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Ciprofloxacin versus levofloxacin in avoidance of prostate biopsy in patients with isolated PSA elevation: a prospective randomized study

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Aim: The efficiencies of ciprofloxacin and levofloxacin on prostate-specific antigen (PSA) elevation were compared in terms of avoidance of prostate biopsy in this study.

Materials and methods: Included in the study were 43 men with PSA levels of ≥3.5 ng/mL. They were randomized into either ciprofloxacin or levofloxacin groups for a 3-week course. PSA and free PSA levels were measured before and after the antibiotherapy. The patients in whom PSA remained ≥3.5 ng/mL after therapy underwent biopsy.

Results: The average age of the men was 64.44 years (standard deviation: 9.54). Following antibiotics, 76.7% of the patients showed a reduction in PSA and 32.6% showed PSA normalization; PSA levels dropped by a rate of 27.1% ($P < 0.001$). In the ciprofloxacin group, the PSA reduction rate and PSA normalization were insignificantly higher than in the levofloxacin group. Ciprofloxacin caused a significant reduction in PSA (–41.6% change, $P < 0.001$), but levofloxacin did not (–5.6% change). With quinolones, positive predictive value improved from 9.3% to 13.8%. Of the 29 patients with persistent PSA levels of ≥3.5 ng/mL after antibiotics, 4 were diagnosed with prostate cancer (13.8%).

Conclusion: Empirical ciprofloxacin seems to be more effective than levofloxacin in men with isolated PSA elevation, leading to the avoidance of unnecessary prostate biopsy in nearly half of the cases, and enhances diagnostic capabilities of both PSA and prostate biopsy.

Key words: Ciprofloxacin, levofloxacin, prostate cancer, prostate-specific antigen

Introduction

Prostate cancer (Pca) is estimated to be the most common cancer, accounting for 1 of every 4 cancers, and it was second highest in terms of the estimated cancer deaths among men in 2008 (1). However, diagnosing Pca accurately and precisely still remains a challenge.

Diagnosis of Pca is ultimately made by transrectal ultrasound (TRUS)-guided prostate biopsy (PB). However, PB is moderately invasive and not easily accepted by the patients. Furthermore, this procedure may be complicated by hemorrhaging and infection or, more seriously, by septicemia. To avoid unnecessary or excessive PB, the diagnostic capabilities of other important currently used diagnostic tools are being augmented in various ways, such as prostate-specific antigen (PSA) derivatives and contrast-enhanced TRUS (2). However, the contribution of all of these efforts to definite diagnosis continues to be debated.

On the other hand, prostatic inflammation may be confused with Pca due to elevated PSA levels (3-7). In addition, diagnostic tools used for prostatitis

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cannot explicitly rule out Pca as being the definite cause of elevated PSA (8-13). Therefore, various antibiotherapies have been attempted to decrease PSA and to avoid unnecessary biopsies. For this purpose, in studies up until now, the effects of antibiotics have been studied on PSA elevation in patients not evaluated in terms of prostatitis or in those with prostatitis diagnosed clinically or histopathologically (5,8,14-17).

Although various antibiotics have been used to decrease PSA, ciprofloxacin and levofloxacin have not yet been sufficiently compared (Table 1) (5,8,9,11,16-20). In this prospective randomized study, the efficiencies of ciprofloxacin and levofloxacin were compared in terms of decreasing PSA, and whether attempts to diagnose prostatitis are absolutely indicated to start antibiotherapy in isolated PSA elevation was examined.

Materials and methods

A group of 50 men, with PSA levels of ≥3.5 ng/mL and no suspicious findings in their digital rectal examination (DRE), no urinary retention, no known Pca, no prostatic surgery, and no urinary tract infection signs in their clinical picture or urinalysis, who were referred to the department of urology were eligible to participate in our study.

Seven patients were excluded for either not attending their follow-up appointment or for refusing PB despite continued PSA elevation after antibiotics. The remaining 43 patients were included in the study. After informed consent was obtained, the patients were randomized, according to their presenting order, to 3 weeks of either 500 mg of ciprofloxacin twice a day or 500 mg of levofloxacin once a day.

Total PSA and free PSA (fPSA) levels were measured before and after the antibiotherapy. Percent fPSA was presented as (fPSA / total PSA) ´ 100. The patients with reduced PSA below 3.5 ng/mL following antibiotics were considered as responding to the antibiotics and did not undergo biopsy. These cases were followed up with serial PSA measurements and DRE at 3-month intervals. The patients in which PSA levels remained at ≥3.5 ng/mL after therapy underwent 12-core PB under TRUS guidance. PB was done with the patient lying in the left lateral decubitus position under antibiotic prophylaxis and infiltrative local anesthesia. Pathological specimens were routinely stained and examined.

Continuous variables given as medians (ranges) were compared using the Mann-Whitney U test for independent groups and with Wilcoxon test for dependent groups, while categorical variables were evaluated with Fisher's exact test. $P < 0.05$ was considered significant.

Results

The average patient age was 64.44 years (standard deviation: 9.54). Of the 43 patients, 33 (76.7%) showed a reduction in their PSA levels, and 14 (32.6%) showed PSA normalization following antibiotics. Overall median PSA values were 6.90 ng/mL (3.47-34.80) and 5.03 ng/mL (1.09-27.03), pre- and posttreatment, respectively (27.1% reduction, $P < 0.001$). Overall median %fPSA values decreased from 17.22 ng/mL (7-44.2) to 16.84 ng/mL (4.2-35.4) following antibiotics (2.2% change, $P = 0.456$).

In the ciprofloxacin group, the rate of PSA reduction was higher than in the levofloxacin group (90% and 65.2%, respectively; $P = 0.058$). Likewise, the PSA normalization rate obtained using ciprofloxacin was insignificantly higher compared to levofloxacin (45% vs. 21.7%, respectively; $P = 0.097$) (Table 2).

Ciprofloxacin caused a statistically significant reduction in PSA values (6.7 ng/mL to 3.91 ng/mL, –41.6% change; $P < 0.001$), but with levofloxacin, an insignificant reduction was obtained in PSA values (6.96 ng/mL to 6.57 ng/mL, –5.6% change, $P = 0.132$). Although the increase in %fPSA after ciprofloxacin was found to be higher than after levofloxacin, the changes before and after treatment for both drugs were insignificant ($P = 0.463$ and $P = 0.778$, respectively) (Table 3).

Of the 29 patients with persistent PSA values of ≥3.5 ng/mL after antibiotics, 4 were diagnosed with Pca (13.8%) (Table 4). In other words, the positive predictive value (PPV) improved from 9.3% (4/43) to 13.8% (4/29) following quinolones. In 3 of the 4 cancer patients, a decrease in their PSA values was found after antibiotherapy (Table 5).

Table 1. Response criteria according to drop in PSA, the rates of patients with decreased and normalized PSA, the rates of decrease in PSA levels, the criteria used in deciding biopsy, and the rates of prostate cancer diagnosed under and over cutoff following antibiotherapy in patients with elevated PSA in some investigations.

Author	No. Pts.	Inclusion criteria	Antibiotics and duration	Response (drop in PSA)	% Pts with decreased PSA	% Pts with normalized PSA	% Decrease in PSA evels	Biopsy if PSA	% Pca under cutoff	% Pca over cutoff
Potts (11)	51[A]	PSA 4-30 ng/mL Asymptomatic	TMP/SMX quinolone 4 weeks	<4 ng/mL	-	43	-	>4 ng/mL	ND	31
Karazanashvili et al. (16)	61	PSA 4-10 ng/mL Prst NIH IV	Oflox 2 weeks	-	80	60	-	Any level	6[B]	83[B]
Bozeman et al. (19)	95	PSA 4-25 ng/mL Prst NIH II-IV	Quinolone, dox TMP/SMX 4 weeks	<4 ng/mL	-	46	36	>4 ng/mL	ND	26
Kaygisiz et al (8)	38	PSA 4-10 ng/mL Prst NIH II-IV	Oflox 3 weeks	-	82[C]	26[C]	22[C]	Any level	0	11[C]
Serretta et al. (9)	99	PSA 4-10 ng/mL	Cipro 3 weeks	<4 ng/mL >70%	60	8	28	Any level	0	28
Kobayashi et al. (18)	51	PSA > 4 ng/mL Prst NIH IV	Levo 4 weeks	>20%	65	10	11	> 10 ng/mL <20% Drop	ND	22.5
Dirim et al. (17)	85	Asymptomatic	Levo, cipro 4-8 weeks	≥10%	55	-	2.5	Any level	28	37
Present series	43	PSA > 3.5 Asymptomatic	Levo, cipro 3 weeks	<3.5 ng/mL	77	33	27	≥3.5 ng/mL	ND	14

[A]The number of patients with laboratory-proven prostatitis; [B]according to lower and higher cutoff values of –6% PSA value changes; [C]according to data of 38 patients on whom prostatic biopsy was done.

Pts, patients; Pca, prostate cancer; prst, prostatitis; NIH, National Institutes of Health; levo, levofloxacin; cipro, ciprofloxacin; oflox, ofloxacin; TMP/SMX, trimethoprim/sulfamethoxazole; dox, doxycycline; ND, not done.

Table 2. The number of patients whose PSA levels (%) decreased or increased generally and those whose decreased below or remained above 3.5 ng/mL after antibiotherapy according to quinolone types.

	Ciprofloxacin	Levofloxacin	Total	P*
Pts with decreased PSA	18 (90.0)	15 (65.2)	33 (76.7)	0.058
Pts with increased PSA	2 (10.0)	8 (34.8)	10 (23.3)	
Total	20 (100)	23 (100)	43 (100)	
Pts with PSA of <3.5 ng/mL	9 (45.0)	5 (21.7)	14 (32.6)	0.097
Pts with PSA of ≥3.5 ng/mL	11 (55.0)	18 (78.3)	29 (67.4)	
Total	20 (100)	23 (100)	43 (100)	

*According to chi-square, Fisher's exact test. Pts, patients.

Table 3. The comparisons between baseline and posttreatment median values (ranges) of PSA and %fPSA in the quinolone groups.

	Ciprofloxacin (n = 20)	Levofloxacin (n = 23)	Total (n = 43)	P**
Baseline PSA	6.70 (3.47-34.80)	6.96 (4.16-15.16)	6.90 (3.47-34.80)	0.670
Posttreatment PSA	3.91 (1.09-11.85)	6.57 (1.33-27.03)	5.03 (1.09-27.03)	0.008
Change (%)	–41.6	–5.6	–27.1	
P*	<0.001	0.132	<0.001	
Baseline %fPSA	18.10 (7.30-44.20)	16.34 (7.00-38.50)	17.22 (7.00-44.20)	0.313
Posttreatment %fPSA	21.49 (4.50-35.40)	16.47 (4.20-30.60)	16.84 (4.20-35.40)	0.138
Change (%)	+18.7	+0.8	–2.2	
P*	0.463	0.778	0.456	

*According to Wilcoxon test. **According to Mann-Whitney U test.

Table 4. Pathological diagnoses of the patients undergoing TRUS-guided prostatic needle biopsy due to continued PSA values equal to or higher than 3.5 ng/mL after antibiotherapy.

Diagnosis	**n**	**%**
Benign prostatic hyperplasia (BPH)	20	68.9
Prostatic adenocarcinoma	4	13.8
BPH + prostatitis	3	10.3
BPH + prostatitis + ASAP	1	3.5
BPH + prostatitis + PIN (low)	1	3.5
Total	**29**	**100.0**

ASAP, atypical small acinar proliferation; PIN, prostatic intraepithelial neoplasia.

Table 5. The changes of PSA levels after antibiotherapy in patients with prostatic adenocarcinoma.

	Baseline PSA values (ng/mL)	PSA values after antibiotics (ng/mL)
Case 1	5.83	4.73
Case 2	15.16	10.01
Case 3	4.76	4.93
Case 4	6.96	5.78

In subjects with decreased PSA, malignancy was not found to be lower (P = 0.571) (Table 6). Likewise, PSA changes were not significantly different between malignant and benign groups. However, the posttreatment median %fPSA was significantly higher in the benign group (P = 0.034) (Table 7).

The numbers of patients with decreased/increased PSA were not different between benign groups (Table 8). Changes of PSA and %fPSA were also similar between benign groups, except for significant PSA decrease in the benign prostatic hyperplasia (BPH) + prostatitis group (P = 0.043) (Table 9).

Table 6. The number of patients (%) with decreased and increased PSA values after antibiotherapy according to malignant and nonmalignant prostatic histopathology.

	Malignant	Nonmalignant	Total	P*
Pts with decreased PSA	3 (75)	16 (64)	19 (66)	0.571
Pts with increased PSA	1 (25)	9 (36)	10 (34)	
Total	4 (100)	25 (100)	29 (100)	

*According to chi-square, Fisher's exact test.
Pts, patients.

Table 7. Median values (ranges) of PSA and %fPSA before and after antibiotherapy in the patients with malignant and nonmalignant prostatic histopathology.

	Malignant (n = 4)	Nonmalignant (n = 25)	Total	P**
Baseline PSA	6.39 (4.76-15.16)	8.48 (4.09-34.80)	7.68 (4.09-34.80)	0.562
Posttreatment PSA	5.36 (4.73-10.01)	6.56 (3.52-27.03)	5.79 (3.52-27.03)	0.444
Change (%)	–16.1	–22.6	–24.6	
P*	0.144	0.143	0.064	
Baseline %fPSA	12.39 (7.00-17.50)	20.24 (8.60-44.20)	17.75 (7.00-44.20)	0.122
Posttreatment %fPSA	11.68 (8.40-16.50)	18.00 (4.50-35.40)	16.82 (4.50-35.40)	0.034
Change (%)	–5.7	–11.1	–5.2	
P*	1	0.472	0.543	

*According to Wilcoxon test.
**According to Mann-Whitney U test.

Table 8. The number of patients (%) with decreased and increased PSA values after antibiotherapy according to benign prostatic histopathology.

	BPH	BPH + prostatitis	Total	P*
Pts with decreased PSA	11 (55)	5 (100)	16 (64)	0.082
Pts with increased PSA	9 (45)	0 (0)	9 (36)	
Total	20 (100)	5 (100)	25 (100)	

*According to chi-square, Fisher's exact test.
Pts, patients.

Table 9. Median values (range) of PSA and %fPSA before and after antibiotherapy in the patients with benign prostatic histopathology.

	BPH (n = 20)	BPH + prostatitis (n = 5)	Total	P**
Baseline PSA	7.69 (4.09-25.11)	11.2 (4.50-34.80)	8.48 (4.09-34.80)	0.530
Posttreatment PSA	6.68 (4.30-27.03)	4.74 (3.52-11.90)	6.56 (3.52-27.03)	0.071
Change (%)	–13.1	–57.7	–22.6	
P *	0.526	0.043	0.143	
Baseline %fPSA	22.49 (9.00-38.50)	12.93 (8.60-44.20)	20.24 (8.60-44.20)	0.208
Posttreatment %fPSA	18.75 (8.40-35.40)	16.81 (4.50-21.50)	18.00 (4.50-35.40)	0.290
Change (%)	–16.6	+30.0	–11.1	
P*	0.311	0.686	0.472	

*According to Wilcoxon test.
**According to Mann-Whitney U test.

Discussion

The main pathologies responsible for elevated PSA are Pca, BPH, and prostatitis (15,18,21). These conditions can commonly share the same clinical symptoms, or occasionally cause no symptoms. In contrast to BPH and category I prostatitis as defined by the National Institutes of Health (NIH I), the effects of prostatitis NIH II, III, and IV on PSA are somewhat controversial. In fact, although it has been stated that prostatitis NIH III and IV do not cause any significant elevation in PSA, it has been generally considered that all categories of prostatitis can lead to a notable rise in PSA (3-7,22,23). For instance, it has been claimed that Pca and NIH IV prostatitis have similar effects on PSA (24).

Immediate PB, particularly in men with moderately elevated PSA, is not considered justified by many urologists. In fact, in the first instance of elevated PSA, instead of immediate PB it is advised that PSA tests should be repeated after a few weeks under similar and optimal conditions as defined in the European Association of Urology guidelines (2a evidence level) (25). Moreover, of the subjects with normal DRE results and elevated PSA levels between 4.1 and 10 ng/mL, 80% are diagnosed as benign in their biopsy specimens (26). Therefore, it seems logical to repeat PSA tests or to rule out prostatitis before PB to preclude unnecessary biopsies (4,9,25).

Prostatitis can be diagnosed histopathologically and/or with a conventional 4-glass test, but the role of symptom indexes in diagnosis is controversial (27). Additionally, can antibiotics be used as a way to avoid unnecessary biopsies in PSA-elevated patients? Indeed, initial antibiotherapy may be attractive,

particularly in cases where patients are willing to postpone their biopsies. Furthermore, the change in PSA after antibiotics was offered as a diagnostic method in men with elevated PSA levels and normal DREs (5,16). In such patients, antibiotherapy has been justified only after proven histological prostatitis or after performing an expressed prostatic secretion (EPS) test; it is not cost-effective in category IV and is not indicated in category III prostatitis (3).

However, in a study of Kaygisiz et al., because no relation was found between the existence of inflammation in the prostatic massage and the effect of antibiotics on PSA, the authors suggested that antibiotherapy can be given without inflammation being found before biopsy (8). The authors suggested that biopsy can be avoided in another 18.8% if antibiotics are also given to EPS-negative men, reaching a biopsy avoidance rate of 37.5% (8). Similarly both Serretta et al. and Chang et al. also found no correlation between PSA values and histological score, and Potts noted positive culture in 55% of the Pca patients with abnormal PSA levels after antibiotics, although there were authors advocating the contrary (9-11,28). In this instance, in a patient with lower inflammatory status but higher PSA levels, EPS testing may not be conclusive, and an unnecessary biopsy could be done. In fact, the clinical usefulness of a 4-glass test has been forcefully questioned (12,13). According to Nickel et al., only 32% of patients with chronic prostatitis/chronic pelvic pain syndrome, versus 20% of the controls, had 10 white blood cells per high-power field in EPS (13). Additionally, the EPS test is only an indirect test and cannot directly point out and identify bacteria. In other words, a 4-glass test can yield an unacceptable false-negative outcome in addition to the expense and the somewhat uncomfortable aspects of prostatic massage for the patients (11). Thus, some investigators have used antibiotics regardless of EPS before biopsy in patients with elevated PSA levels (3,14,15,17)

Consequently, in spite of the potential risk for bacterial resistance and resultant infective complications, empirical antibiotic management seems logical, since antibiotics will already be given in a case with a positive EPS test and can be given in a subject with a negative test due to the fact that inflammation cannot be ruled out completely (29). PSA normalization after empirical antibiotics, therefore, might feasibly show prostatic inflammation and avoid an unnecessary biopsy, as well.

Many studies have shown that antibiotics actually reduce PSA levels in patients who would be otherwise be candidates for PB (5,8,9,11,16-19). In these studies, quinolones were much more widely used, probably due to their efficacy against gram-negative bacteria found in higher concentration levels in the prostate and urine; 55% to 82% of the patients showed a decrease in PSA and 8% to 60% showed PSA normalization. Additionally, PSA levels significantly decreased after antibiotics by a rate of 11% to 36% (Table 1) (8,16-19,30). Consistently in the literature we found a PSA decrease of 77% and PSA normalization in 33% of patients after antibiotics. Posttreatment PSA levels were significantly lower by a rate of 27%.

In the literature, only scarce studies comparing ciprofloxacin with levofloxacin have been published (9,17,18). In our comparative study, ciprofloxacin significantly reduced PSA levels from 6.7 ng/mL to 3.91 ng/mL, while levofloxacin did not. However, although the percentage of patients whose PSA levels decreased or normalized was higher in the ciprofloxacin group, this difference was statistically hardly significant. In other investigations, no correlation was observed among serum PSA levels and type and duration of quinolone, and no difference was found between levofloxacin and ciprofloxacin in terms of lowering PSA and treating chronic bacterial prostatitis (5,17,20). However, Schaeffer et al. noted that a little more microbiological eradication was obtained with ciprofloxacin in subjects whose PSA normalized after therapy compared to levofloxacin (93.3% and 90.9, respectively) (5).

Percent fPSA insignificantly increased after quinolones, although the change was little higher in the ciprofloxacin group than in the levofloxacin group (19% vs. 0.8%, respectively) in our study. In other studies, an increase in %fPSA of between 0.5% and 14% was seen (8,9,17,18). Kaygisiz et al. found this rise to be statistically significant, but others considered it insignificant, like our study. However, in our series, posttreatment %fPSA values were significantly higher ($P = 0.034$) in nonmalignant cases than in malignant ones, which should suggest

that antibiotics could enhance the diagnostic power of %fPSA. Similarly, in a study by Dirim et al., the increased ratio of fPSA to total PSA was more evident in benign cases (17).

We diagnosed 4 cases of Pca among the 29 patients (13.8%) whose PSA values remained over cutoff after quinolones. We found that 3 of the 4 patients with malignancy had decreased PSA levels after antibiotics, although there was no significant difference between malignant and nonmalignant cases in terms of the patients whose PSA level increased/decreased and the change of PSA after antimicrobial therapy. Similarly, Kaygisiz et al. found this rate to be 2 out of 4 patients with malignancy (8). In other words, we determined 1 case of cancer among 10 patients (10%) with increased PSA, and 3 cases of cancer among 19 patients (15.8%) with decreased PSA. The difference between these rates was insignificant. On the contrary, Serretta et al. found a significant difference (P = 0.02) (9). In fact, they diagnosed Pca in 40% of the cases with increased or unchanged PSA and in 20.3% of the patients with reduced PSA (9).

We did not require PB in patients showing PSA normalization. Likewise, many investigators performed no biopsy for men with reduced PSA levels below the cutoff value after antibiotics (11,17-19). However, although some authors preferred to do a biopsy for all patients even if they had PSA normalization after treatment, most of them diagnosed no cancer in patients with normalized PSA levels (8,9).

Additionally, in our study, PSA levels reduced by a rate of 16.1% in malignant and 22.6% in benign pathology, although this was considered insignificant. Similarly, the 4.8% decrease of PSA in malignant cases after therapy found by Bozeman et al. was insignificant (19). However, the authors found that a 52.2% decrease of PSA levels in patients with nonmalignant pathology was significant, contrary to our findings.

On the other hand, our finding of significant PSA reductions in the BPH + prostatitis group could indicate a mechanism by which antibiotherapy can decrease the need for a biopsy in patients with elevated PSA. In the same way, Magri et al. noted higher PSA reduction rates in the patients with the pathology of prostatitis without BPH when compared to those with the BPH pathology only (30).

In our clinical study, we noted that ciprofloxacin prevented PB in 9 patients (45%) and levofloxacin in 5 patients (21.7%), a total of 14 patients (32.6%), although this was considered statistically insignificant. In other words, with quinolones, the PPV estimated in our study improved from 9.3% (4/43) to 13.8% (4/29). In fact, in various studies, PPVs rose from 7%-32% to 11%-85% after antibiotics (8,9,11,16-19).

These findings suggest that empirical ciprofloxacin can preclude unnecessary biopsies more effectively than levofloxacin. In addition, patients with histopathological prostatitis respond much better to antibiotics, constituting the rationale underlying antibiotic treatment in PSA elevation. Management of patients showing moderately elevated PSA with quinolones seems to be reasonable due to the fact that they are well tolerated and have mostly acceptable side effects (9,20).

Empirical ciprofloxacin seems to be more effective than levofloxacin in men with isolated PSA elevation, leading to the avoidance of unnecessary PBs in nearly half of the cases, and enhances the diagnostic capability of PSA, although continued studies with larger series and long-term outcomes should be conducted.

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