Long-term Fluoroquinolone Use Before the Prostate Biopsy May Increase the Risk of Sepsis Caused by Resistant Microorganisms

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OBJECTIVES To evaluate the effect of long-term fluoroquinolone treatment before the biopsy in terms of post procedure sepsis. Three-week fluoroquinolone management before the biopsy may lower serum prostate specific antigen (PSA) levels and prevent unnecessary biopsies.

METHODS A total of 558 patients were referred to our clinic for transrectal ultrasound (TRUS)–guided prostate biopsy. Of the patients, 205 had received levofloxacin 500 mg once a day for 3 weeks before the biopsy to lower the serum PSA levels (group 1). A total of 353 patients had not received any antibiotics before the procedure (group 2). In terms of the postbiopsy sepsis rate, group 1 and group 2 as well as patients who underwent biopsies in the early period and the latter period of the study were compared.

RESULTS Sepsis was diagnosed in 17 patients (3.0%) after biopsy. Of these patients, 11 (5.4%) and 6 (1.7%) were in group 1 and group 2, respectively ($P = .0297$, OR: 3.28, 95% CI: 1.10-10.13). Sepsis was diagnosed in 7 patients (1.9%) and 10 patients (5.0%) in the early and the latter period of the study, respectively ($P = .0771$, OR: 0.38, 95% CI: .13-1.09). *Escherichia coli* was the causative agent in all patients with a positive culture. In addition, 1 patient also had meticillin-resistant *Staphylococcus epidermidis* (MRSE). All of the *E. coli* isolates were resistant to fluoroquinolones, and 55.6% were positive for extended spectrum β-lactamases (ESBL).

CONCLUSIONS Long-term fluoroquinolone use to prevent unnecessary prostate biopsy may result in postbiopsy sepsis caused by fluoroquinolone resistant microorganisms. UROLOGY 78: 250–256, 2011.

Transrectal ultrasound (TRUS)–guided prostate biopsy is a standard procedure for the detection of prostate cancer in patients with high serum prostate specific antigen (PSA) levels. Although considered a relatively safe procedure, it may cause hematuria, hematospermia, hematochezia, and infectious complications.[1,2] In addition to cases of prostate cancer, elevated serum PSA levels may be seen in patients with benign prostate hyperplasia (BPH), urinary tract infections, and chronic prostatitis. Evidence from the literature indicates that antibiotic treatment may lower the serum PSA levels to what is considered the normal range in a group of patients and prevents unnecessary biopsies.[3]

Febrile urinary infections are seen in up to 7% of patients who undergo the procedure. When it does occur, it is typically serious and leads to hospitalization. In an attempt to prevent these serious infections, antibiotics, mainly fluoroquinolones, have been used before, during, and after the procedure.[4] Because of its nature and the increase in the use of these drugs, recent studies have reported the emergence of resistant infections to fluoroquinolones.[5,6] It has also been reported that long-term fluoroquinolone use may increase the risk of evolving resistance to fluoroquinolones in *E. coli*.[7]

The goal of this study was to evaluate the effect of long-term antibiotic treatment before the prostate biopsy to lower serum PSA levels in terms of developing post-procedure sepsis. We also analyzed the evolution of resistance to fluoroquinolones during the study period.

MATERIAL AND METHODS

Between 2007 and 2009, a total of 558 patients, who had abnormal digital rectal examinations or serum total PSA levels of greater than 4 ng/mL, were referred to our clinic for TRUS-guided prostate biopsy. Of the patients, 205 of them had received levofloxacin 500 mg once a day for 3 weeks before the biopsy to lower the serum PSA levels (group 1). A total of 353 patients had not received any long-term antibiotics before the procedure (group 2). All the patients were asymptomatic before the procedure. All prostate biopsies were carried out under TRUS guidance, and an automatic biopsy gun with an 18-gauge

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Table 1. Age, serum PSA level, rectal examination findings, and biopsy results of patients

	All Patients	Group 1	Group 2	*P* Value
Patients (n)	558	205	353	
Age (y)	65.6	64.3	66.3	.014
Total PSA (median)	7.9	6.9	8.9	.656
Rectal examination				.0043
Abnormal (%)	173 (31.1)	48 (23.4)	125 (35.5)	
Normal (%)	385 (68.9)	157 (76.6)	228 (64.5)	
Histopathology				.0055
Adenocarcinoma		41 (20.0)	113 (32.0)	
Benign prostate hyperplasia		100 (48.9)	158 (44.8)	
Chronic prostatitis		64 (31.1)	82 (23.2)	

needle was used to obtain 10-core biopsies. None of the patients had received an enema before the procedure.

The patients were also divided into 2 groups consisting of patients whose biopsies were done in the early period of the study (n = 359) and patients whose biopsies were done in the late period of the study (n = 199), respectively. Antibiotic prophylaxis with levofloxacin 500 mg once a day was given to all patients beginning the day before the procedure and continuing for 5 days. We modified our biopsy protocol in 2008. In addition to our standard biopsy protocol, a single dose of gentamicin 160 mg i.v. was administered to the patients .5 hours before the procedure beginning mid-2008 (latter group). All biopsies were carried out as outpatient procedures.

Age, the histopathologic results of biopsy specimens, serum PSA levels, rectal examination findings of patients and postbiopsy sepsis rates were compared between the groups. Patients having fever greater than 38°C within 5 days of the procedure were hospitalized, and detailed medical histories and physical examinations were performed. Before initiating the antibiotic treatment in each case, a consultation was requested from the Department of Infectious Diseases and a urine analysis, complete blood count, and urine and blood samples for cultures were obtained for bacterial evaluation. Sepsis was defined according to the 2001 Society of Critical Care Medicine (SCCM)/European Society of Intensive Care Medicine (ESICM)/American College of Chest Physicians (ACCP)/American Thoracic Society (ATS)/Surgical Infection Society (SIS) International Sepsis Definitions Conference (RF1) as a clinical syndrome defined by the presence of both infection and a systemic inflammatory response syndrome (SIRS) [8]. All organisms isolated from urine or blood cultures were tested for antibiotic susceptibility. Parenteral ceftriaxone or imipenem treatment was started empirically until culture results and antibiotic susceptibility test results were available.

In terms of the postbiopsy sepsis rate, patients receiving long-term antibiotic treatment to lower the PSA and patients who did not receive long-term antibiotics to lower the PSA before the biopsy, as well as patients who were biopsied in the early period of the study and patients who were biopsied in the latter period of the study were compared using chi-square and Fisher's exact chi-square tests. $P < .05$ was considered significant. The *P* value was shown with an odds ratio and a 95% confidence interval.

RESULTS

The mean age, median serum total PSA level, rectal examination findings, and histopathological results of biopsy specimens of all patients, inclusive of the patients in group 1, and the patients in group 2 are given in Table 1. There was no statistically significant difference between the 2 groups in terms of median PSA. The patients in group 2 were older and had a higher percentage of an abnormal findings in the rectal examination compared to group 1. Histopathologic examination showed chronic prostatitis in 31.1% of the patients in group 1 and 23.2% of the patients in group 2, whereas adenocarcinoma of the prostate was reported in 20% of the patients in group 1 and 32% of the patients in group 2 ($P = .005$). No patients had known risk factors, such as lymphoma, AIDS, cirrhosis, granulocytopenia, or immunosuppressive treatment. The patients in group 1 and 2 were compared in terms of having other risk factors for sepsis, such as diabetes mellitus and chronic renal failure, and there was no statistical significance between the 2 groups ($P = .276$, and $P = 0344$, respectively).

A total of 17 patients (3.0%) were admitted to the hospital following biopsy with the diagnosis of sepsis as no other infectious focus was detected. Of these 17 patients, 11 (5.4%) were in group 1 and 6 (1.7%) were in group 2 ($P = .0297$, OR: 3.28, 95% CI: 1.10-10.13). The mean interval between biopsy and presentation to the emergency room with fever was 1.4 day (range 0-3 days). One patient presented on the same day of biopsy, 10 presented on the following day, 4 presented on the second day, and 2 presented on the third day following the procedure.

Of the 17 patients 10 had positive urine and/or blood cultures (only urine cultures were positive in 5, only blood cultures were positive in 3 and both blood and urine cultures were positive in 2 patients) *E. coli* was the causative agent in all of them. One of the 3 patients with positive blood cultures for *E. coli* also had MRSE bacteremia in addition to *E. coli*. Seven patients had either negative blood and urine cultures or their culture results were reported as "contaminated." Of the *E. coli* isolates from the 10 patients with positive cultures only 9 patients' isolates were tested for antimicrobial susceptibility. One patient's urine culture grew only 4000 cfu (cfu) of *E. coli*, so antimicrobial susceptibility testing was not done for this isolate. Of the 9 *E. coli* isolates which had an antimicrobial susceptibility testing result, all of them

were resistant to quinolones, 5 (55.6%) were positive for ESBL, 6 (66.7%) of them were resistant to trimethoprim-sulfamethoxazole (TMP-SMX) and 6 (66.7%) of them were resistant to gentamicin.

The patients diagnosed with sepsis were hospitalized and emprical ceftriaxone was started in 12 patients, while imipenem was started in 5 patients. In 2 patients emprical ceftriaxone treatment was changed to imipenem. One of these patients had ESBL (+) *E. coli* in his urine and the other had ESBL (+) *E. coli* and MRSE in his blood cultures so emprical ceftriaxone treatment was changed to imipenem plus teicoplanin in this patient. Of the 5 patients who were treated with imipenem emprically, 1 patient's blood and urine cultures grew ESBL (−) *E. coli* which was susceptible to ceftriaxone so the treatment was changed to ceftriaxone. The blood cultures and urine cultures of the other 2 patients grew ESBL (+) *E. coli* so imipenem treatment was continued. One patient developed prostatic abscess with blood cultures positive for ESBL (+) *E. coli* so transurethral prostatectomy was performed in addition to imipenem treatment. The last patient had 4000 cfu *E. coli* in his urine culture with no antimicrobial susceptibility testing result so imipenem treatment was continued in this patient too. In summary after modification of emprical treatment according to the culture results, 6 patients received imipenem, and 11 patients received ceftriaxone. No mortality was seen in all 17 patients. Patient characteristics, as well as the culture and antimicrobial susceptibility testing results of the patients with postbiopsy sepsis are shown in Table 2.

Seven of 359 patients (1.9%) had sepsis after the procedure in the early period of the study while 10 out of 199 patients (5.0%) had sepsis after the procedure in the late period of the study. This difference was not statistically significant ($P = .0771$).

COMMENT

It has been reported that prostate inflammation is related to elevated serum PSA levels.[9,10] There are several studies in the literature advocating the use of different antibiotics, mostly floroquinolones, and/or antiinflammatory medications for 3-4 weeks in patients with gray-zone serum PSA levels.[3,11-13] Bozeman et al reported that in almost half of the patients diagnosed with elevated PSA and chronic prostatitis, serum PSA levels normalized with a 4-week course of antibiotics and a nonsteroidal anti-inflammatory agent treatment, and there was no longer indication for biopsy.[3] In a different study, prostate cancer was not detected if the patients' serum PSA levels were lower than 4 ng/mL after antibiotic treatment.[11] Kaygisiz et al showed that antibiotic treatment independent of the presence or absence of inflammation reduced the unnecessary prostate biopsies by 37.5% (12). These small sample size studies started a trend of the administration of a long-term antibiotic treatment for almost every patient with a high serum PSA level before prostate biopsy. Recently, a prospective randomized controlled study showed that antibiotic therapy was effective only in patients with prostate inflammation.[13] In a very large sample sized study, it was also shown that there was no safe zone preventing unnecessary biopsies regarding serum PSA levels.[14] The sensitivity of the serum PSA level at a cut-off level of 1.1 ng/mL was reported as 83.4%.[14] It is possible that a certain number of patients with prostate cancer will be undiagnosed with this method. There are several limitations in the use of empiric antibiotic therapy for patients with an elevated PSA. A decrease in PSA after antibiotic therapy does not rule out the presence of prostate cancer even if the PSA decreases to very low levels, and conversely, a stable or increasing PSA after treatment does not absolutely indicate that prostate cancer is present. In addition to its economic impacts, the indiscriminate use of empiric fluoroquinolones could lead to the development of resistant organisms and, thereby, potentially increase the risk of infectious complications. As an alternative, repeated PSA measurement could be a more reasonable solution for asymptomatic patients than the use of long-term antibiotics.[15]

The overall incidence of infectious complications in our study was 3.0% (17/558). This result was consistent with the reported rates.[5,16,17] Of these 17 patients, 11 (5.4%) were in group 1 and 6 (1.7%) were in group 2 ($P = .0297$, OR: 3.28, 95% CI: 1.10-10.13). This difference is statistically significant, and thus it can be concluded that long term emprical floroquinolone treatment may increase the risk of post biopsy sepsis rate. Consistent with the other studies in the literature, sepsis was observed in the early period after biopsy (mean interval: 1.4 days, range: 0-3 days) [16,18]. Our results showed that *E. coli* was the causative agent in all patients with a positive culture result. As a limitation of our study, there were only 9 evaluable cases with an antimicrobial testing result (5 in group 1 and 4 in group 2). We believe that, it may be useful to take multiple blood and urine cultures to increase the chance of isolating the causative agent and to overcome the risk of contamination. One patient also had MRSE bacteremia in addition to *E. coli* bacteremia. Of the *E. coli* isolates from patients with positive culture results, all of them were resistant to quinolones, 55.6% (5/9) were positive for ESBL, 66.7% of them were resistant to TMP-SMX and 66.7% of them were resistant to gentamicin. All the ESBL(+) *E. coli* isolates were resistant to levofloxacin. Three of them were resistant to levofloxacin, gentamicin and TMP-SMX at the same time. Increasing resistance rates to fluoroquinolones in *E. coli* poses a problem. Fluoroquinolone resistant infections after prostate biopsy are also increasing. Similar to our results, recent data have shown that the causative pathogen in urinary tract infections after transrectal prostate biopsy was mainly *E. coli* with complete resistance to fluoroquinolones.[2,5,17] Patients receiving fluoroquinolones for longer periods may be colonized by quinolone-resistant Enterobacteriaceae in the intestinal tract.[19-21]

Table 2. Patient characteristics, culture, antimicrobial susceptibility testing results, and treatment choice of the patients with postbiopsy sepsis

Patient	Age (y)	3 Weeks of Levo Treatment	Blood Culture	Urine Culture	Antimicrobial Susceptibility of the Blood Isolate	Antimicrobial Susceptibility of the Urine Isolate	Treatment
1	62	+	NG	ESBL(+) *E. coli*		R: Levo, CN, TMP-SMX, CRO	IMP (14 d)
2	60	−	ESBL(−) *E. coli*				IMP(2 d) + CRO (12 d)
3	69	+	NG	Contaminated			CRO (14 d)
4	73	+	NG	NG			CRO (14 d)
5	74	−	MRSE and ESBL(+) *E. coli*	NG	*E. coli*: R.Levo, CN, CRO S.TMP-SMX, IMP		CRO (3 d), IMP + TEC for (14 d)
6	73	+	NG	NG			CRO (14 d)
7	59	−	ESBL(+) *E. coli*	Contaminated			IMP (14 d)
8	76	+	NG	4000 cfu *E. coli*		Not done	IMP (14 d)
9	50	+	ESBL(–) *E. coli*				CRO (14 d)
10	66	+	NG	ESBL(+) *E. coli*			CRO + CN (3 d), IMP (14 d)
11	57	+	NG	NG			CRO (14 d)
12	66	−	NG	NG			CRO (14 d)
13	44	+	NG	NG			CRO (10 d)
14	57	−	NG	NG			CRO (14 d)
15	69	−	NG	ESBL(−) *E. coli*			CRO (14 d)
16	52	+	NG	ESBL(−) *E. coli*			CRO (14 d)
17	67	+	ESBL(+) *E. coli*	NG			IMP (14 d) and prostatectomy for abscess

Eleven patients were in group 1. Six patients were in group 2. NG = no growth; Levo = levofloxacin; CN = gentamicin; CRO = ceftriaxone; TMP-SMX = trimethoprim-sulfamethoxazole; IMP = imipenem; R = resistant; S = susceptible; d = days.

In a study by Horcajada et al, 29 patients with acute prostatitis were treated with ciprofloxacin for one month, and half of the patients were transiently colonized with new floroquinolone-resistant strains of *E. coli*.[7] The transient nature of the fecal carriage of high-level quinolone-resistant *E. coli* strains after quinolone therapy has also been reported in neutropenic patients.[22] It may be useful to wait 1 month for prostate biopsy after the completion of antibiotics to allow more time for the intestinal flora to return to normal after empirical long-term quinolone treatment.[15] Another possibility is that cultures of expressed prostatic secretions or a urine specimen after prostatic massage could be used to identify patients with inflammation who may be more likely to respond to antibiotic therapy. Repeated PSA measurements after a period of observation without antibiotic therapy may provide more valid information for patient management and reduce the confounding aspects of PSA variability which is particularly true for many cases of prostatitis not caused by a known bacterial pathogen. A different antibiotic class can be used for prophylaxis at the time of biopsy for patients who received previous long-term empirical quinolone treatment.[15]

In addition to fluoroquinolone resistant strains of *E. coli*, we may encounter patients with urinary tract infections due to ESBL producing strains of *E. coli* after transrectal prostate biopsy more frequently. In our study 55.6% of the *E. coli* was ESBL (+). Similarly, cases of gram-negative sepsis after prostate biopsy because of extended-spectrum β-lactamase–producing organisms have been reported.[23] Özden et al reported that 43% of the *E. coli* isolated from patients with postbiopsy urinary tract infection was ESBL (+) [16]. The high frequency of multiple antibiotic resistances among ESBL (+) strains limits the therapeutic alternatives and the possibility of administering adequate empirical therapy. Patients with bacteremia caused by ESBL (+) strains may have greater mortality. Inadequate empirical antimicrobial therapy is an independent risk factor for mortality in these patients.[24] It has also been shown that previous use of fluoroquinolones is associated with infections due to ESBL producing strains.[16] In our study, 3 of the 5 ESBL (+) *E. coli* strains were isolated from patients in group 1 who had received 3 weeks of prebiopsy empirical levofloxacin treatment to lower serum PSA levels.

In the clinical setting, using a carbapenem is the only way to ensure that an effective empirical antibiotic therapy for a patient suspected of having a possible ESBL producing *E. coli* infection. In our study, all the patients in whom an ESBL producing *E. coli* was isolated (n = 5) as the causative agent and 1 patient with 4000 cfu *E. coli* in the urine culture in whom an antimicrobial susceptibility result was not available were treated with a carbapenem. Eleven patients with negative culture results and/or with an ESBL(−) and ceftriaxone sensitive *E. coli* isolate were treated with ceftriaxone successfully. No mortality was seen in any of the 17 patients.

In 6 of the 17 patients (35.3%) diagnosed with sepsis, no bacteria were isolated from either the urine or blood and in 1 patient the blood culture was negative and the urine culture was contaminated. This is relatively high when compared to some other study results in the literature.[19] Because improvement of clinical symptoms and leukocytosis were observed in all of these patients after adequate antimicrobial treatment, we may consider the bacterial etiology. It can be concluded that it is important to take multiple blood cultures from different sites in patients presenting with sepsis.

The sepsis rate increased to 5.0% in the late period of the study from 1.9% in the early period. Although this increase was not statistically significant ($P = .0771$), it could be inferred that there was an increasing trend. One should consider that patients who were biopsied in the late period of the study received a single dose of gentamicin 160 mg i.v. before the biopsy in addition to our standard floroquinolone prophylaxis. The difference between these 2 groups in terms of antibiotic prophylaxis is a limitation of our study. There are also other limitations within our study. In addition to its retrospective manner, we did not obtain patients' prostatic secretion analysis before the long-term antibiotic use as most of the patients were referred to our clinic after long-term antibiotic use. The lack of a molecular analysis of the strains made it difficult to determine the relatedness of the bacterial isolates; therefore we could not assess the risk of cross-contamination.

In conclusion, long-term floroquinolone treatment to lower the PSA before biopsy may increase the risk of postbiopsy sepsis rate with fluoroquinolone resistant *E. coli*. We may encounter infections with ESBL producing strains more frequently in patients with previous fluoroquinolone use and it is important to keep in mind that these strains have a high frequency of multiple antibiotic resistance. We consider that the patients should have received prophylactic levofloxacin for a shorter period before biopsy; furthermore, and repeated PSA measurements and analysis of prostatic secretion may be helpful to avoid unnecessary long-term antimicrobial use and the generating of fluoroquinolone resistant bacteria. As intestinal colonization with fluoroquinolone resistant strains have a transient nature waiting 1 month for prostate biopsy after the completion of antibiotics to allow more time for the intestinal flora to return to normal may be useful. Sepsis after prostate biopsy may develop, usually in the early period after the procedure. When sepsis is diagnosed after biopsy in patients with previous fluoroquinolone use, antibiotics other than floroquinolones, such as carbapenems or a third-generation cephalosporin should be started empirically. Multiple blood cultures and urine cultures should be sent before antimicrobial therapy to modify the initial empirical regimen and avoid additional emergence of resistance.

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EDITORIAL COMMENT

Several recent studies have reported an increasing frequency of serious infectious complications after prostate biopsy. For example, Nam et al[1] reported in a Canadian population that the rate of hospitalization for infection within 30 days of prostate biopsy increased from 0.6% in 1996 to 3.6% in 2005. Our group found a similar trend among Medicare participants in the United States.[2] In light of these concerning trends, the identification of risk factors for serious infectious biopsy-related complications is important.

The present study asks whether patients who receive empiric antibiotics for elevated serum prostate-specific antigen (PSA) levels have an increased risk of infection after prostate biopsy. At first glance, this report seems to suggest that the answer is yes. Among patients receiving empirics levofloxacin for 3 weeks before biopsy, postbiopsy sepsis was reported in 5.4%. This was significantly greater than the raw frequency of 1.7% among patients not previously receiving levofloxacin ($P = .03$).

However, it is noteworthy that both groups of patients were given levofloxacin for prophylaxis at biopsy, in addition to intravenous gentamicin later in the study period. Thus, it is possible that the use of a different antibiotic or delaying the biopsy longer after the empirics levofloxacin therapy might have produced different results.[3]

In addition, because this was not a randomized trial, the data must be interpreted with caution. The 2 groups were unbalanced with regard to several clinicopathologic features (see their Table 1), and other unmeasured confounders could also have influenced their results. Thus, prospective studies are necessary to corroborate whether previous antibiotic therapy is independently associated with an increased risk of sepsis after prostate biopsy.

Even if these results were confirmed prospectively, we should step back to look at the whole picture. The purpose of empirics antibiotic therapy is to increase the specificity of PSA testing for prostate cancer detection by reducing confounding from prostatitis. Because these men had received long-term antibiotic treatment before referral to the authors' clinic, we do not know how many other patients whose PSA values decreased after antibiotic therapy might have been spared a biopsy. Thus,