

# Effect of empirical antibiotic treatment on prostate specific antigen in men with borderline raised serum prostate specific antigen

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## ABSTRACT

**Introduction:** Raised levels of serum Prostate Specific Antigen (PSA) may not always indicate a malignant condition, and may be due to bacterial prostatitis. It is necessary to avoid an undue suspicion of malignancy and not perform interventions, even needle biopsies, when not indicated. A trial of antibiotic therapy is warranted before such interventions, so that if the PSA levels fall to normal or near normal, the case may be considered a non-malignant condition.

**Objective:** To assess the effect of four weeks Ciprofloxacin treatment on serum Prostate Specific Antigen (PSA) in men with PSA 4-10 ng/ml.

**Materials & Methods:** This Randomized Control Trial (RCT) was conducted in Urology Department, Institute of Kidney Diseases, Hayatabad Medical Complex, Peshawar over a period of six months from February 15 to August 15, 2019. Sixty patients were assigned to the two study groups (30 per group) by block randomization. Treatment Group received Tab Ciprofloxacin 500mg 1 tab per oral at interval of 12 hours for four weeks and Control Group was followed without any treatment for four weeks. Serum PSA level was re-checked after 4 weeks in both the groups. Descriptive and comparative data analysis was done by SPSS 21, keeping  $p \leq 0.05$  as significant.

**Results:** A total of 60 male patients were included in the study. In the treatment group the mean baseline serum PSA level was  $5.4 \pm 0.47$  ng/ml, repeat serum PSA levels was  $3.3 \pm 0.49$  ng/ml and mean change in serum PSA was  $1.95 \pm 0.60$  ng/ml. In the control group the mean baseline serum PSA levels was  $5.4 \pm 0.32$  ng/ml, repeat serum PSA levels was  $4.7 \pm 0.38$  ng/ml and mean change in serum PSA was  $0.6 \pm 0.24$  ng/ml. The mean Repeat Serum PSA and the Change in Serum PSA in the treatment group were significantly lower than the control group ( $p=0.030$  and  $p=0.011$  respectively).

**Conclusion:** Empirical antibiotic treatment in men with PSA 4-10 ng/ml, normal DRE, and normal prostate on TRUS significantly decreases the serum PSA levels and may help to avoid unnecessary biopsies in patients with borderline raised PSA levels.

**Keywords:** Prostate; Prostatitis; Prostatic Hyperplasia; Prostate Cancer; Prostate-Specific Antigen; Anti-Bacterial Agents.

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## INTRODUCTION

Prostate Specific Antigen (PSA) is a serine protease produced by prostate tissue.<sup>1</sup> Normal serum PSA values are less than 4 ng/ml.<sup>1,2</sup> In prostate cancer, its level significantly increases, and men with PSA greater than 4ng/dl are at higher risk for prostate cancer.<sup>3</sup> These patients are usually referred for prostate biopsies. However, increased serum PSA level is also observed in conditions other than cancer, such as benign prostatic hyperplasia (BPH) and prostatitis. Therefore, proceeding for prostate biopsy based upon slightly raised serum PSA level may actually expose patients to unnecessary negative biopsies.<sup>4,5</sup> Different strategies have been employed to decrease the number of unnecessary negative prostate biopsies, dictated by borderline raised PSA level. One way is to repeat the PSA test as an appropriate initial approach in asymptomatic patients with a raised PSA level and a normal digital rectal examination (DRE).<sup>6</sup>

Treatment with antibiotics has been shown to decrease serum PSA level significantly in such patients by treating the underlying inflammation and may provide a cost-effective approach to decrease the number of negative biopsies.<sup>7</sup> The present study was undertaken to assess the effect of four weeks Ciprofloxacin treatment on serum PSA in older men with serum PSA of 4-10 ng/ml.

## MATERIALS & METHODS

This Randomized Controlled Trial (RCT) was conducted in Urology Department, Institute of Kidney Diseases Hayatabad Medical Complex Peshawar over a period of six months (February 15, 2019 to August 15, 2019). The study was approved by the Institutional Research and Ethical Board (IREB) of the hospital. Men aged 50-80 years with serum PSA 4-10 ng/ml, normal DRE, and no hypoechoic lesion in prostate on TRUS were included in the study. Patients with family history of prostate cancer, symptoms or history of acute or chronic prostatitis during the past one year, history of prostate surgery, biopsy or radiotherapy, symptoms of UTI, pyuria > 10 pus cells/HPF in urine on urinalysis, history of catheterization in the urinary system during the last 4 weeks, previous use of a 5- $\alpha$  reductase inhibitor in the last 4 weeks and history of hypersensitivity to ciprofloxacin were excluded from the study.

The patients were assessed with detailed history of lower urinary tract symptoms and physical examination including DRE. All the baseline investigations were done including urinalysis and initial measurement of serum PSA. The serum PSA was measured from blood sample by ELISA technique, before performing DRE. The prostate size was measured by trans-rectal ultrasound. Patients were then assigned to the two study groups randomly by block randomization. Treatment Group received Tab Ciprofloxacin 500mg 1 tab per oral at interval of 12 hours for four weeks and Control Group was followed without any treatment for four weeks. Serum PSA level was re-checked after 4 weeks in both the groups.

Data were analyzed by using SPSS version 21. The findings were expressed as Mean  $\pm$  SD for quantitative variables and frequency & percentages for qualitative variables. Unpaired t-test and Paired t-test were applied to compare the mean change in PSA

level within a group and between the groups respectively, keeping  $p \leq 0.05$  as significant.

## RESULTS

A total of 60 male patients were included in the study (30 each in the treatment and control groups). In the treatment group the mean age of patients was  $63.9 \pm 9.54$  years, while the mean age of patients in the control group was  $67.2 \pm 6.65$  years ( $p=0.893$ ); the mean prostate size in treatment group was  $32 \pm 1.03$  gm compared to  $32 \pm 1.68$  gm in the control group ( $p=0.235$ ); the mean baseline serum PSA levels was  $5.4 \pm 0.47$  ng/ml in the treatment group compared to  $5.4 \pm 0.32$  ng/ml in the control group; repeat serum PSA level in the treatment group was  $3.3 \pm 0.49$  ng/ml, while in the control group it was  $4.7 \pm 0.38$  ng/ml ( $p=0.030$ ); and the mean change in serum PSA in the treatment group was  $1.95 \pm 0.60$  ng/ml compared to  $0.6 \pm 0.24$  ng/ml in the control group ( $p=0.011$ ), as seen in Table 1.

**Table 1: Comparison of mean values of treatment and control groups (n=30 each).**

Variables	Treatment Group (n=30)	Control Group (n=30)	p-value
Age (years)	$63.9 \pm 9.54$	$67.2 \pm 6.65$	0.893
Prostate Size (gm)	$32 \pm 1.03$	$32 \pm 1.68$	0.235
Baseline Serum PSA (ng/ml)	$5.4 \pm 0.47$	$5.4 \pm 0.32$	0.423
Repeat Serum PSA (ng/ml)	$3.3 \pm 0.49$	$4.7 \pm 0.38$	0.030
Change in Serum PSA (ng/ml)	$1.95 \pm 0.60$	$0.6 \pm 0.24$	0.011

## DISCUSSION

The empirical use of antibiotics in older men with serum PSA in the range of 4-10 ng/ml is controversial. The current study analyzed the effect of four weeks empirical use of ciprofloxacin in this group of patients. We observed that empirical use of ciprofloxacin for four weeks in older men with serum PSA significantly reduced serum PSA in comparison to the control group. Our study findings are consistent with the results of Buddingh et al.,<sup>8</sup> who assessed the effect of antibiotics versus placebo or no treatment in men with prostatitis, serum PSA level decreased from 5.2 to 4.0 ng/ml in the antibiotics group (levofloxacin 500 mg once daily for four weeks), there was no decrease in control group ( $p < 0.001$ ).

In another RCT, conducted by Saribacak et al.,<sup>9</sup> Ofloxacin decreased serum PSA level in asymptomatic patients whose PSA levels were between 4-10 ng/ml. In the treatment group the mean change in serum PSA level was  $1.7 \pm 2.31$  ng/ml and in the control group the mean change in serum PSA level was  $0.24 \pm 1.36$  ng/ml. Taha et al.,<sup>10</sup> conducted a similar study. They reported that antibiotic therapy normalize serum PSA level in 16-59% of the patients with 17-80% decrease in serum PSA level.

On the contrary Eggenner et al.,<sup>11</sup> reported that empiric use of antibiotics for asymptomatic men with an elevated serum PSA level does not appear to be of clinical benefit. Furthermore Heldwein et al.,<sup>12</sup> proved that PSA levels tend to fall when repeated after 45 days, regardless of antibiotic use.

The prevalence of chronic prostatitis in older men is high which may be responsible for the rise in serum PSA in these patients.<sup>13</sup> The empiric use of antibiotics to treat underlying inflammation in these patients may be responsible for the decrease in serum PSA. We suggest that antibiotic treatment in patients with a serum PSA level between 4 and 10 ng/mL can be beneficial, before a decision for TRUS-guided prostate biopsy. By reducing the serum PSA levels below the threshold value, many unnecessary prostate biopsies can be avoided.

## LIMITATIONS

The limitations of our study include a small sample size; no prostate biopsies were performed in both groups.

## RECOMMENDATION

Further research is warranted to study the effect of empirical antibiotics use on the outcome of prostate biopsy in asymptomatic men with serum PSA of 4-10 ng/ml.

## CONCLUSION

Our study concluded that empirical antibiotic treatment in men with PSA 4-10 ng/ml, normal DRE and normal prostate on TRUS significantly decreases the serum PSA levels and can be a useful tool to avoid unnecessary biopsies in patients with borderline raised PSA levels. However long-term follow-up is essential in these patients to detect prostate cancer at an early age.

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