Comparison of amikacin with fosfomycin as an add-on to ciprofloxacin for antibiotic prophylaxis in transrectal prostate biopsy: A single-center retrospective study

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Purpose: To assess the effect of ciprofloxacin (CP) and fosfomycin compared with CP and amikacin in patients with a fluoroquinolone (FQ)-resistant rectal flora who have undergone transrectal ultrasound-guided prostate biopsy (TRUSPB).

Materials and Methods: In total, 516 patients with FQ-resistant rectal flora based on rectal swab cultures were divided into two groups according to prophylactic antibiotics. Patients in both groups were administered CP (400 mg, intravenous [IV], twice daily) on the same day as TRUSPB and 1 day after biopsy. The amikacin group (n=260) was administered a single injection of amikacin (1 g, IV) 1 hour before TRUSPB, whereas the fosfomycin group (n=256) was administered fosfomycin (3 g, orally) the night before the procedure. The primary endpoint was the rate of infectious complications in the two groups.

Results: Overall, 13 patients (2.5%) reported infectious complications: 12 patients (4.62%) in the amikacin group compared with 1 patient (0.39%) in the fosfomycin group (risk ratio, 0.09; 95% confidence interval [CI], 0.01–0.65), respectively, which was a statistically significant difference (p=0.017). This corresponds to a number needed to treat of 24 patients (95% CI, 15–65) to prevent one infectious complication. In the multivariate analysis to assess variables related to infectious complications, prophylactic antibiotics with added fosfomycin was associated with infectious complications (odds ratio, 0.060; 95% CI, 0.008–0.459).

Conclusions: In the era of FQ resistance, CP and fosfomycin may reduce the rate of infectious complications compared with CP and amikacin prophylaxis.

Keywords: Antibiotic prophylaxis; Biopsy; Ciprofloxacin; Fosfomycin; Prostate

INTRODUCTION

The prevalence of health checkups for prostate cancer screening is increasing after the introduction of the prostate-specific antigen (PSA) test, with transrectal ultrasound-guided prostate biopsy (TRUSPB) becoming the “gold standard” procedure. However, TRUSPB can lead to infectious complications, such as urinary tract infection (UTI), acute prosta-
titis, bacteremia, and life-threatening sepsis, some of which can cause severe morbidity and even death [1]. Therefore, several guidelines strongly recommend antibiotic prophylaxis to reduce these complications at the time of TRUSPB, and fluoroquinolones (FQs) are broadly prescribed because of their ease of administration, safety profile, and high penetrability into prostate tissues [2-4].

Recently, the incidence of infectious complications has consistently increased, despite the wide use of FQs as the standard antibiotic prophylaxis in TRUSPB. Moreover, the incidence of infectious complications caused by FQ-resistant Escherichia coli, especially the extended-spectrum β-lactamase (ESBL)-producing E. coli, has markedly increased [5-7]. Hence, numerous physicians have questioned the old prophylaxis regimens and are trying to establish new drug protocols for “extended or targeted antibiotic prophylaxis.” Several studies have focused on the addition of single-dose amikacin to standard FQ prophylaxis and have reported a reduced incidence of infectious complications after TRUSPB. However, no consensus has been reached regarding appropriate extended or targeted antibiotic prophylaxis, and in fact, to the best of our knowledge, no trial has been conducted to date on patients with FQ-resistant rectal flora [7-12].

In the present study, we developed a combined regimen of ciprofloxacin (CP) and fosfomycin. Fosfomycin is an oral, bactericidal, broad-spectrum antibiotic with favorable pharmacokinetics and pharmacodynamics profiles that promote its effectiveness against UTIs [13]. In addition, the bacterial resistance rate to fosfomycin is extremely low, cross-resistance with FQs is rare, and fosfomycin is reportedly effective against β-lactamase-producing bacteria [14]. However, to the best of our knowledge, no study has investigated the efficacy of fosfomycin with quinolone-based antibiotic prophylaxis for TRUSPB. Therefore, this study aimed to investigate whether the addition of fosfomycin to CP-based antimicrobial prophylaxis reduces the rate of infectious complications compared with the addition of single-dose amikacin to standard FQ prophylaxis after TRUSPB during the era of high FQ-resistant rectal flora.

**MATERIALS AND METHODS**

1. Data collection

This retrospective study was performed between January 2011 and June 2019 at Chonnam National University Hwasun Hospital, Korea. All patients undergoing TRUSPB were examined for rectal flora by use of a rectal swab within 2 weeks of biopsy. Among 3,603 patients who underwent TRUSPB during this period, 3,087 patients were excluded from this study for the following reasons: absence of culture data (n=448), growth of other rectal flora (n=692), growth of FQ-sensitive rectal flora (n=1,262), and use of other antibiotics (n=685).

Rectal swabs (KOMED, Sungnam, Korea) were plated directly onto MacConkey agar (KOMED) with or without 1 μg/mL of CP and were incubated overnight at 37°C in ambient air. All isolates were characterized on the Vitek® 2 microbial identification system using the GN and AST-GN30 cards (bioMérieux, Durham, NC, USA) for identification and susceptibility testing, respectively.

A total of 516 patients with FQ-resistant rectal flora based on rectal swab cultures were divided into two groups according to prophylactic antibiotics: the amikacin group and the fosfomycin group. From 2011 through April 2018, amikacin and CP were administered as optimal extended antibiotic prophylaxis. After that, from May 2018 through June 2019, fosfomycin and CP were administered as another optimal extended antibiotic prophylaxis. Patients in both groups were administered CP (400 mg, intravenous [IV], twice daily) on the same day as TRUSPB and 1 day after biopsy. In the amikacin group (n=260), a single injection of amikacin (1 g, IV) was administered 1 hour before TRUSPB, and in the fosfomycin group (n=256), fosfomycin (3 g orally) was administered the night before the procedure.

All patients who underwent TRUSPB were administered an enema (COLCLEAN-S ENEMA® 133 mL; a mixture of dibasic sodium phosphate and monobasic sodium phosphate, Taejoon Pharmaceutical Co., Seoul, Korea) on the day of biopsy. Rectal cleansing with povidone-iodine (10% solution) was performed immediately before biopsy. Rectal disinfection with povidone-iodine was used as a potential adjunct to antibiotic prophylaxis, with the rationale that povidone-iodine rectal cleansing would reduce the rectal bacterial burden before biopsy and decrease the size of the microbial inoculum introduced during the biopsy procedure [15]. Currently, European Association of Urology guidelines recommend rectal cleansing with povidone-iodine before transrectal prostate biopsy [16].

All biopsy procedures were conducted using a LOGIQ E9 TRUS device (GE Healthcare, Milwaukee, WI, USA). An ACECUT automatic biopsy gun (CIVCO Medical Solutions, Kalona, IA, USA) with an 18-gauge needle was used to obtain standard 8- to 12-core biopsies, using the same protocol.

Patient characteristics were obtained from the patients’ medical records. These included age, serum PSA level, prostate volume, diabetes mellitus, surgical history, history of prostatitis or UTI, antibiotic exposure (FQ or others) within 6 months, and previous history of prostate biopsy (within 1
year or >1 year before) before TRUSPB. In addition, peri-procedural data, such as the number of biopsy cores, type of prophylactic antibiotic, duration of antibiotic use, local anesthesia, infectious complications after TRUSPB, and pathological results, were obtained from all patients.

We investigated the rate of infectious complications, history of acute urinary retention, and hematuria after TRUSPB. Infectious complications included hospital admission because of infection, fever, symptomatic UTI, acute prostatitis, bacteremia, sepsis, or systemic inflammatory response syndrome (SIRS). UTI and fever were defined as postprocedural bacteriuria associated with clinical signs of UTI (dysuria, frequency, and urgency) and a body temperature of ≥38°C, respectively. Acute prostatitis was defined as fever, myalgia with clinical signs of UTI, and leukocytosis with an abruptly elevated PSA level. Bacteremia was defined as the existence of bacteria in blood culture. Sepsis was defined as SIRS caused by infection. SIRS was defined as being present when two or more of the following conditions were met: body temperature ≥38°C or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or respiratory alkalosis, or a white blood cell count >12,000/mm³ or <4,000/mm³, or the presence of >10% immature band forms [4].

The assessment of infectious complications was limited to 30 days after TRUSPB to accurately include only those patients with biopsy-related events. If the patients were admitted because of infectious complications, blood and urine samples were collected from these patients and examined to confirm the pathogens and their antibiotic sensitivities.

2. Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Chonnam National University Hwasun Hospital (IRB no. CNUHH-2017-040). As this is a retrospective study, the need for informed consent of the patients was waived off. The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies.

3. Statistical analysis

Statistical analyses were performed using SPSS (version 23.0, IBM Corp, Armonk, NY, USA). Continuous variables are presented as means and standard deviations, and categorical variables are presented as frequencies (%). Fisher’s exact test was conducted to assess associations between covariate distributions and FQ resistance, ESBL positivity, and infectious complications. Multivariate logistic regression (stepwise backward procedure) was performed to determine factors influencing infectious complications. Statistical significance was set at p<0.05 for all analyses.

RESULTS

As shown in Table 1, no significant differences in patient characteristics were noted between groups except for history of antibiotic exposure within 6 months (7.4% vs. 18.1% in the fosfomycin and amikacin groups, respectively, p=0.001) and duration of prophylactic FQ intake (15 days vs. 20 days in the fosfomycin and amikacin groups, respectively, p<0.001). Before prostate biopsy, the fosfomycin and amikacin groups were similar in terms of prostate volume (33.6 vs. 33.6 g, respectively, p=0.777), history of prostatitis (0.8% vs. 2.3%, respectively, p=0.285), and positive rectal swab culture results for ESBL-producing organisms (31.6% vs. 31.9%, respectively, p=0.999).

The rectal flora obtained from rectal swab cultures before TRUSPB included mostly E. coli (92.1%), Klebsiella pneumoniae (19%), and other species (60%). ESBL positivity was 31.8% on rectal swab cultures. There were no significant intergroup differences in rectal swab culture findings (p=0.093) or ESBL positivity (p=0.999).

The primary endpoint was the efficacy of extended antibiotic prophylaxis in patients with FQ-resistant rectal flora. In the total study population, 13 patients (2.5%) reported infectious complications 12 (46.2%) patients (8 acute prostatitis, 3 SIRS, and 1 sepsis) in the amikacin group and 1 (0.39%) patient with acute prostatitis in the fosfomycin group (risk ratio, 0.09; 95% confidence interval [CI], 0.01–0.65), respectively; this difference was statistically significant (p=0.017). This corresponds to a number needed to treat of 24 patients (95% CI, 15–65) to prevent one infectious complication.

In the univariate and multivariate analysis to assess variables related to infectious complications, prophylactic antibiotics with added fosfomycin was associated with infectious complications (odds ratio [OR], 0.103; 95% CI, 0.013–0.797, p=0.029). However, no such statistically significant association was noted for the other clinical parameters. Although the frequency of antibiotic exposure within 6 months in each group was different (7.4% vs. 18.1% in the fosfomycin and amikacin groups, respectively, p<0.001; Table 1), it was not associated with infectious complications, as revealed by regression analysis (OR, 1.032; 95% CI, 0.263–4.055; Table 2).

Multivariate analysis was performed to evaluate parameters that were associated with ESBL positivity of the rectal flora. The frequency of antibiotic exposure within 6 months was found to be associated with ESBL positivity of the rectal flora (OR, 20.04; 95% CI, 1.090–3.686; p=0.025; Table 3).
Details of the pathogens cultured from infected patients are presented in Table 4. Among the patients with infectious diseases, the bacteria identified in urine culture were quinolone resistant, except in one case. The concordance rate of FQ resistance between rectal swab and urine cultures was 88.9%. The most common pathogens in patients with FQ-resistant rectal flora was FQ-resistant E. coli. All E. coli pathogens isolated belonged to amikacin-susceptible species. Patients with infectious complications were successfully treated using IV imipenem or piperacillin–tazobactam.

DISCUSSION

With the increasing incidence of FQ-resistant rectal flora, urologic specialists in the field of infection have difficulty in providing optimal antibiotic prophylaxis after TRUSPB. This has led to several research studies investigating alternative antibiotics as extended or targeted antibiotic prophylaxis for TRUSPB. However, no optimal method has yet been established for extended antibiotic prophylaxis. In the present study, we investigated whether the addition of single fosfomycin to CP in patients with FQ-resistant rectal...
flora might reduce the rate of infectious complications after TRUSPB compared with extended antibiotic prophylaxis with CP and amikacin. We found that the addition of single-dose fosfomycin was associated with a lower incidence of infectious complications.

To date, FQs have been considered as the first choice of antibiotic prophylaxis for TRUSPB, and several guidelines strongly recommend FQs to reduce the rate of infectious complications after TRUSPB owing to the ease of administration, safety profile, and high bioavailability in prostate tissues [2-4]. Nevertheless, the steadily increasing prevalence of FQ-resistant bacteria in rectal flora and the resulting infectious complications are concerning in most countries and may result in significant socioeconomic burdens [56].

Therefore, many clinicians have focused on extended or targeted antibiotic prophylaxis for infectious complications after TRUSPB. Among other antibiotics, amikacin was selected as the additional antibiotic in several studies because of the low rate of amikacin resistance of isolated pathogens from prostate biopsy specimens and the high levels of the antibiotic in prostatic tissue with a single dose [7-9]. The results of these previous studies have shown that adding amikacin to FQ prophylaxis may reduce the rate of infectious complications after TRUSPB [7-9]. In contrast, there are several reports with conflicting findings regarding the benefits associated with adding aminoglycosides to standard FQ prophylaxis. In a prospective randomized trial performed by Miyazaki et al. [10], the addition of amikacin to levofloxacin prophylaxis showed no advantage compared with levofloxacin alone in febrile UTI after TRUSPB. This previous study examined 447 patients and found two patients with febrile UTI in the levofloxacin group and one with febrile UTI in the amikacin co-treatment group. The pathogens isolated from the three patients were FQ-resistant E. coli

Table 3. Results of univariate and multivariate analysis results for ESBL positivity

| Parameter                  | Univariate | Multivariate |
|----------------------------|------------|--------------|
| Age                        | 1.014 (0.992–1.036) | 1.016 (0.994–1.040) |
| Prostate-specific antigen   | 1.001 (0.999–1.002) | 1.006 (0.997–1.015) |
| Prostate volume             | 1.005 (0.997–1.014) |             |
| Prior prostate biopsy       | 0.759 (0.269–2.144) |             |
| Prior operation history within 6 mo | 2.846 (1.523–5.319) | 2.061 (0.990–4.289) |
| Diabetes mellitus           | 0.824 (0.539–1.262) |             |
| Antibiotics exposure within 6 mo | 2.615 (1.549–4.417) | 2.004 (1.090–3.686) |
| Histological prostate cancer detection | 0.919 (0.634–1.331) |             |

ESBL, extended-spectrum β-lactamase; OR, odds ratio; CI, confidence interval.
*Statistically significant p<0.05.

Table 4. Results for cultures in patients with infectious complications

| Patient | Group | Type of infectious complication | Urine culture | Blood culture | FQ resistance | ESBL positivity |
|---------|-------|---------------------------------|---------------|---------------|---------------|----------------|
| 1       | FM    | AP                              | *Escherichia coli* | NG            | Yes           | No             |
| 2       | AK    | Sepsis                          | *Staphylococcus aureus* | No       | NR            |                |
| 3       | AK    | AP                              | *E. coli* | NG            | No            | No             |
| 4       | AK    | AP                              | NG            | NG            | NR            | NR             |
| 5       | AK    | AP, bacteremia                  | *E. coli* | *E. coli* | Yes           | No             |
| 6       | AK    | AP                              | NG            | NG            | NR            | NR             |
| 7       | AK    | AP, bacteremia                  | *E. coli* | *E. coli* | Yes           | Yes            |
| 8       | AK    | AP                              | *Enterococcus spp.* | NG       | Yes           | NR             |
| 9       | AK    | SIRS                            | *E. coli* | NG            | Yes           | Yes            |
| 10      | AK    | AP                              | *E. coli* | NG            | Yes           | Yes            |
| 11      | AK    | SIRS                            | *Klebsiella spp.* | NG       | Yes           | Yes            |
| 12      | AK    | SIRS                            | NG            | NG            | NR            | NR             |
| 13      | AK    | AP                              | *E. coli* | NG            | Yes           | No             |

FQ, fluoroquinolone; ESBL, extended-spectrum β-lactamase; FM, fosfomycin; AP, acute prostatitis; NG, no growth; AK, amikacin; NR, not reported; SIRS, systemic inflammatory response syndrome.
in two patients and ESBL-positive E. coli in the remaining patient; however, all isolates were susceptible to amikacin [10]. In addition, Gopal Rao et al. [11] retrospectively analyzed 503 patients and reported that infectious complications after TRUSPB cannot be completely eliminated by appropriate antimicrobial prophylaxis, including CP and amikacin prophylaxis. In our previous study, we investigated whether the use of amikacin with CP reduces the rate of infectious complications after TRUSPB but found no significant reduction in this rate in patients with antibiotic-resistant rectal flora [12].

This discrepancy can be explained by differences in the antibiotic resistance and ESBL positivity of rectal flora. Most previous studies have stated that western countries have a relatively lower rate of antibiotic resistance than Asian countries. In our previous study, we evaluated FQ resistance and ESBL positivity of rectal flora before biopsy in patients who were undergoing TRUSPB, and the results showed higher antibiotic resistance of rectal flora than that reported in western countries (FQ resistance, 10.6%–22.0% vs. 48.1%–54.9% ESBL positivity, 13%–11.0% vs. 11.8%–17.2%) [12,17,18]. In addition, Ozlen et al. [19] reported that ESBL-positive E. coli showed a significant reduction in activity for most antibiotics, including FQ, amikacin, and cephalosporin, suggesting that extended antibiotic prophylaxis with amikacin is useful if the antibiotic resistance of the rectal flora is low. However, according to the results of our previous study, antibiotic resistance of the rectal flora, especially ESBL-positive bacteria, was relatively high, and the extended antibiotic prophylaxis with amikacin showed no benefit [12]. Considering these results, the addition of single-dose amikacin to CP is not sufficient as extended antibiotic prophylaxis to prevent infectious complications after TRUSPB in the era of high FQ-resistant rectal flora.

As mentioned above, there is no consensus regarding appropriate targeted or extended antibiotic prophylaxis for TRUSPB. Recently, a single 3-g oral dose of fosfomycin was suggested as a potential alternative antibiotic for TRUSPB prophylaxis [20]; however, to the best of our knowledge, no study has been conducted to investigate the efficacy of fosfomycin with quinolone-based antibiotic prophylaxis, especially in patients with FQ-resistant rectal flora. We combined CP and fosfomycin to reduce the rate of infectious complications after TRUSPB. Moreover, we found that the addition of fosfomycin to CP in patients with FQ-resistant rectal flora was associated with a lower incidence of infectious complications.

There are several rationales for the use of fosfomycin as a second antimicrobial agent. The first is to prevent the emergence of fosfomycin-resistant strains and provide a synergistic effect. Fosfomycin inhibits bacterial cell wall biosynthesis by acting on the initial stages of peptidoglycan cross-linking, whereas other antibiotics act on the late stages of bacterial cell wall synthesis [21]. This unique mechanism may provide a synergistic effect to other antibiotics, including β-lactams, aminoglycosides, and FQs. The second rationale is that, in contrast with aminoglycosides, fosfomycin is not nephrotoxic. In cases of oral administration, no dosage adjustment is necessary in patients with hepatic or renal failure. In addition, oral fosfomycin is well tolerated, with a low incidence of adverse events. These events are mainly gastrointestinal symptoms that are transient, mild, and self-limiting and reportedly include diarrhea (10%), nausea (5%), abdominal pain (2%), and dyspepsia (1%–2%). Other adverse effects including headache, dizziness, back pain, weakness, vaginitis, rhinitis, and pharyngitis are extremely rare [22]. The third rationale considers the pharmacokinetics and pharmacodynamics profiles of fosfomycin. In a prospective study examining the penetration of fosfomycin into benign prostatic tissue, Gardiner et al. [23] reported that fosfomycin was well distributed to prostate tissues and that reasonable intraprostatic concentrations were reached after a single 3-g oral dose. However, aminoglycosides do not penetrate prostatic tissue well, and their levels in prostatic tissue are likely inadequate to eradicate gram-negative bacteria [24]. In our previous study, we found no significant reduction in the rate of infectious complications after TRUSPB, despite different groupings according to FQ resistance and the addition of amikacin (p=0.107). Furthermore, all E. coli pathogens isolated from specimens of infectious complications were amikacin-susceptible species [12].

In the present study, the addition of single-dose fosfomycin to CP showed promise for reducing the rate of infectious complications after TRUSPB; however, dosages and administration schedules of fosfomycin are still in question. Theoretically, fosfomycin is primarily excreted unchanged through the kidneys. This can result in very high urinary concentrations within 2 to 4 hours, while maintaining therapeutic concentrations for at least 36 hours [23]. Nevertheless, fosfomycin is not recommended for systemic infections, as the levels reached in serum after administration are significantly lower than those in urine, and are not high enough to cover bloodstream infection after TRUSPB [25]. To overcome the low serum concentrations of fosfomycin, a dosing regimen of 6 to 12 g daily divided into three doses has been proposed to treat systemic bacterial infections to obtain efficacious exposure; however, this is associated with a risk for gastrointestinal adverse effects [26]. Furthermore, in a
randomized prospective study using multiple doses of fosfomycin for TRUSPB, no significant differences were reported in clinical outcomes between the regimens [27]. Considering the high prostate/plasma ratio up to 17 hours after oral administration of a single dose [23], we used a single dose of fosfomycin as an additional antibiotic prophylaxis to CP the night before performing TRUSPB. However, further trials with other dosages and administration schedules are warranted in the future.

Targeted prophylaxis as directed by pre-biopsy rectal cultures may also serve to reduce the rate of infectious complications, similar to the addition of fosfomycin to CP prophylaxis [28,29]. However, the associated logistics or cost burden of these methods is yet to be prospectively assessed in the era of FQ-resistant rectal flora [30]. Further prospective studies regarding the cost-effectiveness and optimal strategy of targeted prophylaxis are needed. While the transperineal approach can decrease the rate of infectious complications compared with the transrectal approach, the requirement for general anesthesia and other equipment probably renders it unfeasible for a large proportion of urologists worldwide [30].

The present study has several limitations. We used MacConkey agar with 1 μg/mL of CP. The rate of quinolone resistance at institutions that use MacConkey agar with 1 μg/mL of CP could be higher than that at other institutions that use agar with 10 μg/mL of CP. We designed this study without including other types of quinolones for antibiotic prophylaxis because of regulatory restrictions by the National Health Insurance Corp (Wonju, Korea). In practice, CP is commonly used for antibiotic prophylaxis in South Korea; therefore, further studies with levofloxacin are recommended. The absence of randomization and blinding of observers to the type of antibiotic prophylaxis used can be considered as limitations. A prospective comparative study with a large sample is needed, wherein all patients are thoroughly investigated.

CONCLUSIONS

To the best of our knowledge, the present study is the first to describe the effect of adding a single dose of fosfomycin to CP prophylaxis in patients with FQ-resistant rectal flora who underwent TRUSPB. The addition of fosfomycin to CP prophylaxis showed advantage in patients with FQ-resistant rectal flora compared with amikacin and CP prophylaxis. However, considering the increase of FQ-resistant rectal flora, additional studies are needed to determine the optimal extended antibiotic prophylaxis of TRUSPB.
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