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Effect of Antibiotic on Men with Raised Prostatic-Specific Antigen (4-10 ng/ml)

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ABSTRACT

Background: The managing of raised Prostate-Specific Antigen (PSA) in a range of 4 to 10 ng/ml is still controversial among urologists. In addition to prostatic cancer, benign prostatic hyperplasia, and prostatitis is established to increase PSA. PSA reduction after antibiotic therapy might detect those patients in whom biopsy can be avoided or postponed.
Objectives: To evaluate the effectiveness of a 6 weeks levofloxacin course on the serum total PSA level and PSA density (PSAD) in patients with PSA 4−10 ng/ml and ordinary digital rectal examination and ultrasonography results.
Materials and methods: The study conducted at Al-Ramadi Teaching Hospital from February 2016 to December 2019. A total of 177 men with benign prostatic hyperplasia or lower urinary tract symptoms were with a normal digital rectal examination, chronic prostatitis (Expressed prostatic secretion was done before treatment), total PSA 4−10 ng/ml, and ultrasonography findings that did not reveal a hypoechoic lesion in the prostate will be included in this study. Serum PSA and PSAD were measured before, and after treatment with a 6 weeks course of levofloxacin.
Results: The age of our 177 men was ranged from 40−80 years with a mean age of 56.52 years ± 7.253. The mean prostatic size was 49.5 ± 28.5 g (range, 23−150 g). In 89 (50.2%) patients of the 177 men, total PSA has normalized to less than 4 ng/ml after antibiotics treatment. In 56 patients of 89 men had a high level of PSAD. PSAD was normalized (less than 0.15 ng/ml/cm3) after treatment in 49 patients of the 56 patients. A significant reduction in total PSA and PSAD after treatment ($p<0.05$).
Conclusion: A 6 weeks course of levofloxacin reduced the total PSA and PSAD to normal levels in significant patients with lower urinary tract symptoms due to benign prostatic hyperplasia and chronic prostatitis with a normal digital rectal examination and ultrasonographic findings. Therefore, this option of treatment might have a benefit in reducing the number of prostatic biopsies.

Keywords: Prostate-specific antigen; Antibiotics; Prostate cancer; Prostatitis.

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INTRODUCTION

It is usually recognized that prostate-specific antigen (PSA) is one of the important markers screening sensitivity and high tissue specificity for prostate cancer (PCa) [1]. Though, Erol et al [2] have suggested that PSA is not an exact cancer marker and other pathological circumstances can raise its levels.

In daily practice, some urologists use antibiotics to decrease the elevated values of the PSA. If these values remain high following the completion of an antibiotics course, then a prostatic biopsy is suggested. If it significantly reduces, a biopsy might be avoided. PSA is increased not only in PCa, but also increased in other pathological benign conditions include chronic prostatitis and benign prostatic hypertrophy (BPH) [2]. In the past 15 years, there has seen a rise in the identification of PCa at early stages. It is difficult to determine the cause whether inflammation, carcinoma, or hyperplasia in an individual with raised PSA values in the gray zone (4 to 10 ng/ml) particularly if he has a normal digital rectal exami-

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nation (DRE) [3]. Many studies have verified that 20-30% of patients with a PSA level among 4 to 10 ng/ml have PCa. So, 70-80% of those patients' prostatic biopsy is unnecessary [4]. There are three probable substitutes for treating a patient with high PSA: 1) the use of empirical antibiotic therapy and a subsequent test of PSA; 2) one simple repetition of the PSA test next 1-2 months and 3) performing direct prostate biopsy [5]. Investigational and clinical studies have shown an association between acute and chronic prostatitis and the rise of PSA values [6].

We aimed to assess the use of levofloxacin antibiotics for 6 weeks in the reduction of PSA values and whether this has a value in avoidance unnecessary prostatic biopsies.

MATERIALS AND METHODS

The present study conducted at Al-Ramadi Teaching Hospital from February 2016 to December 2019. 177 subjects with BPH or specific symptoms of the lower urinary tract (LUT) were enrolled in the present study. The current study was approved by the scientific committee of the hospital. The patients age included in this study are more than 40 years with a normal DRE, total PSA of 4−10 ng/ml, and there is no hypoechoic lesion on the ultrasonography examination in the prostate. Following the use of the levofloxacin course for 6 weeks, the PSA level was rechecked of the enrolled subjects. Patients with signs of acute prostatitis or chronic bacterial prostatitis, an indwelling catheter, a history of acute urinary retention, pyuria, or history prostatic operation or those on finasteride or dutasteride were excluded from the present study. From all subjects, informed consent was obtained.

General urine examination was done for every patient, if the number of white blood cells > 20 in the examined smear of expressed prostatic secretion (EPS) under the microscope, chronic nonbacterial prostatitis is diagnosed. Serum total PSA and PSA density (PSAD) were measured before and after 6 weeks course of levofloxacin treatment. Serum PSA, PSAD values before and after the antibiotic course were compared. These data were analyzed using IBM SPSS (Statistical Package for the Social Sciences) version 20. The findings were expressed as means ± SD. T-test was used to match the mean values of continuous variables. A P-value < 0.05 was reflected statistically significant.

RESULTS

One hundred seventy-seven subjects were enrolled in the study. The age of our subjects was ranged from 40 to 80 with a mean age of 56.52 years ± 7.253. The mean size of the prostate was 49.5 ± 28.5 g (range, 23−150 g). The mean total PSA of the subjects was 5.6 ± 1.4 ng/ml and 4.05 ± 2.1 ng/ml pre and post-antibiotic course, correspondingly. There was a statistically significant variance in the total PSA (P-value <0.05) Figure 1. The PSAD altered from 0.13 ± 0.04 ng/ml/cm3 to 0.10 ± 0.05 ng/ml/cm3 pre and post-antibiotic course, correspondingly, which also revealed a statistical significant variance (P-value <0.05) Figure 2. After 6 weeks of levofloxacin treatment, the raised total PSA level of 89 patients (50.2%) returned to normal. Fifty-six patients had a PSAD more than 0.15 ng/ml/cm3, the PSAD level returned to normal in 49 patients (87.5%) following 6 weeks of levofloxacin treatment Table 1.

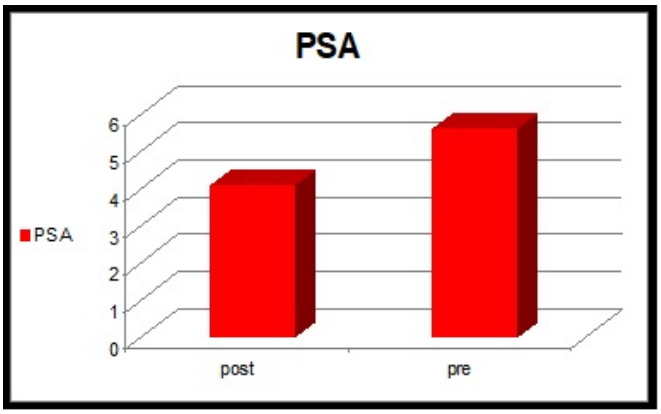

Figure 1. Expression of PSA in 177 patients pre and post-treatment with levofloxacin.

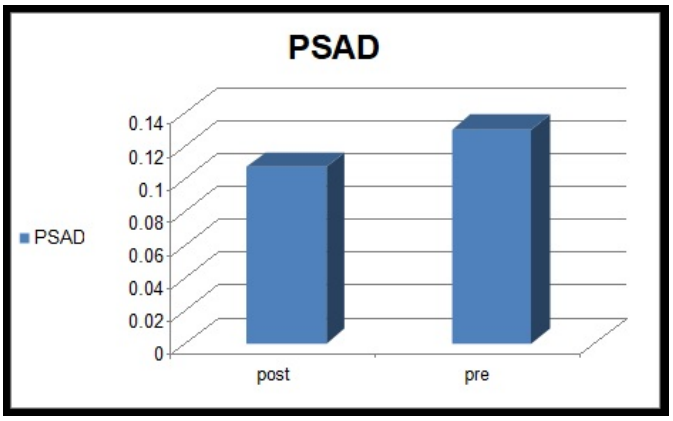

Figure 2. Expression of PSAD in 177 patients pre and post-treatment with levofloxacin.

DISCUSSION

Serum PSA is considered a useful diagnostic tool for PCa [7]. The use of this marker has allowed increasing the diagnosis of PCa in the early stages. BPH and inflammatory diseases can induce an increment in PSA levels in the absence of PCa [8]. Trials and scientific studies have revealed an association between acute and chronic prostatitis as well as an increment of PSA values [9, 10]. The alteration of normal anatomical barriers between prostatic ducts and the bloodstream induced by inflammation plays a key role in the increment of serum PSA values. In some cases, prostatitis is an incidental histological finding and is clinically asymptomatic. This type of prostatitis is classified as type IV prostatitis, prostatitis asymptomatic inflammatory disease, according to the National Health Institutes and the National Institute of Diabetes [3].

Some authors have recently suggested that the immediate decision to perform a prostate biopsy may be inappropriate in the medical management of patients with PSA 4−10 ng/ml. Indeed the latter can be postponed in cases of negative DRE up to a second test of the PSA. The use of medical therapy with an antibiotic is a common practice for a subsequent re-evaluation of the PSA level. This can determine the therapeutic decision of whether to continue monitoring the level of

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Table 1. Changes in total PSA and PSAD pre and post-treatment with levofloxacin in 177 patients.

Variable	Pre-levofloxacin treatment (mean±SD)	Post-levofloxacin treatment (mean± SD*)	P-value	Normalized patients%
Total PSA (ng/ml)	5.6±1.4	4.05±2.1	<0.001	89/177 (50.2%)
PSAD (ng/ml/cm3)	0.13±0.04	0.10±0.05	<0.001	49/56 (87.5%)

* SD= standard deviation.

PSA or to complete the diagnosis through a prostate biopsy [11]. Moreover, a prostatic biopsy can be delayed, with a little risk of missing a PCa, if PSA reduces >70% or below 4ng/ml after antibiotic therapy [10].

In recent years, many types of researches have evaluated the outcome of antibiotic treatment on PSA levels to treat subclinical inflammation. G. Karazanashvili et al [12] have highlighted the importance of PSA test pre- and post-antibiotic therapy in increasing the accuracy of PCa diagnosis in patients with chronic prostatitis. In that study, the author reported the use of antibiotics to treat elevated PSA levels. When PSA levels were decreased following antibiotic use, PCa was reported in 6% of treated patients in which chronic inflammation was confirmed by the histological finding of prostate parenchyma. On the other hand, the occurrence of PCa was 83% when, after antibiotic therapy, PSA levels showed no decrease when histological findings of inflammation were 17% [12]. In another study, S. W. F.Busato et al and V. Serretta et al showed a percentage reduction in PSA approximately 60% of asymptomatic patients treated for 3 weeks with quinolone, with an average reduction of 28% of the same and with normalization in 8% of cases while concluding that the treatment should be reserved only for selected cases in which it is indicated postpone a prostate biopsy [9, 10]. Also, normalization of PSA in 42% of patients with a moderate rise in PSA and diagnosed with chronic prostatitis [13]. Bozeman showed that biopsy in all patients which, after therapy, the PSA has normalized (<4 ng / ml) can be omitted in 50% of cases, thus highlighting how chronic prostatitis is a significant reason that increase in PSA and conservative management may lead to a decrease in the number of unnecessary biopsies [14]. In contrast, some studies suggest that the current use of antibiotic therapy, in common practice, is not justified. Recent work reports that, in patients in which the PSA normalizes below 4 ng/ml, the percentage Positivity for PCa can reach 29%, the percentage not negligible for correct therapeutic management [15]. At present, there is still controversy about the reduction in the PSA values is due to the usage of antibiotics or by the usual difference of the PSA. PSA is until now the keystone of PCa screening and diagnosis in present clinical rehearsal. The inexactness of PSA partially ascribes to the effect of some genetic, clinical (infection or inflammation), and biological aspects altering PSA blood levels. Outcomes of a big multicenter trial recommended the use of serum total PSA larger than 4 ng/mL as a beginning for performing prostate biopsies [16]. A physiological variation of 10 - 20% was detected in the PSA values of normal males while screening was resulted [17]. Comparable to the studies of Serretta et al [10], in the current study after the antibiotic course, PSA levels revealed a significant reduction. The reduction in PSA values after 6 weeks antibiotic course was not related to the diagnosis of PCa, but we studied the relation between chronic prostatitis and PSA level changes.

There is a wide range (16-59%) of the PSA reduction to normal following antibiotic treatment [15]. Our study result was in the upper limit of the range. Therefore, we recommend the usage of antibiotics before prostatic biopsy in patients with high PSA values in the gray zone. However long term surveillance of those patients by regular clinical follow-up, ultrasound examination, and measuring the serum PSA is of utmost importance to detect the PCa in an early stage. In a recent systematic review study about the antibiotic therapy in patients with high PSA showed that 6 used ofloxacin, 6 used 500 mg ciprofloxacin, and 5 studies used levofloxacin.

While 6 studies used the combination of the antibiotic and NSAIDs. Moreover, there was one study used the combination of antibiotic therapy and the plant extracts, Ningbitai and Yunnan Baiyao. And Another study used 2 antibiotics, ciprofloxacin (500 mg/day) and azithromycin (500 mg/day)[15]. Despite that the ciprofloxacin is cheaper than levofloxacin, we used in our study levofloxacin because of the misuse and abuses with its resistant consequence of ciprofloxacin in our country.

The courses of antibiotic therapy vary from 2-4 weeks [2] to 6-8 weeks [18]. While the current study used a 6 weeks levofloxacin course for the target patients. This indicates that there is still controversy about the ideal duration of the usage of antibiotic therapy.

There are shortcomings of the present study include the study not used a control group, and no comparison of the results with histopathological evaluation. Anyhow, the study revealed that patients with BPH and chronic prostatitis with abnormally high values of total PSA (4 and 10 ng/ml) and PSAD, normal DRE and ultrasonographic finding, a 6 weeks course of antibiotic therapy results in a significant reduction in serum PSA and PSAD. So, this modality of treatment can reduce the prostatic biopsies, but long term surveillance of the patients is necessary to detect PCa in an early stage.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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