TURKISH JOURNAL OF UROLOGY Turk J Urol 2017; 43(2): 210-5 • DOI: 10.5152/tud.2017.76390

URINARY INFECTION

Original Article

Infective complications in patients after transrectal ultrasound-guided prostate biopsy and the role of ciprofloxacin resistant *Escherichia coli* colonization in rectal flora

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ABSTRACT

Objective: In the present study, we aimed to invastigate the ciprofloxacin resistance in rectal flora of the patients undergoing prostate biopsy in our department. Additionally, the possible effects of the presence of ciprofloxacin resistant bacteria in faecal flora on the risk of infective complications after the procedure as well as the effect of antibiotic prophylaxis on such infectious complications have been evaluated.

Material and methods: A total of 142 patients undergoing transrectal ultrasound-guided prostate biopsy were included into the study program. Rectal swab samples were taken from all patients prior to biopsy. The presence of complications have been evaluated after a week following the biopsy procedure. Patients with fever were also evaluated. The possible correlation between the presence of ciprofloxacin-resistant bacteria in faecal flora and the risk of urinary tract infection development and the other complications were evaluated.

Results: *E. coli* bacteria were present in all cultures of rectal swab samples obtained from 142 patients prior to prostate biopsy. Of all these patients, while ciprofloxacin-resistant *E. coli* (CR *E. coli*) grew in 76 (53.5%) patients; ciprofloxacin susceptible *E. coli* (CS *E. coli*) was obtained in 66 (46.5%) patients. In 16 patients (11.3%), infectious complications were observed. While the infective complications were present in the 14.5% of patients with CR *E. coli*; they were present in the 7.6% of patients with CS *E. coli* (p=0.295). High fever was observed in nine patients (6.3%). Of these nine patients, although six had CR *E. coli* growth as detected during culture sensitivity tests; three had CS *E. coli* growth in their rectal swab culture tests. Sepsis was observed in three (2.1%) of these patients with high fever. Ciprofloxacin-resistant *E. coli* grew in all of the rectal swab cultures obtained from these patients with sepsis.

Conclusion: In the light of our findings we may say that, it will be appropriate to reconsider the ciprofloxacin prophylaxis and prefer to use other prophylactic agents for a certain period of time in populations with higher rates of resistance to this medical agent. Furthermore, it will be appropriate again to obtain rectal swab specimens for culture tests before biopsy procedure in order to perform targeted prophylaxis according to the culture antibiogram test results. This approach will enable us to evaluate the cost- effectiveness of the procedure in detail.

Keywords: Ciprofloxacin resistance; infective complications; prostate biopsy; rectal flora.

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Submitted: 21.03.2016

Accepted: 13.12.2016

Available Online Date: 03.05.2017

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Available online at www.turkishjournalofurology.com

Introduction

In the diagnosis of prostate cancer transrectal ultrasound (TRUS)-guided prostate biopsy" is a standard method.[1] However following biopsy, urinary system infections as acute prostatitis, epididymitis, acute cystitis, and rarely urosepsis might develop.[2] The most important preventive approach is administration of various prophylactic antibiotherapy protocols before application of prostate biopsy.[1,3] In the whole world most frequently fluoroquinolones are preferred for the prebiopsy prophylaxis.[1,3]

As a known fact, basic source of pathogens of urological infections after biopsy is contamination/inoculation. Urology patients sched-

uled for biopsy mostly have a history of recurrent quinolone use different from the normal population, and therefore increased possibility of quinolone resistance with uropathogens of fecal, and urinary origin may be expected. Indeed recently, increasing number of reports about enhanced quinolone resistance in urologic population have been published.[4-6] Testing of the quinolone resistance with antibiograms, may demonstrate the effectiveness of pre-biopsy antibiotic prophylaxis, and its association with infectious complications.

In this study, we aimed to investigate ciprofloxacin resistance of rectal bacteria in normal flora in patients who underwent prostate biopsy in our clinic, and the effect of prophylactic antibiotic use on infectious complications developed following biopsy procedure.

Material and methods

This study was conducted in urology department of our hospital between February 2014, and June 2014. For this study the approval of the Ethics Committee of Dr. Lütfi Kırdar Kartal Training and Research Hospital was obtained. Besides before the biopsy procedure signed informed consent forms of all patients were retrieved.

A total of 175 patients in whom biopsy was indicated were included in the study. Indication of prostate biopsy was determined for patients with abnormal digital rectal examination findings and/or those whose prostate- specific antigen (PSA) levels above 2.5 ng/mL. Before the procedure, microscopic analysis, and cultures of the urine samples were performed, and rectal swabs were obtained from all patients. Thirty-three patients were excluded from the study because their rectal swabs could not be evaluated, and the study was maintained with a total of 142 patients. Treatment of the patients who were receiving anticoagulants was discontinued 7 days before biopsy. For prophylaxis, the patient was given oral ciprofloxacin for a total of 7 days (500 mg bid the day before the biopsy, 500 mg in the morning of the biopsy, and 500 mg bid for 5 days after biopsy). Before the biopsy bowel cleansing enemas were used, and local anesthetic lidocaine was injected. Before and after the procedure povidone-iodine. was applied on the rectum. None of the patients required intravenous sedation, and narcotic analgesic.

Biopsy procedure was performed using 7.5 MHz transrectal probe (Pie Medical 240 Parus 402150 ultrasound system), and sterile attachment. Biopsy was performed while the patients were in the left lateral decubitus position with their knees, and hips in flexion. All TRUS-guided biopsies were obtained from 12 quadrants (standard sextant 6 quadrants plus bilateral base, middle lobe, apex, and lateral lobes) using an automatic biopsy gun, and 18 gauge, 22 cm long thin biopsy needle. The pieces obtained were placed in preprepared bottles numbered one by one which contained 10% formol, and sent to pathology laboratory of our hospital for histopathological analysis.

One week after biopsy, all patients were called up, and questioned for the presence of complications. Treatment, and monitorization of all patients with complications were maintained in our urology service, and outpatient clinic. The patients who were applied to the hospital with complaints of fever, urinary retention, and dysuria, and pyuria in complete urinalysis were evaluated as patients with infectious complications.

Procedural complications seen in patients, and their incidence rates were evaluated. The observed complications were classified based on their grades (Grade 1: Complications regressed without the need for treatment, Grade 2: Complications regressed with ambulatory treatment, Grade 3: complications treated during hospitalization). The correlation between the preexisting ciprofloxacin-resistant intestinal bacteria and development of urinary infection, and other complications after prostate biopsy was evaluated.

Statistical analysis

Data were expressed as mean ± standard deviation. For statistical analysis of data GraphPad Prism 5.0 program, nonpaired t, and chi-square tests were used. $P<0.05$ was accepted as the level of statistical significance.

Results

A total of 142 male patients aged between 47-81 (mean, 66.24±7.32 years) were included in the study. Growth of *E. coli* was detected in all rectal swab cultures of the patients who underwent prostate biopsies. Besides growth of ciprofloxacin-resistant *E.coli* (CR *E.coli*) (n=76; 53.5%), and ciprofloxacin –sensitive *E.coli* (CS*E.coli*; n=66; 46.5%) was detected in respective number of patients. When the patients were evaluated as for ciprofloxacin-resistance, a significant difference was not detected between CR *E. coli*, and CS *E. coli* patients as for mean age, prostate volume, number of patients with abnormal rectal examinations, and prostate cancer, and mean C Reactive Protein (CRP) values ($p>0.05$, Table 1).

The patients were grouped as those with less (n=61), and more than 65 (n=81) years of age in order to evaluate correlation of advanced age with complications developed after prostate biopsy. A significant difference was not detected between age groups as for *E.coli* in rectal swab cultures resistant to antibiotherapy ($p=0.613$).

As complications high fever (n=9), dysuria (n=12), hematuria (n=26), rectal bleeding (n=18), hematospermia (n=18), and

Turk J Urol 2017; 43(2): 210-5
DOI:10.5152/tud.2017.76390

acute urinary retention (n=5) were observed. In many patients with complications more than one concomitant complication was observed. A significant correlation was not detected between minor complications, and age, while hematospermia was observed in 67%, and 33% of the patients aged less, and more than 65 years of age, respectively (p=0.04). Any significant difference was not detected between the age groups regarding both infectious, and non-infectious complications (p=0.486).

Grade 1 (n=60), Grade 2 (n=6), and Grade 3 (n=3) complications developed in respective number of patients and three patients had to be treated on inpatient basis. In all of these patients sepsis, and related high fever were observed. In three patients ciprofloxacin-resistant *E.coli* was grown in rectal swab cultures. Three patients who developed sepsis survived (Table 2).

Among patients presented with high fever following biopsy procedures, growth of CR *E. coli* was detected in rectal swab cultures of 6 cases. In none of the patients with bleeding, and hematospermia blood transfusion was n required and 3 of these patients received inpatient treatment because of concurrent high fever.

When patients were evaluated based on ciprofloxacin –resistance in rectal swab cultures, infectious complications were seen in CR *E. coli* (14.5%), and CS *E. coli* (7.6%) groups in respective percentage of patients (p=0.295), while non-infectious complications were observed in 39.5% of CR *E. coli*, and 39.4% of CS *E. coli* patients (Table 3).

Discussion

Transrectal ultrasound-guided prostate biopsy is a frequently applied, reliable, and well-tolerated method.[7] However despite measures taken before, and during biopsy, unwanted minor, and major complications can occur following biopsy.[8] One of the frequently seen complications which may cause significant morbidities is development of infection. Antimicrobial prophylaxis used to prevent this complication has been included in standard procedures.[9] Various treatment protocols have been published about pre-biopsy prophylaxis, and post-biopsy antibiotherapy. Tekdoğan et al.[10] from Turkey could not detect a significant difference among different treatment protocols as for infectious complications.[10] The antibiotic used, its dose, route of administration, and duration of treatment are still debatable issues. Indeed after biopsy many different microorganisms (*E. coli, lactobacilli, enterococcus, klebsiella, staphylococci* and various anaerobic agents) can lead to infectious complications. In post-biopsy positive urine cultures most frequently *E. coli* is isolated.[11,12] Nowadays, in pre-biopsy prophylaxis ciprofloxacin is the most frequently preferred antibiotic.

In a review article, Loeb et al.[13] observed post-biopsy infectious complications in 0.5-17.5% of the patients, while incidence rates of sepsis ranged between 0, and 3.6 percent. Infectious complications were indicated as the most frequent reason for hospitalization.[13] In the guidelines of European Association of Urology, increase in the incidence of post-biopsy infection related to antimicrobial resistance has been indicated.[14] Within years a significant increase in the incidence of fluoroquinolone-resistant urinary system infections

Table 1. General demographic characteristics of the patients

Variables	CR *E. coli* (n=76)	CS *E. coli* (n=66)	p*
Age (year)	66.11±0.83	66.41±0.94	0.808
Prostate volume (mL)	51.27±2.70	46.91±2.31	0.222
PSA (ng/mL)	10.41±1.10	18.49±3.19	0.015
CRP (mg/L)	9.11±1.80	6.30±0.81	0.164
Abnormal DRE finding, n (%)	17 (22.3)	20 (30.3)	0.339
Prostate cancer, n (%)	21 (27)	17 (25)	0.851

CR *E. coli*: Ciprofloxacin-resistance *E. coli*; CS *E. coli*: Ciprofloxacin-sensitive *E. coli*; PSA: Prostate specific antigen; CRP: C Reactive Protein; DRE: Digital Rectal Examination

*Non-paired t test

Table 2. Distribution of the complications observed based on the grade of the complications

	Grade of the complications			
Complications	1	2	3	Total
High fever	0	6	3*	9
Dysuria	7	4	1	12
Hematuria	22	3	1	26
Rectal bleeding	14	2	2	18
Hematospermia	18	0	0	18
Urinary retention	4	0	1	5

*The patient received inpatient treatment because of urosepsis

Table 3. Total number of infectious, and non-infectious complications in patients divided in groups based on ciprofloxacin –resistance in rectal swab culture

	Infectious complication	Non-infectious complication	Lack of complication
CR *E. coli*	11 (14.5%)	30 (39.5%)	43 (56.6%)
CS *E. coli*	5 (7.6%)	26 (39.4%)	38 (57.6%)

CR *E. coli*: Ciprofloxacin- resistant *E. coli*; CS *E. coli*: Ciprofloxacin-sensitive *E. coli*

has been observed.[6,15] In multi-center studies where patients with urinary infection have been evaluated in many geographic regions of Turkey, rates of quinolone-resistance of *E. coli* strains isolated from urine cultures have been reported to range between 8.3, and 38 percent.[16,17]

In a study by Atılgan et al. [18] urine culture positivity was detected in 13 (3.3%) patients, and growth of *E. coli* was detected in all of these cultures.[18] Feliciano et al.[6] reported infectious complication rate of 2.4% (1% in febrile cases) in patients in whom fluoroquinolone was used for prophylaxis. In the same study, in 17 of 19 patients with positive urine cultures, growth of *E.coli* was observed. In 14 of these 17 patients *E. coli* resistant to fluoroquinolones were reported. Choi et al.[19] detected febrile post-biopsy urinary system infection in 3.1% of their patients. In the same study in 80% of the patients with positive culture, as a pathogenic agent *E. coli* was isolated, and in 88% of these patients resistance to fluoroquinolones was detected In the same study, 5-fold increase in infectious complications, and gradual increase in fluoroquinolone resistance have been observed in recent years. In a study by Kandemir et al.[20] urine antibiograms of 83 of 99 (83.8%) patients demonstrated fluoroquinolone resistance, and a significant increase in antimicrobial resistance rates after the year 2008 when compared with previous years. Uddin et al.[21] reported infectious complications in their 91 (30.7%) patients. However in our study 11.3% of our patients biopsized under ciprofloxacin prophylaxis infectious complications developed.

Upon demonstration of resistance to quinolone, antimicrobial prophylaxis had been achieved with amoxicilline trihydrate, and during this treatment period, decrease in quinolone resistance down to 57% had been also observed.[21] In the same study, similarly, as antimicrobial prophylaxis with gentamicin was maintained for longer periods of time, rate of development of resistance to this antibiotic increased from 20% up to 57 percent. In a study performed by Kehinde et al.[15], sepsis had been observed in 8% of the patients under ciprofloxacin prophylaxis, but in only 1.7% of the patients who had received ciprofloxacin plus amikacin prophylaxis. In another study performed, in 50% of the infectious complications developed after biopsy fluoroquinolone –resistant bacteria had been held responsible, and empirical treatment with cephalosporines or amikacin was recommended until culture-specific treatment was initiated.[6]

Presence of ciprofloxacin-resistant bacteria in fecal flora has been reportedly ranged between 1, and 63%, in various publications issued by many centers.[4] Liss et al.[22] estimated fluoroquinolone resistance as 20.5% in rectal swab cultures of the patients who had been biopsized. Steensels et al.[23] detected ciprofloxacin-resistant *E. coli* in rectal swab cultures of 22% of biopsized patients, and pointed out to significant infection risk in these patients. Duplessis et al.[24] isolated ciprofloxacin-resistant *E. coli* from pre-biopsy rectal swab cultures in 14% of their patients. However in our study, growth of ciprofloxacin –resistant *E. coli* was detected in 53.5% of pre-biopsy rectal swab cultures which was higher than incidence rates reported in other studies. In our study, the percentage of infectious complications in the group which demonstrated ciprofloxacin-resistant *E. coli* in rectal swab cultures was nearly 2-fold higher than those detected in CS *E. coli* group. However, we think that because of inadequate number of patients in our study, a statistically significant result could not be obtained (7.6 vs. 14.5%, p=0.295). Besides post-biopsy sepsis did not develop in any patient in whom ciprofloxacin-sensitive *E. coli* had been isolated.

Fluoroquinolone resistance in rectal swab culture, has been significantly correlated with post-biopsy development of infection, and hospitalization.[22] As determined in various studies, fluoroquinolone –resistant rectal swab culture positivity increases the risk of infection nearly 4 times, and probability of hospitalization for 5-fold.[22] Among fluoroquinolone-resistant bacteria, mostly *E. coli* has been observed.[22] As one of the reasons for increased incidence of quinolone –resistant bacteria in rectal flora in recent years, long-term fluoroquinolone use has been blamed. Use of fluoroquinolone during 6 months before biopsy has been determined as an important risk factor for ciprofloxacin resistance detected in cultures of rectal flora.[23]

Since in biopsized patients, bacteria localized on rectal region inoculate in prostate tissue, urine, and blood vessels and may lead to infectious complications, presence of resistant bacteria in rectum conveys much greater importance.[25] Although it has not been confirmed that bacteria in rectal flora lead to infection following biopsy, presence of resistant intestinal bacteria has been assumed to increase risk of infection with resistant bacteria. Therefore, the state of resistance of strains isolated from rectal swab cultures against prophylactic agents other than fluoroquinolones will aid in the determination of the most accurate regimen to be applied for biopsy procedures. The patients received targeted antimicrobial prophylaxis before biopsy based on the results of the antibiograms of the culture material, and any sign of infection was not observed in any patient after biopsy.[24,26] Analyses of cost-effectiveness have demonstrated much lower cost of targeted prophylaxis relative to standard prophylaxis.[26]

In conclusion, in our study, higher rates of post-biopsy infectious complication, and also ciprofloxacin- resistant *E. coli* in rectal flora were detected. Therefore, quinolone prophylaxis should be re-considered, and in communities with higher re-

Turk J Urol 2017; 43(2): 210–5
DOI:10.5152/tud.2017.76390

sistance rates, another prophylactic agent should be used at least for a certain period of time or it will be appropriate to obtain culture of the rectal swab, and administer target-directed prophylaxis based on antibiotic susceptibility test results after re-evaluation of cost-effectiveness of the procedure.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr. Lütfi Kırdar Kartal Training and Research Hospital (12.06.2012 / 9).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.B.H., F.T., R.H.; Design – M.B.H., F.T., R.H.; Supervision – G.A.Ö., M.K.D., A.K., Ö.Y.; Resources – F.T., R.H., G.A.Ö., Ö.Y.; Materials – M.B.H., F.T., R.H., G.A.Ö.; Data Collection and/or Processing – G.A.Ö., M.K.D., A.K.; Analysis and/or Interpretation – M.K.D., A.K., Ö.Y.; Literature Search – M.B.H., F.T., R.H.; Writing Manuscript – M.B.H., F.T., R.H.; Critical Review – M.K.D., A.K., Ö.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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