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Original Research Article.

Raised Serum Prostate Specific Antigen Levels with Negative Digital Rectal Examination, Is Immediate Prostate Biopsy Warranted: Retrospective Study

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ABSTRACT

Introduction: S. PSA is an important tool in diagnosing Prostate cancer but is not disease specific per see. Half of men who had one abnormal PSA level subsequently had normal levels. A second normal PSA level avoids a considerable number of unnecessary prostate biopsies in a select group of patients. The study aimed to evaluate role of antibiotic treatment in reducing the number of prostate biopsies in patients with upfront raised S. PSA levels with negative digital rectal examination.

Methods: We conducted a retrospective analytical study in patients who had Benign Prostatic Hyperplasia (BPH) with serum Prostate specific antigen (PSA) levels greater than four ng/ml, a negative digital rectal examination and no overt signs of infection. Data collected included patients age, comorbidities, baseline PSA levels, second PSA levels after four weeks of antibiotics and third PSA, free PSA, % free PSA and PSA density after six weeks of antibiotics in patients with PSA levels between four to ten ng/ml. Whether prostate biopsy was performed eventually and its results. Data is expressed as Mean±SD, Median or proportions; paired t-test and Sign test was applied as appropriate.

Results: A total of 64 patients were taken into study and 44 met the inclusion criteria. Their average age was 66.84± 10.34 years. The mean difference in first and second PSA level was 13.37±16.10 for 44 patients and second and third PSA level was 0.34 ± 1.02 for 21 patients. There was statistically significant difference in PSA 1 and PSA 2 levels (p<0.000) after four weeks of antibiotic course and no statistically significant difference in PSA 2 and PSA 3 levels (p=0.664) after six weeks of antibiotics. Eleven (25%) of these patients underwent prostate biopsy; the pathologic findings were prostate cancer in six (54.54%), BPH with chronic prostatitis in three (27.27%) and BPH in two (18.18%).

Conclusions: Antibacterial therapy to patients with upfront raised S.PSA obviates the need for prostate biopsy in majority of patients.

Key Words: Prostate specific antigen (PSA), Benign Prostatic Hyperplasia (BPH), Antibiotic, Biopsy.

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INTRODUCTION

The prostate specific antigen (PSA) is one of the most important cancer marker used in urological practice amongst the aged men presenting with LUTS (Lower urinary tract symptoms) in urology clinics. Certain countries have PSA screening programmes but utility of PSA screening and the issues of overdiagnosis and overtreatment are still overshadowing the benefits of screening.[1,2] Prostate cancer diagnosis is driven most of the time by elevation in serum PSA levels, which triggers a prostate biopsy.[3] However, PSA is far from ideal as a tumour marker, as its accuracy/specificity is low, and leads to many unnecessary prostate biopsies.[4] PSA variability has been extensively investigated and EAU guidelines recommend a second PSA test, before any prostate biopsy.[5] It is reported in literature that nearly half of men who had one abnormal PSA level subsequently had normal levels.[6] Singh et al,[7] reported that a second normal PSA level avoids a considerable number of unnecessary prostate biopsies. The elevated PSA levels can be dealt with the use of empiric antibiotic treatment followed by a repeat PSA, or repeat PSA measurement after 1-2 months or immediate prostate biopsy.[8-13] The use of antibiotics appears to be more rational, given that sub clinical prostatitis and not malignancy leads to the majority of cases of spurious PSA elevation.[8-14] In order to deal more rationally with raised PSA levels, we conducted a retrospective study at our institute for evaluating the effect of antibiotics on PSA levels and role of free PSA, % free PSA and PSA density in obviating the need for prostate biopsy.

MATERIALS AND METHODS

We conducted a retrospective analytical review of all the patients of BPH seen in urology outpatient department in government tertiary care centre in Punjab, between August 2017 and December 2021 who had upfront raised S.PSA levels, a negative digital rectal examination but tender prostate and no overt clinical signs of infection. Patients with retention urine on per urethral catheter, previous prostate surgery, positive DRE (Nodular or Hard Prostate), with previous negative biopsies and Prostatic abscess were excluded from study. The data collected included patients age, comorbidities, baseline S. PSA levels on First visit (PSA 1), whether standard (Levofloxacin 500mg) or culture specific antibiotic therapy had been given for four weeks before the second PSA measurement on second visit (PSA 2) and if it was extended for another two weeks in patients whose PSA levels had fallen drastically (≥30%) but still in range of four to ten ng/ml. Whether Total PSA (PSA 3), free PSA, % free PSA and PSA density were measured at end of total Six weeks in these patients on Third visit, (Table 1). All patients received NSAIDS also for two weeks. The patients with PSA level between four to ten ng/ml and had not undergone biopsy were followed up for one year. All the samples were analysed in the biochemistry laboratory of our institution by ELISA method for S. PSA estimation. Whether a finger guided six core prostate biopsy (as per available resources) was performed eventually and its results. All patients received injection amikacin one gm i.v on the day of biopsy and Tablet ciprofloxacin +tinidazole for three days after biopsy. Biopsy was done with BARD MAX-CORE Disposable core Biopsy Instrument with sample notch length of 1.9 cm, penetration depth of 22mm and gauge size and needle length of 16g x 16 cm. Six core finger guided prostate biopsies were taken in every patient. Data was analysed using statistical package for social sciences. Data is expressed as Mean±SD, Scores (Median and Interquartile range) or proportions. Paired t-test and related sample sign test was applied to study the effect of antibiotics on S.PSA levels as appropriate. A p-value of less than 0.05 was considered statistically significant.

Table 1: Number of patients with PSA levels on different visits and after 4 or 6 weeks of antibiotic course.

S. No		PSA 1 (First Visit) Baseline	PSA2 (Second Visit)	PSA 3 (Third Visit)	FREE PSA/ % FREE PSA	PSA Density
1.	**No. of Patients**	N=44 >4ng/ml	N=44 >4ng/ml & ≥30%↓ N =21 < 4 ng/ml &≥30%↓ N=17 >20% ↑ N=4 <10% ↓ N=2	N=21 (4-10 ng/ml) N=15 < 4 ng/ml N =6	N=21/ N=21	N=15
2.	**Antibiotic course**	Yes (4 weeks) Levofloxacin 500 mg OD or culture specific N=44	Yes (Another 2 weeks) Levofloxacin 500mg OD or culture specific N=21			

Table 2: Paired Samples Statistics

S. No	PSA	No	Mean	Std. Deviation	Std. Error Mean
Pair 1	**PSA1 (Baseline)**	44	21.22	14.57	2.19
	PSA2 (After 4 wks of Antibiotics	44	7.85	10.27	1.54
Pair 2	**PSA2 (After 4 wks of Antibiotics)**	21	5.65	1.12	.245
	PSA3 (After 6 wks of Antibiotics)	21	5.31	1.87	.409

Table 3: Paired T-test on S.PSA levels, Baseline & 4 wks.

S. No.	PSA	No.	Mean	Std. Deviation	Std. Error Mean	95% Confidence interval (Difference)		t	df	Sig.(2-tailed)
						LB	UB			
1.	**PSA1 (Baseline)- PSA2 (After 4 wks of Antibiotics)**	44	13.37	16.10	2.42	8.48	18.27	5.51	43	.000

Table 4: Related Samples Sign Test on S. PSA levels, 4wks & 6 wks.

S. No.	PSA	No.	Mean difference ±SD	Median of difference	Min.	Max.	Range	Inter-quartile Range	Z	Sig.(2-tailed)
1.	**PSA2 (After 4 wks of Antibiotics)- PSA3 (After 6 wks of Antibiotics)**	21	0.34± 1.02	0.17	-1.08	2.50	3.58	1.57	-.436	.664

Table 5: Number of patients who underwent Prostate biopsy (Based on PSA Parameters) and its outcome

S.No		PSA 2 ↑with >20% Variation	PSA 2 ↓with <10% Variation	% FREE PSA <25%	PSA Density >0.15	Prostate Size (cc) (Mean±S.D)	Prostate Biopsy	Biopsy Result
1.	No. of Patients	4(9.09%)	2(4.54%)	5(11.36%)	5(11.36%)	51.93± 13.84	11(25%)	
2.	Carcinoma Prostate							6(54.54%)
3.	BPH with Chronic Prostatitis							3(27.27%)
4.	BPH							2(18.18%)

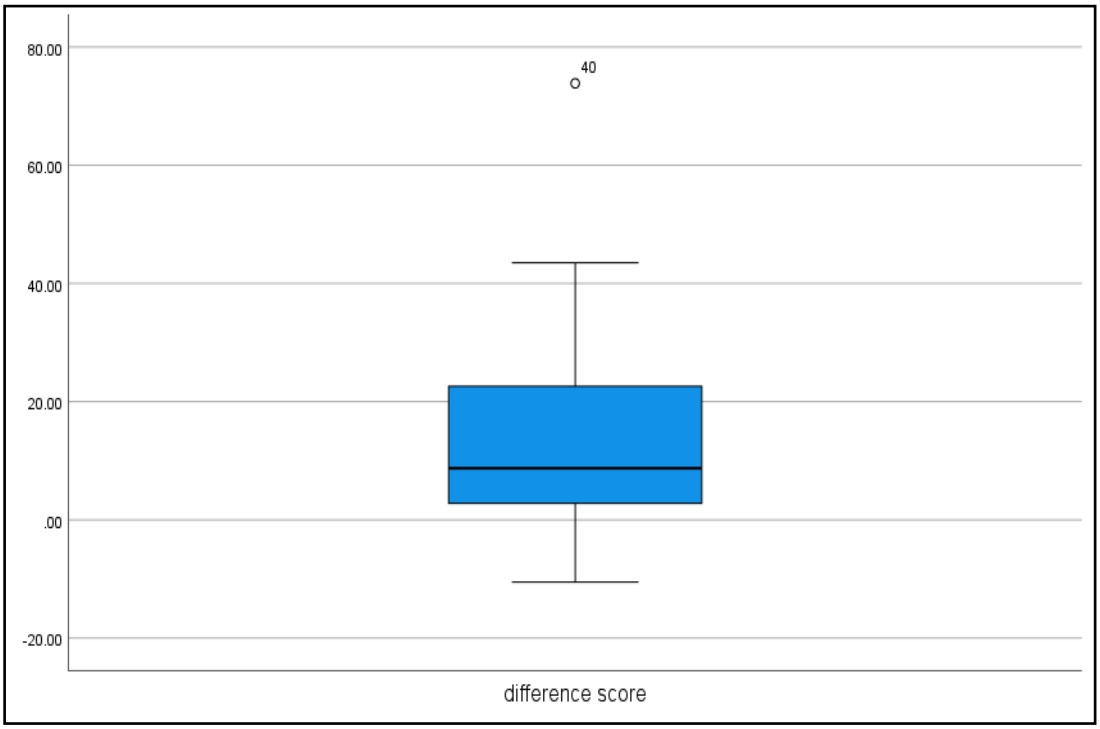

Figure 1: Box Plot of difference in score between Baseline & four weeks of Antibiotics.

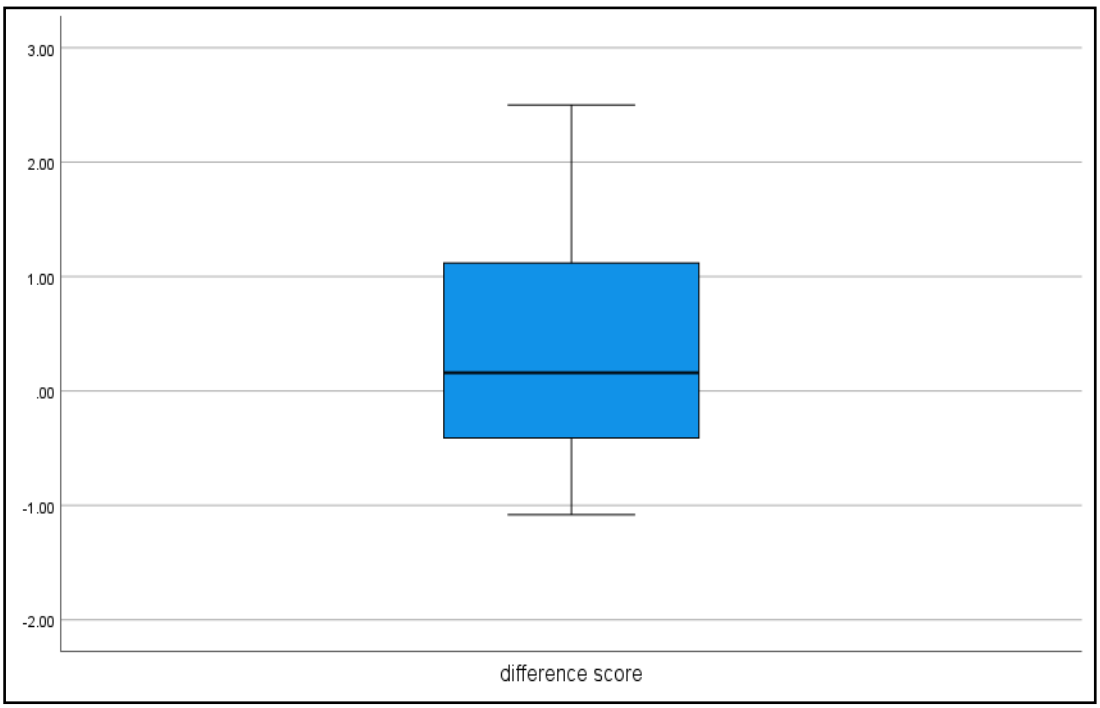

Figure 2: Box Plot of difference in score between four and six weeks of Antibiotics.

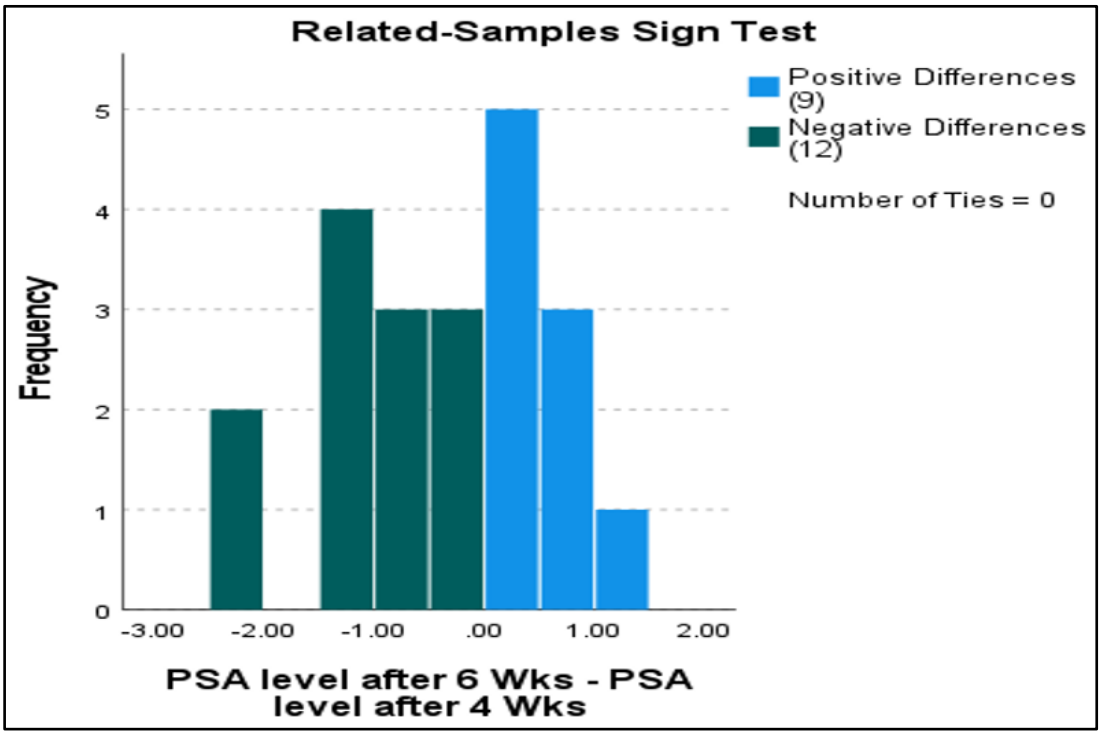

Figure 3: Related Samples Sign Test for 21 Patients (4 & 6 wks of antibiotics)

RESULTS

A total of 64 patients were taken into study and 44 met the study inclusion criteria within the study period. Twenty patients were excluded as they had presentation of retention urine due to BPH with raised PSA level and were on catheter. The average age was 66.84 ±10.34 years. There were 22(50%) patients of Diabetes Mellitus,19(43.18%) of Hypertension, 2(4.5%) of CAD, one each (2.27%) of COPD, Renal stone disease, Cholelithiasis, Fistula-in-ano and Left inguinal hernia. The average initial PSA and second PSA level after four weeks of antibiotic course for 44 patients and average second PSA and third PSA level after another two weeks of antibiotic course for twenty patients is shown in (Table:2). : A paired-samples t-test was used to determine whether there was a statistically significant mean difference between the S.PSA levels when 4 weeks of antibiotics were used as compared to no antibiotics. Data are mean±standard deviation, unless otherwise stated. One outlier was detected which was more than 1.5 box length from the edge of box in a boxplot. Removal of its value did not alter the result, so it was kept in the analysis. The assumption of normality was not violated, as assessed by Kolmogrov-Smirnov test (p= .031), Fig:1. PSA decreased after antibiotic use of 4 weeks (7.85±10.27) as opposed to without antibiotics (21.22±14.57), a statistically significant decrease of S.PSA levels as compared to no antibiotic use of 13.37±2.42, t(44)=5.51, p<.000, d=16.10. There was statistically significant difference between means (p<.000), (Table :3). The data for 21 patients was skewed as assessed by Kolmogrov-Smirnov test (p= 0.200) but there were no outliers, Fig: 2. A sign test with continuity correction was conducted to determine the effect of six weeks of antibiotics use on S. PSA levels. Data are median unless otherwise stated. S. PSA decreased after six weeks of antibiotics; a median decrease in the difference of 0.17ng/ml. Of the 21 patients recruited to the study, the six weeks of antibiotics elicited a decrease in S. PSA levels in twelve patients whereas it marginally increased in nine patients, Fig:3. The six weeks of antibiotics did not elicit statistically significant median decrease in S.PSA level compared to four weeks of antibiotics. Z=-.436, p=.664. (Table:4). Further free S. PSA, % Free S. PSA and PSA density was considered for decision regarding biopsy. Out of total Eleven patients underwent prostate biopsy; the pathologic findings were prostate cancer in Six, BPH with chronic prostatitis in three and BPH in the remaining two (Table :5).

DISCUSSION

Most of the patients visiting the urology OPD in a tertiary care centre in south-western Province of Eastern Punjab were referred from secondary care Physicians, self-employed Physicians or internal medicine physicians of Medical College itself and already had S.PSA done on the very first visit and it is high. A good number of them have co-morbidities e.g Diabetes mellitus, Hypertension, Coronary artery disease or COPD etc. This is probably a type of selective screening done by physicians without adhering to guidelines. Two randomized trials on prostate cancer screening have not thrown much light on the benefit of screening in general population.[1,2] A US Preventive Task force has substantiated the fact that PSA screening led to overdiagnosis and overtreatment and does not reduce mortality to justify the adverse outcome resulting from the treatment and has given grade D recommendation.[15]

In countries like India where incidence of prostate cancer is lower than the western population, doing PSA for all men after one particular age as recommended in the west ,would not be useful because of limited resources.[16] PSA was adopted as initial screening tool and a cut-off level of 4 ng/ml was suggested ,PSA level as a screening test was started being used clinically based on two clinical trials in early 1990s.[17,18] This cut-off with a sensitivity of 79% and a specificity of 59% became the most commonly used cut-off for TRUSS guided prostate biopsy all over the world.[17,19] The Ideal screening test should have high sensitivity

and specificity but PSA is very organ specific and not disease specific.

According to EAU guidelines, limited PSA elevation alone should not prompt immediate prostate biopsy.[5] Roehrborn et al in 1997,[20] evaluated PSA variations within 90 days and found that only 6% of the patients had the same PSA level on both occasions. They concluded that clinicians should not rely on a single PSA measurement; however, they did not analyse the oncological outcomes of PSA fluctuations. Nordstrom et al,[21] has elaborated on this issue. They evaluated biopsy outcomes of 1686 men from the Stockholm 3 study (STHLM3) with a PSA level between three-ten ng/ml, and two PSA tests were undertaken within eight weeks and before prostate biopsy. According to their analysis, a stable second PSA level increased the risk of high-grade prostate cancer; whilst an increase/decrease in the second PSA level decreased the risk of high-grade prostate cancer. Moreover, they concluded that omitting prostate biopsy for men with PSA values decreasing to levels of less than equal to three ng/ml would save 17% of biopsy procedures, whilst missing five percent of high-grade cancers. More specifically, in our study, omitting prostate biopsy in patients with a decrease in PSA levels of ≥30% and with PSA falling within normal range after four weeks of antibiotics saved 38.63% of biopsy procedures as majority of our referred patients were diabetics(50%) and having tenderness on digital rectal examination, likely having subclinical prostatitis and few, Six(13.63%)of them had positive urine cultures .Moreover, it was seen that patients with an increase in PSA levels of >20% or fall in PSA levels of <10% from baseline at four weeks were at an increased risk of prostate cancer disease and had undergone prostate biopsy in the first go(Table 1).

The use of antibiotics is prevalent among some of the urologists who intended to reduce PSA elevation presumably caused by an inflammatory process. It has previously been suggested that all patients should receive empiric antibiotic therapy for prostatitis or inflammation after their first elevated PSA result and before recommending a biopsy .[7,9,10,12,13,21] There is ,however, a mean variation in the measurements of total, free and percent free PSA that does not appear to be significantly affected by age and total PSA level.[10] Okada et al,[22] assessed high PSA readings due to inflammation and based on histological findings, concluded that acute inflammation within the prostate is a significant contributor to elevated serum PSA levels, especially in patients with small prostates. Schatteman et al,[23] studied the inflammation in prostate biopsies in which there was no cancer and found inflammation in virtually every one of them, even in the ones without any signs of clinical prostatitis. These authors concluded that sub clinical inflammation could cause PSA elevation, emphasizing that nearly half of all clinically asymptomatic men with an elevated PSA level have laboratory signs of prostatitis. They suggested that two weeks of ciprofloxacin administration would result in a drop in the elevated PSA levels of almost 50% of patients with LUTS and normal Digital Rectal Examination (DRE) results, thus avoiding prostate biopsy. This approach, however, requires careful follow up, especially for patients whose PSA levels fail to decrease to normal levels.[8] In Kaygisiz et al,[12] study all 48 of their patients were administered antibiotics and underwent biopsies. The PSA level decreased below four ng/ml in 18(37%) of them and the biopsies of these men were negative for malignancy. The findings for the other 30 men were prostate cancer in 10.8%. These authors suggested that antibiotic therapy should be administered for 3 weeks, regardless of inflammation findings, when PSA levels are mildly high i.e four-ten ng/ml, subsequently followed by the decision of whether or not to carry out biopsy. Bozeman et al, [13] reported that when serum PSA had normalized with treatment there was no longer an indication for transrectal ultrasound guided biopsy, in almost half of their 95 patients diagnosed with elevated PSA and chronic inflammation, suggesting that chronic prostatitis is an important cause of elevated PSA and that when identified, treatment can decrease the percent of negative biopsies.[7] Our study corroborates with that of Kaygisiz et al [2] (37% vs 38.63%) and Bozeman et al (50% vs 38.63%) as 17(38.63%) of our patients had less than four ng/ml of PSA levels after four week of antibiotic course as testified by our results that there was statistically highly significant decrease in S. PSA level after four weeks of antibiotic use. We omitted biopsy in these patients outrightly and findings for other 27 (61.36%) men were that we extended the antibiotics course for two more weeks in patients who had drastic fall in PSA (≥30%) level after four weeks of antibiotics, but their PSA levels were still between 4-10 ng/ml. Our results showed that the S. PSA decreased further on antibiotics, but it was not statistically significant (p=.664). Subsequently we considered the total, free, % free PSA and PSA density on third visit to further crop down on the biopsy procedures. At the end of 4 or 6 weeks we did biopsy in total 11 patients out of which six had prostate cancer, three had BPH with chronic prostatitis and two had BPH, thus omitting biopsies in another16(36.36%) patients, thus totalling 33(75%) patients. On the other hand, Habermacher et al,[24] noted that almost all cases of asymptomatic prostatitis are not caused by bacteria, thus eliminating the need for antibacterial therapy. Any elevation of PSA, be it spurious or true, should be an indication for repeat PSA testing, but we advocate withholding antibiotics until a bacterial cause has been identified.

The influence of inflammatory foci on total and free PSA concentrations remains a controversial issue.[9] Ozen et al,[14] claim that benign prostatic hyperplasia (BPH) and BPH with prostatitis appear to be more frequent causes of PSA elevation. In our study three (6.81%) and two (4.54%) of our patients were found to have BPH with prostatitis and BPH respectively. These are fewer than that of Ozen et al[14] as we used prolonged antibiotic course (4 weeks in all and 6 weeks in some) along with NSAIDS for two weeks which may have eradicated the sub clinical infection or inflammation. A study by Scardino,[11] criticized the unjustified use of antibiotics in a group of patients contrary to ours and emphasized the various inherent disadvantages associated with this approach, such as cost, toxicity and promotion of resistant bacterial species development that exposed the patient to more resistant and aggressive sepsis should the biopsy be eventually done. But according to our study there appeared to be an advantage for antibacterial therapy use for decreasing upfront raised PSA levels (> four ng/ml), especially in patients who had BPH and tender prostate on DRE, associated with diabetes mellitus and obviously with patients having positive urine culture with prostatitis. Moreover, it obviates the need for unnecessary prostate biopsies as they are associated with complications like bleeding, UTI, urosepsis, injury to rectal and urethral mucosa, catheterization, apprehension and of course a cost per see of the procedure.

CONCLUSION

Antibacterial therapy, impirical or culture specific, for four weeks to patients with upfront raised S. PSA levels especially in diabetics or patients with subclinical prostatitis with tender Prostate and further considering free PSA, % free PSA and PSA density for PSA levels dropped between four-ten ng/ml obviates the need for unwarranted prostate biopsies in two-third of patients.

LIMITATIONS

Our study is limited by being retrospective, relatively small, lack of EPS cultures, dealing with heterogenous co-morbidities, using finger guided technique and not TRUSS guidance, taking only six cores instead of twelve cores which may have missed some of cancers as it is a multifocal disease.

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