA reduction (<4 ng/ml) were followed up.Biopsy results were classified as benign or those showing cancer

Differences in variations in PSA levels between patients with and without prostate cancer were analyzed by Student's t test. Comparisons of PSA variations before and after antibiotic treatment were evaluated by paired t test. ROC curves were used to describe the performance of diagnostic value of PSA modifications. Statistical analysis was done using MedCalc (MedCalc® v 15.4, Belgium) software. A p value less than 0.05 was considered significant.

RESULTS

The mean age of patients was 67 ± 6.7 years. 47 out of 102 patients in whom antibiotic therapy was given showed a reduction in repeat PSA levels < 4 ng/ml. (46.07%). In Group B, only 10 out of 40 patients had

Table 1. Effect of antibiotics on PSA

	n=102			
	Pre Antibiotic Therapy	Post Antibiotic therapy	% Change	p value
t-PSA (ng/ml)	6.09 ± 1.34	3.84 ± 1.25	-36.9	0.001
f-PSA (ng/ml)	1.82 ± 0.48	1.23 ± 0.31	-32.4	0.012
% f-PSA	29.88	32.03	+7.19	

Table 2. Change in PSA without antibiotics

	n=40			
	Basal levels	Repeat Levels after 4 weeks	% Change	p value
t-PSA (ng/ml)	6.82 ± 1.23	5.61 ± 1.36	-17.7	0.124
f-PSA (ng/ml)	1.71 ± 0.36	1.54 ± 0.29	-9.9	0.095
% f-PSA	25.07	27. 45	+9.49	

reduction in PSA < 4ng/ml. (25%) (p<0.001)

The change in PSA levels in patients with/without antibiotic therapy has been shown in **tables 1, 2.**

There was statistically significant reduction in total PSA levels (36.9 %, p = 0.001) and free PSA (32.4 %, p = 0.012) in patients who were given antibiotics. On the other hand the change of t-PSA and f-PSA in patients without antibiotics was only 17.7 and 9.9% respectively which was statistically insignificant.

Out of 55 patients who underwent prostate biopsy in Group A, 30 (54.54%) patients did not harbor malignancy. 19 out of these 30 patients (63.33%) had chronic prostatitis on histological examination. The comparison of variables pre and post antibiotic therapy in patients undergoing biopsy is depicted in **table 3.**

Although mean total PSA (t-PSA) and Free-PSA (f-PSA) decreased after treatment in both groups, the reduction of t-PSA in patients with prostate cancer was insignificant (p = 0.14). The change in f-PSA was significant in only those patients who harbored malignancy. On the other hand, the change in % f-PSA (f/t PSA ratio) was statistically significant in both the patients having benign disease as well as malignancy. Hence % f-PSA seemed to be a better tool to evaluate patients after a course of antibiotics.

Receiver Operating Characteristics (ROC) curve analysis of both parameters (t-PSA and f-PSA) revealed that f-PSA was more sensitive for detection of malignancy (AUC – 0.82 ± 0.15) as compared to t – PSA (AUC – 0.68 ± 0.19).

Table 3. Comparison of variables pre and post antibiotic therapy in patients undergoing biopsy (n = 55)

	Prostate Cancer (25)				Benign (30)			
	Pre Antibiotic Therapy	Post Antibiotic therapy	% Change	p value	Pre Antibiotic Therapy	Post Antibiotic therapy	% Change	p value
t-PSA (ng/ml)	6.67 ± 1. 69	5.57 ± 1.62	-16.4%	0.14	6.12 ± 1.31	4.56 ± 1.61	-25.4%	0.001
f-PSA (ng/ml)	1.17 ± 0.43	1.04 ± 0.54	-11.1%	0.012	1.91 ± 0.47	1.51 ± 0.47	-20.9	0.092
% f-PSA	17.54	18.6	+6.04%	0.002	31.05	33	+6.28%	0.015

DISCUSSION

PSA has been identified as a gamma-semino protein from the seminal plasma. Wang et al. reported the possibility that PSA might be a tumor marker for prostate cancer and Papsidero et al. applied PSA to the clinical diagnosis of early prostate cancer and the follow- up of prostate cancer patients.[5,6] However, because PSA is a serine protease secreted by prostate epithelial cells as well as primary gastric, mammary gland, and breast cancer tissue, PSA is nonspecific to the prostate.[7] Moreover, the PSA level is increased by prostate cancer as well as by BPH, prostatitis, and other circumstances such as prostate biopsy, DRE, and acute urinary retention. This leads to potentially unnecessary biopsy procedures in patients with borderline elevated PSA levels. Studies have revealed the lack of specificity of PSA measurement as the only biopsy indicator.

Prostate biopsy has been generally recommended for men with total PSA greater than 4 ng/ml and palpably normal DRE as the rate of prostatic cancer detection in this population is 20% to 30%. This rate reflects the lack of specificity of PSA and remains a major problem for using PSA to screen for prostate cancer. Prostatic inflammation is thought to be a cause of PSA increase and several studies investigated the relationship between increased serum PSA and asymptomatic prostatic inflammation.[8,9] Some of these studies revealed that subclinical prostatic inflammation contributes to PSA increase in patients without clinically detectable prostate cancer. In contrast, some others reported no significant influence of prostatic inflammation on serum PSA.[10,11]

Several studies regarding this issue used expressed prostatic secretion (EPS) or first urine following the prostatic massage (VB3) to demonstrate prostatic inflammation.[9] In our study we did not use EPS or VB3, as in daily practice many urologist prescribe antibiotics for men with a newly increased PSA. The identification of chronic prostatitis was made based on clinical history and urine microscopy only.

The results of our study showed that antibiotic treatment resulted in significant reduction in PSA in patients with marginally elevated marker levels. This reduction in PSA was 36.9 % in our study and it has been reported as 23.4 to 30 % in other studies.[12] Although this reduction may partly be due to antibacterial therapy of prostate in-

flammation, one could argue that a significant degree of biological variation could also be observed in PSA in normal men. However, Komatsu and colleagues observed a physiological fluctuation in PSA from only 10% - 20% of men in a screening population.[13] The reduction in PSA levels in our study group was upto 46% of patients.

Bozeman et al reported that in 44 of their 95 patients (46.3%) with PSA greater than 4 ng/ml, serum PSA decreased to less than 4 ng/ml after antibiotic treatment and these 44 patients were considered to have no clear indication for biopsy.[12] Karazanashvili and Managadze detected no cancer among their 37 patients in whom PSA concentration decreased to less than the 4 ng/ml level after antibiotic treatment.[14] In the study by Kaygısız et al PSA values decreased to less than 4 ng/ml after antibiotic therapy in 18 of 48 patients (37.5%) and 10 of these 18 patients underwent biopsy. None of these 10 patients had prostate cancer on biopsy.[9] In the study by Kobayashi et al the treatment response was a PSA decrease greater than 20% from baseline and 15 patients had such a response. Of these 15 patients, 9 underwent biopsy and had no cancer. The authors reported that watchful observation may be an optional tool for patients showing a significant PSA decrease following antibiotic treatment.[15]

It has been reported that % f-PSA would increase after prostatitis therapy.[16] Kaygısız et al also reported significantly reduced f-PSA and significantly increased % f-PSA after antibiotic therapy.[9] In our study PSA reduction to less 4 ng/ml was seen in 47/102 patients (46.07%). Like mean total PSA, in our study mean f-PSA also decreased after treatment and % f-PSA increased.

Contrary to the above studies few authors have doubted the benefit of antibiotic therapy in reducing the identification of prostate cancer. Baltaci and colleagues observed that antibiotic therapy would decrease serum total prostate specific antigen, however it would not decrease the risk of prostate cancer even if the prostate specific antigen decreases to less than 4 ng/ml. Therefore, prescribing antibiotics for asymptomatic men with a newly increased prostate specific antigen may not be an appropriate method of management according to their study.[17]

CONCLUSIONS

Empirical antibiotic therapy with Ofloxacin significantly reduce PSA levels in males with clinically benign prostate with borderline elevated PSA (Between 4 – 10 ng/ml). A repeated value of PSA after one month course of antibiotics could help to select patients requiring prostate biopsy. % f-PSA seemed to be a better tool to evaluate patients after a course of antibiotics. Unnecessary prostate biopsies in patients with borderline elevated PSA could thus be avoided especially when increased incidence of subclinical prostatitis in community is anticipated.

END NOTE

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