



## Optimal Modified Extended Antibiotic Prophylaxis for Prostate Biopsy: The Addition of Two Intravenous Doses of Amikacin to Ciprofloxacin

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**Purpose:** This retrospective study was undertaken to investigate whether increasing amikacin dosage for ciprofloxacin prophylaxis in patients with fluoroquinolone (FQ)-resistant rectal flora reduce infectious complications after transrectal ultrasound-guided prostate biopsy (TRUSPB).

**Materials and Methods:** A total of 430 patients with FQ-resistant rectal flora based on rectal swab cultures were divided into two groups. Patients in both groups were administered ciprofloxacin (400 mg, intravenous [IV], twice daily) on the same day as TRUSPB and one day after biopsy. However, whereas group 1 patients (n=202) were administered a single injection of amikacin (1 g, IV) one hour before TRUSPB, patients in group 2 (n=228) were administered two injections of amikacin (1 g, IV) before one hour TRUSPB and again on the day after TRUSPB.

**Results:** Of the 430 study subjects, 129 (30.0%) showed extended-spectrum beta-lactamase (ESBL) positivity. The overall incidence rate of infectious complications was 2.8% (12/430). Infectious complication rates were 4.0% (8/202) in group 1 and 1.3% (3/228) in group 2 (p=0.075). Urinary tract infection and acute prostatitis were more frequent in group 1 (3.5% vs. 0.4%, p=0.029). Infectious complication rates in ESBL negative patients were 3.4% (5/145) in group 1 and 1.3% (2/156) in group 2, whereas those in ESBL positive patients were 7.0% (4/57) in group 1 and 1.4% (1/72) in group 2.

**Conclusions:** Increasing the dosage of amikacin for ciprofloxacin prophylaxis reduce infectious complications in patients with FQ-resistant rectal flora and to be more effective in ESBL positive patients with FQ-resistant rectal flora.

**Keywords:** Prostate; Biopsy; Fluoroquinolones; Amikacin; Infection

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## INTRODUCTION

Transrectal ultrasound-guided prostate biopsy (TRUSPB) is recognized as the “gold standard” diagnostic procedure for prostate cancer despite its possible risks and complications, which include pain, dysuria, hematuria, hematospermia, rectal bleeding, urinary retention, and urinary tract infection (UTI) [1]. Accordingly, antibiotic prophylaxis is being

increasingly used to reduce infectious complications, such as fever, acute prostatitis, bacteremia, and life-threatening sepsis, some of which can cause severe morbidity and even death [2]. Guidelines issued by the American Urological Association and the European Association of Urology recommend fluoroquinolones (FQs) for prophylaxis due to their broad-spectrum activities against gram-positive and gram-negative bacteria [3,4]. However, the incidence of

infectious complications has consistently increased despite the use of FQs and their proven efficacies. Moreover, a simultaneous and marked increase in infectious complications involving FQ-resistant *Escherichia coli*, especially extended-spectrum beta-lactamase (ESBL)-producing *E. coli*, has occurred over the last 20 years [5-8].

Numerous clinicians have focused on the use of targeted or extended antibiotic prophylaxis to reduce infectious complications following TRUSPB, and several have suggested that the addition of aminoglycoside as an targeted or extended might be both beneficial and cost-effective [9-12]. However, unfortunately, the dosage and administration method for extended antibiotic prophylaxis have not been established.

The present study aimed to determine whether increasing amikacin doses for ciprofloxacin prophylaxis in patients with FQ-resistant rectal flora reduce infectious complications after TRUSPB.

## MATERIALS AND METHODS

### 1. Data Collection

This retrospective study was performed between January 2015 and February 2018 in Chonnam National University Hwasun Hospital, Korea. All patients that underwent TRUSPB with a rectal flora specimen collected using a rectal swab within 2 weeks before biopsy were included. Patients negative for rectal swab culture growth were excluded.

Rectal swabs (KOMED, Seongnam, Korea) were directly plated onto MacConkey agar (KOMED) with or without 1 µg/ml ciprofloxacin and incubated overnight at 37°C in ambient air. All isolates were characterized on VITEK® 2 using GN and AST-GN30 cards (bioMérieux, Durham, NC, USA) for identification and susceptibility testing, respectively. Rectal swab samples were obtained within 2 weeks prior to TRUSPB.

Four hundred and thirty patients with FQ-resistant rectal flora based on rectal swab cultures were enrolled in this study. These patients were divided into two groups. Patients in group 1 (n=202) received a single intravenous dose of 1 g amikacin one hour before TRUSPB in addition to intravenous ciprofloxacin (400 mg, twice daily) on the day of biopsy and one day after TRUSPB. Patients in group 2 (n=228) received two intravenous doses of 1 g amikacin were administered at one hour before TRUSPB and one

day after TRUSPB in addition to ciprofloxacin, which was administered as described for group 1.

Enema (133 ml) containing a mixture of dibasic sodium phosphate and monobasic sodium phosphate (COLCLEAN-S ENEMA®; Taejoon Pharmaceutical Co., Seoul, Korea) was administered on the day of biopsy and rectal cleansing with povidone-iodine (10% solution) was performed immediately before biopsy in all patients.

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

Patient characteristics, including age, serum prostate-specific antigen (PSA) level, prostate volume, rectal swab culture results, 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 prior) before TRUSPB, were retrieved from medical records. Moreover, periprocedural data on numbers of biopsy cores, types of prophylactic antibiotics, duration of antibiotic use, local anesthesia, rectal enema use, rectal cleansing with povidone-iodine, infectious complications after TRUSPB, and pathological results were acquired for all patients.

Infectious complications, history of acute urinary retention (AUR), and hematuria after TRUSPB were investigated. Infectious complications included hospital admission due to infection, fever, symptomatic UTI, acute prostatitis, bacteremia, sepsis, and 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  $\geq 38^{\circ}\text{C}$ , 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  $\geq 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , heart rate  $> 90$  beats per minute, respiratory rate  $> 20$  breaths per minute or respiratory alkalosis, or a white blood cell count  $> 12,000/\text{mm}^3$  or  $< 4,000/\text{mm}^3$ , or the presence of  $> 10\%$  immature band forms [13,14].

Infectious complications were limited to those that occurred

up to 30 days after TRUSPB to include only biopsy-related events. In the event of a patient admission due to an infectious complication, blood and urine samples were collected and examined to confirm the presence of pathogens and to determine their antibiotic sensitivities.

## 2. Statistical Methods

Statistical analyses were performed using IBM SPSS Statistic ver. 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean values and standard deviations, and categorical variables as frequencies (%). Fisher's exact tests were used to assess associations between covariate distributions and FQ resistance, ESBL positivity, and infectious complications. Statistical significance was accepted for p-values <0.05.

## 3. Ethics Statement

The study protocol was reviewed and approved by the institutional review board of Chonnam National University Hwasun Hospital (IRB no. CNUHH-2015-158, CNUHH-2017-040). In addition, the study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies.

## RESULTS

Rectal swab culture results before TRUSPB showed 28.2% were ESBL positive in group 1 and 31.6% in group 2 (Table 1). No significant intergroup difference was found for patient characteristics with the exception of prostate volume ( $p=0.022$ ) and a history of antibiotic exposure within the previous 6 months ( $p=0.003$ ). In group 1, 8 patients (4.0%) developed an infectious complication; AUR and hematuria were detected in one patient each (0.5%). In group 2, 3 patients (1.3%) developed an infectious complication, and no case of hematuria or AUR was encountered. Notably, the overall incidence rates of complications in the two study groups were significantly different ( $p=0.027$ ), whereas the overall incidence rate of infectious complications after TRUSPB was non-significantly lower in group 2 (4.0% vs. 1.3%,  $p=0.075$ ). On the other hand, the incidence of UTI or acute prostatitis was significantly lower in group 2 (3.5% vs. 0.4%,  $p=0.029$ ).

Regarding the effect of ESBL positivity on infectious complications, we found the infectious complication rate

**Table 1.** General characteristics of patients

Variable	Group 1 (n=202)	Group 2 (n=228)	p-value
Age (y)	69.7±8.3	68.8±9.3	0.324
PSA (ng/ml) <sup>a)</sup>	0.97±0.53	0.95±0.53	0.646
Prostate volume (ml)	39.04±22.42	34.23±20.65	0.022
Rectal swab culture			0.518
<i>Escherichia coli</i>	188 (93.1)	217 (95.2)	
<i>Klebsiella pneumoniae</i>	6 (3.0)	8 (3.5)	
<i>Enterobacter</i> spp.	2 (1.0)	1 (0.4)	
<i>E. coli</i> + <i>K. pneumoniae</i>	1 (0.5)	0	
Others	5 (2.5)	2 (0.9)	
ESBL positivity	57 (28.2)	72 (31.6)	0.462
Diabetes mellitus	53 (26.2)	42 (18.4)	0.062
Surgical history	22 (10.9)	16 (7.0)	0.176
History of prostatitis (mo)			0.515
<6	6 (3.0)	4 (1.8)	
≥6	1 (0.5)	3 (1.3)	
History of UTI	4 (2.0)	5 (2.2)	>0.999
Prior prostate biopsy (y)			0.438
No	169 (83.7)	181 (79.4)	
<1	7 (3.5)	7 (3.1)	
≥1	26 (12.9)	40 (17.5)	
Antibiotic exposure <6 mo			0.003
No	162 (80.2)	208 (91.2)	
Others	5 (2.5)	3 (1.3)	
Quinolone	35 (17.3)	17 (7.5)	
Complication			0.027
No	192 (95.0)	225 (98.7)	
Infectious complications	8 (4.0)	3 (1.3)	
Acute urinary retention	1 (0.5)	0	
Hematuria	1 (0.5)	0	
Infectious complications	8 (4.0)	3 (1.3)	0.075
Hospital admission due to infection	5 (2.5)	2 (0.9)	0.261
Fever	6 (3.0)	3 (1.3)	0.316
UTI, acute prostatitis	7 (3.5)	1 (0.4)	0.029
Bacteremia	2 (1.0)	1 (0.4)	0.603
Sepsis, SIRS	4 (2.0)	2 (0.9)	0.426

Values are presented as mean±standard deviation or number (%).

Group 1: administered a single injection of amikacin (1 g, intravenous [IV]) one hour before TRUSPB, Group 2: administered two injections of amikacin (1 g, IV) one hour before TRUSPB and again on the day after TRUSPB, PSA: prostate-specific antigen, ESBL: extended-spectrum beta-lactamase, UTI: urinary tract infection, SIRS: systemic inflammatory response syndrome.

<sup>a)</sup>Logarithmically adjusted.

was higher in ESBL positive patients in group 1 (7.0%) than in group 2 (1.4%) (Table 2), whereas infectious complication rates in ESBL negative patients were 3.4% (5/145) in group 1 and 1.3% (2/156) in group 2.

Table 3 details the pathogens cultured from infected patients. The most common pathogens in patients with FQ-resistant rectal flora were FQ-resistant and ESBL-producing *E. coli*. All *E. coli* pathogens isolated were amikacin-susceptible species. Patients with infectious complications were

**Table 2.** Infectious complications after prostate biopsy according to ESBL positivity

Variable	ESBL (-) (n=301)			ESBL (+) (n=129)		
	Group 1 (n=145)	Group 2 (n=156)	p-value	Group 1 (n=57)	Group 2 (n=72)	p-value
Infectious complications	5 (3.4)	2 (1.3)	0.268	4 (7.0)	1 (1.4)	0.169
Hospital admission due to infection	2 (1.4)	2 (1.3)	>0.999	3 (5.3)	0	0.084
Fever	3 (2.1)	2 (1.3)	0.675	3 (5.3)	1 (1.4)	0.321
UTI, acute prostatitis	3 (2.1)	0	0.111	4 (7.0)	1 (1.4)	0.169
Bacteremia	1 (0.7)	1 (0.6)	>0.999	1 (1.8)	0	0.442
Sepsis, SIRS	2 (1.4)	2 (1.3)	>0.999	2 (3.5)	0	0.193

Values are presented as number (%).

ESBL: extended-spectrum beta-lactamase, Group 1: administered a single injection of amikacin (1 g, intravenous [IV]) one hour before TRUSPB, Group 2: administered two injections of amikacin (1 g, IV) one hour before TRUSPB and again on the day after TRUSPB, UTI: urinary tract infection, SIRS: systemic inflammatory response syndrome.

**Table 3.** Results of cultures for patients with infectious complications

Case	Group	Type of infectious complications	Urine culture	Blood culture	FQ resistance	ESBL positivity
1	1	Sepsis	No growth	<i>Staphylococcus aureus</i>	No	NR
2	1	AP	<i>Escherichia coli</i>	No growth	No	No
3	1	UTI, bacteremia	<i>E. coli</i>	<i>E. coli</i>	Yes	Yes
4	1	AP	<i>Enterococcus</i> spp.	No growth	Yes	NR
5	1	SIRS	<i>E. coli</i>	No growth	Yes	Yes
6	1	AP	<i>E. coli</i>	No growth	Yes	Yes
7	1	SIRS	<i>Klebsiella</i> spp.	No growth	Yes	Yes
8	1	SIRS	No growth	No growth	NR	NR
9	2	SIRS	No growth	No growth	NR	NR
10	2	Sepsis	No growth	<i>E. coli</i>	Yes	No
11	2	AP	<i>E. coli</i>	No growth	Yes	Yes

FQ: fluoroquinolone, ESBL: extended-spectrum beta-lactamase, NR: not reported, AP: acute prostatitis, UTI: urinary tract infection, SIRS: systemic inflammatory response syndrome.

successfully treated using intravenous imipenem or piperacillin-tazobactam.

## DISCUSSION

In this era of rectal flora with high FQ resistance, optimal antibiotic prophylaxis after TRUSPB is a main objective of urologic infection research. Several studies have indicated the addition of amikacin to FQ prophylaxis might reduce infectious complications [9,10,12]. However, no optimal dosage or administration method for extended antibiotic prophylaxis has yet been established. In the present study, we investigated whether two administrations of supplementary intravenous amikacin to ciprofloxacin might reduce infectious complications after TRUSPB. We found this increase reduced infectious complications in patients with FQ-resistant rectal flora, and that it was particularly more effective in ESBL positive patients with FQ-resistant rectal flora.

The prevalence of antibiotic resistance in normal rectal

flora, especially FQ-resistant and ESBL-positive rectal flora, is steadily increasing in the majority of countries [15,16]. Recent studies conducted in the West to determine rectal flora and antibiotic resistance patterns before TRUSPB using rectal swab cultures revealed FQ-resistant and ESBL-producing bacteria rates of 10.6% to 22.0% and 1.3% to 11.0%, respectively [17,18]. However, antibiotic resistance in the rectal flora appears more common in Asian countries. Chung et al. [7] reported prevalences of 48.1% and 11.8% for FQ-resistant and ESBL-positive rectal flora, respectively, in the Korean population, and Tsu et al. [19] reported prevalences of 40.4% and 41.0%, respectively, in Chinese patients in Hong Kong. However, these differences between reported prevalences may have been caused by different rectal swab culture methods and antibiotic susceptibilities. In the present study, of the 430 study subjects, 129 (30.0%) were ESBL positive.

Several clinicians have emphasized the need for extended or targeted antibiotic prophylaxis before TRUSPB due to

the increasing numbers of infectious complications caused by FQ-resistant and ESBL-producing bacteria. Furthermore, numerous recent studies have reported the addition of a single dose of amikacin to standard FQ prophylaxis reduced the incidence of infectious complications after TRUSPB. Amikacin was selected as an additional aminoglycoside antibiotic in these studies because of the low resistance to amikacin observed in isolates from specimens and high amikacin levels in prostatic tissue after a single dose [9]. Batura et al. [9] in a retrospective review, showed the incidence of febrile infections decreased from 3.9% to 1.4% after the addition of amikacin, and Kehinde et al. [10], in a survey of 1,200 patients, showed the addition of amikacin to ciprofloxacin prophylaxis significantly reduced the incidence of septicemia from 8% to 1.7% after TRUSPB ( $p < 0.001$ ). With respect to cost-effectiveness, Adibi et al. [12] concluded adding a single dose of amikacin was significantly more cost-effective than standard FQ prophylaxis when the risk of admission for an infectious complication after TRUSPB and year-on-year increases in the number of biopsies were taken into account.

Other effective combined regimens for antibiotic prophylaxis before TRUSPB have also been reported. The addition of gentamicin, another aminoglycoside, was reported to have significantly reduced the rate of hospitalization for infectious complications and to be cost-effective [11]. Unnikrishnan et al. [20] compared rates of infection after TRUSPB between two FQ regimens, namely 500 mg ciprofloxacin and 750 mg levofloxacin, which were both used in combination with an intramuscularly administered aminoglycoside. It was found levofloxacin was the better option because of its longer half-life and higher oral bioavailability than ciprofloxacin, and consequently, the authors concluded levofloxacin was superior to ciprofloxacin in terms of preventing severe infections after TRUSPB when used in combination with aminoglycosides.

Some have reported contrary findings regarding the benefits associated with adding aminoglycosides to standard FQ prophylaxis. In a prospective randomized trial performed by Miyazaki et al. [21], the addition of one intravenous dose of amikacin to one oral dose of levofloxacin had no advantage over levofloxacin alone in terms of antimicrobial prophylaxis after TRUSPB, although it should be added this study was underpowered by an unexpectedly low overall incidence of febrile UTI. Furthermore, in this

previous study, all pathogens isolated from febrile patients were sensitive to amikacin. In addition, Gopal Rao et al. [22] reported infectious complications after TRUSPB cannot be wholly eliminated by appropriate antimicrobial prophylaxis, including ciprofloxacin and amikacin prophylaxis. Actually, in a previous retrospective study that included 503 patients who underwent TRUSPB, we found the addition of a single dose of amikacin to ciprofloxacin prophylaxis did not reduce infectious complications in patients with FQ-resistant rectal flora [23].

As mentioned above, no consensus has been reached regarding the appropriate dosage of amikacin for targeted or extended antibiotic prophylaxis, and in fact, no trial has been conducted to date on patients with FQ-resistant rectal flora. In the present study, we developed a combined regimen consisting of ciprofloxacin and amikacin, because other FQs are restricted by the National Health Insurance Corporation and because our rectal swab culture results showed FQ-resistant and ESBL-positive rectal floras were more susceptible to amikacin than gentamicin.

In the present study, we investigated the effect of adding two intravenous doses of amikacin in 430 patients with FQ-resistant rectal flora. The results obtained showed the addition of two intravenous doses of amikacin to ciprofloxacin prophylaxis reduced infectious complications in patients with FQ-resistant rectal flora as compared with the addition of a single dose of amikacin. Therefore, the results indicate additional amikacin has potential for extended antibiotic prophylaxis after TRUSPB. We suggest additional studies be undertaken to elucidate the kinetics of amikacin in prostate, as this might lead to the development of more efficient methods for antibiotic prophylaxis.

Recently, a number of studies have reported on the emergence of ESBL-producing bacteria and on their relations with infectious complications after TRUSPB. ESBL production is a mechanism of antibiotic resistance, and Ozden et al. [8] showed that ESBL-producing isolates had a significant reduction in activity for most antimicrobial agents, including FQs, amikacin, cefazolin, ceftriaxone, and cefepime. In the present study, 30.0% of patients with FQ-resistant rectal flora were ESBL-positive, and this high rate of ESBL positivity might have resulted from the excessive use of broad-spectrum antibiotics in our hospital. Actually, some case-control studies have reported prior use of third-generation cephalosporin or FQ is an independent risk factor of

infection by ESBL-producing organisms [24,25]. In addition, in a previous study, we observed the incidence of ESBL-positive *E. coli* isolation was significantly higher in patients with a history of antibiotic treatment within 6 months ( $p=0.005$ ) [23].

Hyle et al. [26] reported inappropriate initial antibiotic treatment is an independent risk factor of mortality in patients with bacteremia caused by ESBL-producing bacteria, which suggests physicians should attempt to identify pathogens before TRUSPB and select appropriate antibiotics. In the present study, the addition of two intravenous doses of amikacin to ciprofloxacin prophylaxis was found to be more effective in ESBL positive patients with FQ-resistant rectal flora. The present study may be the first to describe the effect of adding two intravenous doses of amikacin to ciprofloxacin prophylaxis. Nevertheless, further studies are needed to investigate the effect of amikacin on ESBL-producing bacteria as this might improve the efficacy of prophylaxis.

The results of the present study indicate that the overall rate of febrile infectious complications in patients with FQ-resistant rectal flora is low, which may have been due to rectal cleansing with povidone-iodine before biopsy and extended antibiotic prophylaxis. Disinfection with povidone-iodine was used as a potential adjunct to antibiotic prophylaxis, and was performed to reduce rectal bacterial burden before biopsy and to reduce the burden imposed by microbial inoculum during biopsy. Based on our previous studies, we believe rectal cleansing with povidone-iodine may have lowered the infectious complication rate by reducing bacterial load [27,28].

The present study has several limitations. First, we used MacConkey agar containing 1 µg/ml ciprofloxacin, and the rates of quinolone resistance in institutions that use this formulation may be higher than those in institutions that use agar containing 10 µg/ml ciprofloxacin. Second, our results may have been affected by selection bias because a significant difference was observed between patient characteristics. We suggest further studies be conducted to address this topic. Furthermore, the two groups differed in terms of history of antibiotic exposure during the 6-month preceding TRUSPB. Third, the study was also limited by its small cohort and retrospective nature.

## CONCLUSIONS

The addition of two intravenous doses of amikacin to ciprofloxacin prophylaxis reduced infectious complications in patients with FQ-resistant rectal flora, and was more effective in ESBL positive than in ESBL negative patients.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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