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Original Article

# Effectiveness of Augmented Prophylaxis with Fosfomycin and Ciprofloxacin Combination for Transrectal Ultrasound-Guided Prostate Biopsy

Şakir Ongün, Çağdaş Şenel, Emre Tüzel

Department of Urology, Balıkesir University School of Medicine, Balıkesir, Türkiye

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**ORCID iDs of the authors:** Ş.O. 0000-0002-8253-4086, Ç.Ş. 0000-0002-4030-002X, E.T. 0000-0002-6432-2434.

## ABSTRACT

**Objective:** We aimed to determine the efficacy of fosfomycin and ciprofloxacin combination on infectious complications in transrectal ultrasound-guided prostate biopsy (TRUGPB) prophylaxis.

**Methods:** Patients who underwent TRUGPB between January 2018 and January 2023 were retrospectively analyzed, and 1109 patients were included in the study. Patients were divided into 2 groups according to the antibiotic prophylaxis used before the procedure: group-1, oral ciprofloxacin 500 mg (2 × 1) 5 days starting 24 hours before biopsy and group-2, oral ciprofloxacin 500 mg (2 × 1) 5 days starting 24 hours before biopsy and oral fosfomycin 3 g single dose the night before biopsy.

**Results:** Evaluation of the antibiotic prophylaxis used by the patients before the biopsy revealed that 323 (29.1%) patients received ciprofloxacin (group 1), and 786 (70.9%) patients received fosfomycin + ciprofloxacin (group 2) prophylaxis. When infectious complications after biopsy were analyzed, 15 patients (1.4%) developed fever, 9 patients (0.8%) developed febrile urinary tract infection (UTI), 9 patients (0.8%) developed afebrile UTI, and4 patients (0.5%) developed sepsis. When infectious complications were compared according to the antibiotic prophylaxis, febrile UTI and sepsis were statistically significantly more common in group 1 ($P = .003$ and $P = .027$).

**Conclusion:** In conclusion, adding fosfomycin to ciprofloxacin in TRUGPB prophylaxis effectively prevents post-biopsy infective complications compared to ciprofloxacin prophylaxis alone.

**Keywords:** Prostate biopsy, fosfomycin, ciprofloxacin, complication

## INTRODUCTION

Most common cancer in men is prostate cancer, with 1.4 million cases per year.[1] The gold standard for the diagnosis of prostate cancer is the transrectal ultrasound-guided prostate biopsy (TRUGPB), but this procedure may cause complications such as infection and hematuria.[2] European and American Urological Associations recommend antibiotic prophylaxis to reduce prostate biopsy-related infections.[3,4]

Although infective complications after prostate biopsy are rare, serious infections may cause mortality. The infection rate after prostate biopsy is around 5%-7% and 1%-3% of these patients develop serious infections requiring hospitalization.[5] Fluoroquinolones are the most commonly used agents worldwide for prostate biopsy prophylaxis.[6] However, overuse of fluoroquinolones has also led to increased resistance to them.[7] Due to this developing resistance, it was found that infection rates decreased by 53% with multiple antibiotic prophylaxis.[8]

In studies on uropathogenic *Escherichia coli* (*E. coli*), fosfomycin resistance was generally found to be <5%.[9] Since fosfomycin can reach therapeutic levels in prostate tissue, studies have shown that it reduces infective complications related to prostate biopsy.[10] Current publications and recommendations suggest that fluoroquinolones should not be used for less than 1 day, and augmented antibiotic prophylaxis may be considered in case of resistance.[11]

**Corresponding Author:** Şakir Ongün **E-mail:** sakirongun@hotmail.com



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In recent studies, the benefit of the combination of fosfomycin and ciprofloxacin in prostate biopsy prophylaxis was investigated, and it was found to be superior.[12,13] Considering that there are limited studies on this subject in our country and the world, we aimed to compare the efficacy of ciprofloxacin prophylaxis with the combination of fosfomycin and ciprofloxacin and examine the risk factors.

## MATERIAL AND METHODS

Following Ethics Committee approval of Balikesir University Health Sciences (date: November 8, 2023, number: 2023/116), the data of patients who underwent TRUGPB between January 2018 and January 2023 were retrospectively analyzed. Patients were divided into 2 groups according to antibiotic prophylaxis used before the procedure: group 1, oral ciprofloxacin 500 mg (2 × 1) 5 days starting 24 hours before biopsy and group 2, oral ciprofloxacin 500 mg (2 × 1) 5 days starting 24 hours before biopsy and oral fosfomycin 3 g single dose the night before biopsy. After excluding patients who had used other antibiotics before the procedure and had more than 12 crores biopsied, 1109 patients were included in the study. All procedures were performed by 3 experienced surgeons in a single center. No urinary tract infection was detected in the pre-procedure examinations of all patients included in the study, and enema for distal colon cleansing on the day of the procedure and rectal cleansing with povidone–iodine (10% solution) immediately before the biopsy was performed. A Voluson 730 Pro model (GE HealthCare, Chicago, Ill, USA) ultrasonography device and transrectal ultrasonography probe were used for imaging. Patients received intrarectal administration of 60 mg lidocaine-containing gel (Cathagel®) followed by 5 mL of 2% prilocaine in the periprostatic area with a 20 G Chiba needle. Prostate dimensions were measured (length × width × height × 0.5236), and prostate volume (mL) was calculated. Using an automated biopsy gun (18 G, 25 cm, Bard Max-Core, Bard Peripheral Vascular Inc., Tempe, Ariz, USA), 12 core systematic prostate biopsies were obtained.

Demographic information of the patients was obtained from their medical records. Age, serum PSA levels, prostate volume, comorbidities, previous urological surgery, antibiotic use in the last 6 months, history of prostate biopsy in the last year, and urethral catheterization status were recorded. Pathology results and infectious complications after the biopsy were recorded. Patients who presented with infectious complications within 30 days after biopsy were screened. Infectious complications were categorized as fever, urinary infection with fever, urinary infection without fever, and sepsis.

Statistical Package for the Social Sciences (SPSS) software was used for statistical analysis (v.25.0, IBM SPSS Corp.; Armonk, NY, USA). In the study, numerical data were calculated as mean ± standard deviation, and categorical data were calculated as percentages because of normal distribution. The significance between categorical groups was analyzed by the chi-square test. The difference between numerical data was evaluated with the Student-*t* test. A value of $P < .05$ was considered statistically significant.

### MAIN POINTS

- Fosfomycin resistance detected in E. coli in the intestinal flora and urinary tract infection resistant to fosfomycin is rarely detected and generally below 5%. In contrast, this rate is above 20% for fluoroquinolones and trimethoprim.
- Current publications and recommendations suggest that fluoroquinolones should not be used for less than one day, and augmented antibiotic prophylaxis may be considered in case of resistance. Adding fosfomycin to ciprofloxacin in TRUGPB prophylaxis effectively prevents post-biopsy infective complications compared to ciprofloxacin prophylaxis alone.

## RESULTS

Between January 2018 and January 2023, 1109 patients who underwent TRUGPB in the urology clinic of our hospital were included in the study. The mean age of the patients was 65.9 (±7.8) years, the mean serum PSA (prostate specific antigen) value was 26.2 (±71.8) ng/mL, and the mean prostate volume was 78.4 (±68.6) mL. When the antibiotic prophylaxis used by the patients before the biopsy was evaluated, 323 (29.1%) patients received ciprofloxacin (group 1), and 786 (70.9%) patients received fosfomycin + ciprofloxacin (group 2) prophylaxis.

There was no significant difference in age and PSA when compared to the antibiotics used ($P = .279$ and $P = .302$). Prostate volume was significantly larger in the ciprofloxacin group (84.2 ± 106 vs. 75.3 ± 36, $P = .031$). When biopsy pathology results were evaluated, prostate cancer was found in 406 patients (36.6%). When pathology results were compared according to the antibiotic group used, there was no significant difference ($P = .144$).

When infectious complications after biopsy were analyzed, fever developed in 15 patients (1.4%), febrile urinary tract infection (UTI) in 9 patients (0.8%), afebrile UTI in 9 patients (0.8%), and sepsis in 4 patients (0.5%). When infectious complications were compared according to the antibiotic prophylaxis, febrile UTI and sepsis were statistically significantly more common in group 1

(*P* = .003 and *P* = .027). A comparison of infectious complications is given in Table 1.

When the risk factors for infective complications after biopsy were investigated, 158 patients (14.2%) had comorbidities, and 43 patients (3.9%) had more than one comorbidity. Ninety-five patients (8.6%) had urethral catheterization during the procedure, and 6 patients (0.5%) had urological surgery in the last 6 months. One hundred twenty-five patients (11.3%) used antibiotics within the last 6 months, and 17 patients (1.5%) had a prostate biopsy within the last year. When risk factors were compared according to the antibiotic prophylaxis used, no statistically significant difference was found in comorbidity, having more than one comorbidity, urethral catheterization status, and antibiotic use in the last 6x months. Urological surgery within the last 6 months and prostate biopsy within the last year were statistically significantly higher in group 1 (*P* = .009 and *P* = .002). However, when the patients who had urologic surgery in the last 6 months and who had a prostate biopsy for the second time in the last year were analyzed, it was found that none of them developed infectious complications. Table 2 compares risk factors for infectious complications between to the groups.

## DISCUSSION

It is an indisputable issue that antibiotics should be used before prostate biopsy, but which antibiotic should be used and for how long is a matter of debate. Due to the increase in fluoroquinolone-resistant *E. coli*, a change in the prophylaxis of TRUGPB has been sought. The most important complications after prostate biopsy are infective complications, and these infections are of bacterial origin. The source of bacterial infections is thought to be rectal bacteria getting into the blood and urinary system during biopsy.[14]

Fosfomycin is an effective antibiotic against both gram-negative and gram-positive bacteria, as well as resistant and multidrug-resistant bacteria.[15,16] Fosfomycin resistance detected in *E. coli* in the intestinal flora and urinary tract infection resistant to fosfomycin is rarely detected and generally below 5%. In contrast, this rate is above 20% for fluoroquinolones and trimethoprim.[9] In 2020, the European Medicines Agency reported that oral fosfomycin provides effective protection against infections in prostate biopsy.[17] The half-life of fosfomycin after oral ingestion is approximately 4 hours. About 50% is excreted through the urinary system and 25% through feces.[18,19] Fosfomycin penetrates effectively into prostatic tissue, and oral administration 1-4 hours before transurethral prostate resection is sufficient to maintain an effective concentration in prostatic tissue[20] and therapeutic concentration for up to 36 hours.[21] Using fosfomycin before prostate biopsy reduces infective complications compared to fluoroquinolones, and urinary infections with or without fever are observed at a lower rate.[22,23] At least 24 hours of protection should be provided after prostate biopsy, and fosfomycin is a good candidate for this due to its low resistance rates and good prostate penetration.[10,21]

**Table 1.** Comparison of the Infectious Complications

| | Group 1 (n = 323) | Group 2 (n = 786) | *P* |
|---|---|---|---|
| Fever | 6 (1.9) | 9 (1.1) | .252 |
| Febrile UTI | 7 (2.2) | 2 (0.3) | **.003** |
| Afebrile UTI | 3 (0.9) | 6 (0.8) | .514 |
| Sepsis | 4 (1.2) | 1 (0.1) | **.027** |

**Table 2.** Comparison of the Risk Factors for Infectious Complications According to the Groups

| | Group 1 (n = 323) | Group 2 (n = 786) | *P* |
|---|---|---|---|
| Comorbidity | 36 (11.1%) | 122 (15.5%) | .166 |
| Urethral catheter | 25 (7.7%) | 70 (8.9%) | .308 |
| Urological surgery in the last six months | 5 (1.5%) | 1 (0.1%) | **.009** |
| Antibiotic use in the last six months | 43 (13.3%) | 82 (10.4%) | .103 |
| Previous prostate biopsy in the last year | 11 (3.4%) | 6 (0.8%) | **.002** |

Among the infective complications seen after prostate biopsy, those due to antibiotic-resistant or multidrug-resistant *E. Coli*, which tend to increase in rectal flora, are on the rise.[24,25] Due to this increase in resistant microorganisms, clinicians are now recommended to choose antibiotic prophylaxis according to local resistance information.[26] Increased antibiotic prophylaxis (use of more than one antibiotic) before prostate biopsy reduced post-biopsy infective complications by 53%.[8] Current studies suggest that ciprofloxacin prophylaxis should be given for at least 1 day and augmented with additional antibiotics.[11] We wanted to compare the effect of ciprofloxacin prophylaxis augmented with fosfomycin on infective complications compared to ciprofloxacin alone.

In our study, there was no statistical difference between the groups regarding the incidence of febrile UTI and fever after biopsy. Febrile UTI was 2.2% in group 1 and 0.3% in group 2. According to these results, febrile UTI was statistically significantly more common in group 1 (*P* = .003). Sepsis was 1.2% in group 1 and 0.1% in group

2. According to these results, sepsis was statistically significantly more common in group 1 ($P = .027$). According to these results, sepsis and febrile UTIs decreased significantly when fosfomycin was added to ciprofloxacin. In a recently published study, amikacin or fosfomycin was added to ciprofloxacin, and its effects on infective complications were compared by Yu et al.[13] and found that approximately 10 times fewer infective complications were observed when fosfomycin was added, similar to our study. In another study, Lim et al.[12] found that the use of the combination of fosfomycin and ciprofloxacin in prophylaxis significantly reduced infective complications compared to those who received only fosfomycin or only ciprofloxacin prophylaxis. In our study, we found that augmented antibiotic prophylaxis with fosfomycin reduced infective complications; these results were similar to Lim et al.[12]

Risk factors of infection after prostate biopsy have been defined as previous prostate biopsy, urethral catheter, ongoing urinary infection, antibiotic use in the last 6 months, previous urologic surgery, and immunosuppression.[3] When the risk factors of the patients who underwent biopsy were evaluated in our study, no difference was found between the antibiotic groups in patients with urethral catheterization and antibiotic use within the last 6 months. Patients who underwent urologic surgery within the last 6 months and had a history of prostate biopsy within the last year were statistically significantly more in group 1 ($P = .009$ and $P = .002$). However, when the complication status of patients who had urologic surgery within the last 6 months and who had a prostate biopsy for the second time within the last year was analyzed, it was found that no infective complication developed in patients with these risk factors. Although studies have shown that the number of biopsy cores does not increase the likelihood of infective complications, we did not include patients other than standard 12-core biopsies.[27] When these results are evaluated, it can be concluded that the groups in our study were homogeneous regarding risk factors.

Currently, European Association of Urology (EAU) guidelines recommend transperineal prostate biopsy due to lower infectious complications.[28] A systematic review reported no significant differences between receiving or not receiving antibiotic prophylaxis on infectious complications for transperineal prostate biopsy.[29] We believe that it will take more time for urologists to abandon transrectal biopsy and adapt to this new method due to decades of habit.

Antibiotic prophylaxis aims to use antibiotics in the shortest possible time and dose to prevent possible infections. It should be remembered that unnecessary and inappropriate antibiotic use may increase antibiotic resistance. Although the simultaneous use of more than one antibiotic in our study seems contrary to these principles, when we look at the prophylaxis we applied in terms of profit and loss, we believe a significant decrease in infective complications is in the public interest.

The limitations of our study are that it was retrospective, and the group receiving only ciprofloxacin was relatively smaller.

In conclusion, adding fosfomycin to ciprofloxacin in TRUGPB prophylaxis is an effective combination to prevent post-biopsy infective complications compared to ciprofloxacin prophylaxis alone.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Balıkesir University Health Sciences (date: November 8, 2023; number: 2023/116).

**Informed Consent:** N/A. Permission was obtained from the hospital management to use patient data.

**Peer-review:** Externally peer-reviewed.

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