Original Article

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Transrectal Prostate Biopsy Prophylaxis in Elderly Patients: Comparison of Two Different Prophylaxis Regimens, Seven Years of Experience

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Abstract

Objective: Recent studies have identified increased fluoroquinolone (FQ) resistance; therefore, alternative prophylactic agents such as fosfomycin have begun to be applied to prevent infectious complications of transrectal prostate biopsy. This study compared the use of FQ and fosfomycin for antibiotic prophylaxis in transrectal prostate biopsy in elderly patients.

Materials and Methods: This study was conducted between January 2011 and December 2017. There were 182 patients over the age of 65 years. Group 1 included 97 patients who received oral FQ twice daily for five days, starting 1 h before the procedure, between January 1, 2011 and January 1, 2014. Group 2 included 85 patients who received a single oral dose of fosfomycin the night before the procedure between January 1, 2014 and December 31, 2017.

Results: The average ages of groups 1 and 2 were 69.90±3,906 years and 70.08±3,566 years, respectively. Afebrile urinary tract infection (UTI) was observed in 10 patients and febrile UTI was observed in 11 patients. Of the 10 patients with afebrile UTI, three received fosfomycin and 7 received FQ treatment. Of the 11 patients with febrile UTI, one received fosfomycin and 10 received FQ therapy. There were 20 FQ-resistant infections, 16 of which were observed after the administration of ciprofloxacin and 4 of which were observed after the administration of fosfomycin.

Conclusions: High resistance to routinely applied drugs such as FQs is a worrying concern. One alternative method to decrease FQ-resistant infection and associated hospitalizations is the use of fosfomycin. It seems to be an option and potent agent for prophylaxis in transrectal prostate biopsy for geriatric patients.

Keywords: Aged, fluoroquinolone, fosfomycin, prostate biopsy, prophylaxis

Introduction

Aging is unavoidable status with chronological, biological, and personal conditions. Because of the prolongation of life expectancy and the increase in the geriatric population, the approach to care for the elderly population has become more important. The number of medical problems associated with the geriatric population is also increasing. Significant advances in medical technology and healthcare are causing an increasing number of elderly patients to benefit from complex surgical procedures. With increasing age, physiological and anatomical changes inevitably emerge. Immune function decreases with age with chronic diseases such as carcinoma affecting human resistance (1). Prostate cancer (PC) is the most common malignant tumor in older men. PC has emerged as the most common cancer in men, and its incidence has been increasing rapidly in Europe over the past two decades (2). PC is one of several urological problems that make up a significant part of the problems that affect the elderly and reduce their quality of life. PC diagnosed early can be successfully treated with radical prostatectomy and radiotherapy (3). Abnormal digital rectal examination (DRE) and serum prostate specific antigen (PSA) levels are associated to the risk of PC (4). Transrectal ultrasonography-guided prostate biopsy (TRUS-Bx) is a commonly used canonical method to diagnose PC. The urinary tract infection (UTI) is the most important complication of TRUS-Bx. Although afebrile or non-complicated UTIs mostly occur after TRUS-Bx (1.2-11.3%), febrile or complicated UTIs are also not rare (1.4-4.5%) (5). It can lead to severe sepsis (0.3-3%), require hospitalization, and cause life -minimum status (5). The European Association of Urology guidelines recommend the

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use of antimicrobial prophylaxis in men before TRUS-Bx (6). The most broadly used antibiotics for prophylaxis are fluoroquinolone (FQ) and trimethoprim-sulfamethoxazole. However, recent studies have identified increased FQ resistance (7). Overuse and misuse of antibiotics is an important factor leading to antibiotic resistance (7). Therefore, alternative prophylactic agents such as fosfomycin (single or double dose) have been applied to prevent infectious complications of TRUS-Bx (8,9). Fosfomycin is an oral, broad-spectrum, bactericidal antibiotic that is opposed to the most general Gram-positive (Gr+) and Gram-negative (Gr-) bacterias (10). Owing to its effectiveness, ease of administration, and safety, fosfomycin is highly recommended and practiced for treating uncomplicated UTI (10). UTI is one of several urological problems affecting the elderly and constitutes an important part of the problems that decrease their quality of life. Here, we aimed to compare the effectiveness and reliability of a single-dose fosfomycin with 5 day administration of 500 mg oral ciprofloxacin (FQ) for prophylaxis in TRUS-Bx. To the best of our knowledge, the use of fosfomycin for prophylaxis in TRUS-Bx has not been reported in elderly patients.

Materials and Methods

We conducted this study at Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey, between January 2011 and December 2017. A total of 182 patients over the age of 65 years were enrolled in this study. The medical records of the patients were retrieved from the hospital database and retrospectively reviewed. Diyarbakır Gazi Yaşargil Research and Training Hospitals Ethical Board confirmed our study (decision number: 12/27, date: 12.02.2018), and all patients signed consent forms. Our study also complied with the principles of the Declaration of Helsinki. TRUS-Bx indications included an elevated PSA level (>2.5 ng/mL), abnormal findings on DRE, and prior prostate biopsy pathology. Urine analysis and urine cultures were negative for infection in all cases. We excluded those who had used antibiotics in the past four weeks, had UTI anamnesis, and had permanent urethral foley. In group 1, there were 97 patients who received oral FQ for 5 days twice daily starting 1 h before the process, between January 1, 2011 and January 1, 2014. FQ resistance was detected in urine culture antibiograms in 33% of patients (in all age group) who applied to our urology department between January 1, 2012 and January 1, 2014. Therefore, as of January 1, 2014, we started using fosfomycin (oral, 3 g) for antibiotic prophylaxis to prevent infectious complications of TRUS-Bx. In group 2, there were 85 patients who received a single dose of fosfomycin (oral, 3 g) the night before the biopsy between January 1, 2014 and December 31, 2017. Acetylsalicylic acid or anticoagulant drugs were administered 5-7 days before TRUS-Bx. All patients received a fleet enema the night before the biopsy. Rectal cleaning was performed using povidone-iodine (10% solution of povidone iodine) just before biopsy during the entire study period. We performed TRUS in the left lateral decubitus position. Local anesthesia was administered transrectally before prostate biopsy. Standard prostate biopsies (12 cores) were obtained using a biopsy device with a disposable 16-gauge 25-cm needle. Prostate volume was measured using the prostate ellipsoid formula: volume=0.52 (HxLxW) where H is the anteroposterior diameter, L is the cephalocaudal diameter, and W is the width. We informed all patients about possible complications after biopsy. All cases were informed to be admitted to the emergency clinic of our hospital in the event of chills, 38.0 °C fever, macroscopic hematuria, and/or serious voiding symptoms. All patients were instructed to visit the controls at 1 and 4 weeks after TRUS-Bx. We planned visits within 4 weeks after TRUS-Bx as a cut-off to conquer infections that could have been linked to TRUS-Bx. Any event that occurred 1 month after prostate biopsy was not considered to be associated with TRUS-Bx. Physical examination, urinalysis, and urine culture were performed in all cases at the 1st week and 1st month after TRUS-Bx. We hospitalized cases with febrile UTI and cured them with intravenous antibiotics, and the drug was altered to an oral type when the patients were discharged. Oral antibiotics were administered to all afebrile UTI patients based on culture results. We evaluated the infectious complications of two antibiotic prophylaxis regimens after TRUS-Bx.

Statistical Analysis

Statistical analyzes were performed using SPSS version 24.0 (Chicago, IL) statistical software package. In the comparison of continuous variables between the groups, it was determined whether they were parametric or non-parametric by the Shapiro-Wilk test. Categorical features were given as numbers, continuous measurements were given as mean ± standard deviation and median IQR. Chi-square test was used to collate categorical variables. The Mann-Whitney U test was used for continuous variables. A p-value of <0.05 was considered statistically significant in all tests.

Results

A total of 182 patients who had received TRUS-Bx were enrolled in this retrospective study. Between January 1, 2011 and January 1, 2014, 97 patients were administered FQ prophylaxis (group 1). Between January 1, 2014 and December 31, 2017, 85 patients were administered fosfomycin prophylaxis (group 2). Patient characteristics are summarized in Table 1 for both the groups. There was no statistically significant difference in terms of age, total PSA level, prostate volume, or previous biopsy for both groups. The mean ages of groups 1 and 2 were 69.90±3,906 years and 70.08±3,566 years, respectively, (p=0.630). The microbiological features and culture findings of cases with afebrile and febrile UTIs are summarized in Table 2. Afebrile UTI was seen in 7 patients in group 1 and 3 patients in group 2 (p=0.318). Febrile UTI was observed in 10 patients in group 1 and in 1 patient in group 2 ($p<0.05$). Positive urine culture was detected in 11 patients with febrile UTI and in 10 patients with afebrile UTI in both groups. Febrile UTI ratio was significantly higher in group 1 (10 vs. 1, $p<0.05$). *E. coli* and *K. pneumoniae* were the most produced agents from urine cultures in all patients. FQ-resistant *E. coli/K. pneumoniae* was determined in 7 patients with afebrile UTI in group 1 and in 3 patients with afebrile UTI in group 2 (p=0,308). FQ-resistant *E. coli/K. pneumonia*e was determined in 9 patients with febrile UTI in group 1 and in 1 patient with febrile UTI in group 2 ($p<0,05$). No patient had experienced extended-spectrum beta-lactamase (ESBL) *E. coli* infection. None of the cases with febrile UTI had positive blood cultures.

Discussion

The aged population is rising worldwide. As a result of this, diseases and health problems have become more widespread. Age-linked variances in immunity, medical comorbidities, invasive interventions, prosthetic/urethral devices, and short- and long-term urinary catheterization increase the sensitivity to UTIs and hospitalization (11). UTI is common in older people and is generally misdiagnosed because of diffuse asymptomatic bacteriuria (11). Cancer incidence and mortality are higher in patients 65 years and older (12). In elderly patients, the procedure of treatment and interventions should be considered individually, based on the characteristics of each patient (13). PC is the most widespread malignancy among elderly men and has emerged as the most widespread cancer among men, with an evident increasing occurrence in Europe over the last two decades (2). PSA testing is performed to decrease and prevent death from PC (14). DRE and serum PSA screening are two ways for early detection of PC (14). The final diagnosis of prostate cancer is made with TRUS-Bx (15). Various antibiotics have been used to prevent the infectious complication of TRUS-Bx, however, standard antibiotic prophylaxis has not yet been described (15). FQs are the most generally used antibiotics because of their dense bioavailability in the prostate, ease of use, and pharmacological biography for TRUS-Bx prophylaxis (16). Unluckily, FQ-resistant *E. coli* derivatives are rising yearly in most countries all over the world (17). Resistance to FQs has been previously known to be related to the use of antibiotics, especially FQs, and previous reports have shown that underlying UTIs tend to expose patients to repeated UTIs and then to antibiotics such as FQs (17). We found FQ resistance in 33% of the patients revealed to our department between January 1, 2012 and January 1, 2014, parallel to the literature in TRUS-Bx (18,19). Numerous studies have recommended that FQ prophylaxis may not be adequate to avert infectious complications of TRUS-Bx (20,21). Some authors recommend rectal swab cultures before the procedure to guide the appropriate antibiotic selection to avert infectious complications of TRUS-Bx (22). Alternative prophylaxis forms, such as single- or double-dose fosfomycin, have been described to avert the infectious complications of TRUS-Bx. In this study, we administered a single dose of fosfomycin for TRUS-Bx prophylaxis. Fosfomycin has broad antibacterial activity against both Gr and Gr+ bacteria, which is known to attack bacteria with mucopeptide synthesis by inhibiting phosphoenolpyruvate transferase, the first enzyme related to the synthesis of peptidoglycan. Fosfomycin is very decently tolerated, and the side effects range is in 1-10% of patients (23). The main side effects of oral fosfomycin are headache, fatigue, and mild gastrointestinal discomfort. The fosfomycin resistance rate is currently considered low despite years of clinical use, and there is also no parallel and/or cross-resistance to fosfomycin and other commonly used agents (10). Shrestha and Tomford (24) reported only 1 case of pseudomembranous colitis observed in a post-marketing study that involved 35,481 patients over 6 years. Gardiner et al. (25) investigated the diffusion of fosfomycin into benign prostate tissue in patients undergoing transurethral resection of the prostate. They found that fosfomycin reached enough intraprostatic aggregations in the inflamed prostate after a single 3 g oral dosage and indicated that fosfomycin can be an effective choice for antibiotic prophylaxis before TRUS-Bx and likely for the medicament of multidrug robust Gr- bacteriuria prostatitis (25). Fosfomycin was first applied by Ongün et al. (8) for TRUS-Bx prophylaxis. Lista et al. (9) in their prospective randomized study collated double doses of fosfomycin with 500 mg oral ciprofloxacin twice daily dispensed for five days beginning one day before biopsy, and Ongün et al. (8) in their

Table 1. Patients characteristic

	Group 1	Group 2	p-value
Patients (n)	97	85	
Age (years) mean ± SD (range)	69.90±3,906 (65-78)	70.08±3,566 (65-77)	0.630
Total Psa (ng/mL) mean ± SD (range)	7.431±3,642 (2.5-20.3)	7,625±3,654 (2.5-20.1)	0.657
Prostate volume (cm^3) mean ± SD (range)	67.43±25,241 (30-156)	67.64±26,610 (33-156)	0.830
Previous biopsy (n)	22	15	0.380

SD: Standard deviation, PSA: Prostate specific antigen

Table 2. Microbiological characteristics and culture results of patients with afebrile and febrile UTIs

	Group 1	Group 2	p-value
Patients (n)	17/97 (17.5%)	4/85 (4.7%)	
Afebrile UTI (n)	7	3	0.308
Fluoroquinolone - resistant *E. coli/K. pneumoniae*	7	3	0.308
Fluoroquinolone - sensitive *E. coli/K. pneumoniae*	-	-	
Febrile UTI (n)	10	1	<0.05
Fluoroquinolone - resistant *E. coli/K. pneumoniae*	9	1	<0.05
Fluoroquinolone - sensitive *E. coli/K. pneumoniae*	1	0	0.149
ESBL *E. coli*[*]	-	-	

[*]Fluoroquinolone-resistant, ESBL: Extended-spectrum beta-lactamases; UTI: Urinary tract infection

retrospective study collated single-dose fosfomycin with 500 mg oral ciprofloxacin twice daily and single dose levofloxacin dispensed for 5 days beginning 1 day before biopsy (9). These two studies showed that fosfomycin is as effective and safe as levofloxacin and ciprofloxacin, indicating that fosfomycin can reduce FQ-resistant infections. Numerous studies have recommended that a single ciprofloxacin prophylaxis cannot be adequate to avert infectious complications of TRUS-Bx (18,20,21). Kehinde et al. (26) argued that combining aminoglycosides decreased infectious complications following TRUS-Bx (26). Marino et al. (27) declared that the combination regimen is more effective than single agents, such as ceftriaxone, ciprofloxacin, and gentamicin, alone for the prophylaxis of TRUS-Bx. Unnikrishnan et al. (28) reported that levofloxacin is more effective than ciprofloxacin when used in combination with aminoglycosides in averting serious infections after TRUS-Bx. Costelloe et al. (29) reported that longer periods and multiple sequences of administered antibiotics are linked with higher rates of bacterial resistance. Today, the prevalence of FQ-resistant and ESBL -positive coliforms is increasing worldwide (20). Bacterial resistance associated with fosfomycin use remains low (9). In the present study, FQ-resistant *E. coli/K. pneumoniae* were detected in 16 patients in group 1 and 4 patients in group 2. In our study, the febrile UTI ratio was significantly higher in group 1. Nowadays, the increase in the number of patients with prostate cancer in active surveillance is associated with recurrent biopsy rates and a higher risk of complications such as urinary infections than primary biopsies (30). Day after day, more infections are observed after TRUS-Bx, and more money is used for the treatment of infectious complications. Prospective common studies are required to decrease infectious complications after TRUS-Bx, including those that analyze selecting prophylactic antibiotics, customizing methods for the patient, and liable possible infection throughout biopsy. Fosfomycin can be used to prevent further development of resistance among elderly patients.

Our research is the first retrospective study collating single-dose fosfomycin with 5-day administration of 500 mg oral ciprofloxacin for prophylaxis in prostate biopsy in geriatric patients. To the best of our knowledge, the use of fosfomycin for prophylaxis in prostate biopsy has not been reported in elderly patients.

Study Limitations

The current study has some significant limitations. First, it's a retrospective nature. Second, as controls, we chose only patients with FQ prophylaxis to make the group as homogeneous as probable for comparison. However, the first study on the use of fosfomycin for TRUS-Bx prophylaxis in the elderly patient population is the strength of our study. The ease of use and low resistance rates are the advantages of fosfomycin. Prospective randomized trials with several cases of fosfomycin use for TRUS-Bx prophylaxis are required.

Conclusion

Antibiotic resistance is a serious issue for doctors and their patients. High levels of bacterial resistance to antibiotics require reassessment of empirical antimicrobial therapy in TRUS-Bx to prevent infectious complications in geriatric patients. Today, variable antibiotic resistance, increasing antibiotic charges, and the use of new antibiotics have made the choice of ideal antibiotic regimens harder than in the past. Fosfomycin can be safely used for TRUS-Bx prophylaxis, especially in geriatric men, because of its easy use, potent antibacterial activity, and low bacterial resistance. We believe that well- designed reports with a larger sample size are needed to confirm our results.

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Ethics

Ethics Committee Approval: Diyarbakır Gazi Yaşargil Research and Training Hospitals Ethical Board confirmed our study (decision number: 12/27, date:12.02.2018).

Informed Consent: All patients signed consent forms.

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Authorship Contributions

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