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Infectious Complications after Prostate Biopsy: A Prospective Multicenter Prostate Biopsy Study

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Purpose: Recent studies have highlighted an increasing trend of infectious complications due to fluoroquinolone-resistant organisms among men undergoing transrectal prostate biopsy. This study evaluated the current incidence of infective complications after trans-rectal prostate biopsy for identification of risk factors in Korean men who received fluoroquinolone prophylaxis.

Materials and Methods: A prospective, multicenter study was conducted in Korea from January to December 2015. Prostate biopsies performed with fluoroquinolone prophylaxis during 3 months in each center were included. A pre-biopsy questionnaire was used for identification of patient characteristics. Clinical variables including underlying disease, antibiotic prophylaxis, enema, povidone-iodine cleansing of the rectum, and infectious complications were evaluated. The primary outcome was the post-biopsy infection rate after fluoroquinolone prophylaxis. Univariable and multivariable analyses were used for identification of risk factors for infectious complications.

Results: The study included 827 patients, of whom 93 patients (11.2%) reported receiving antibiotics in the previous 6 months and 2.5% had a history of prostatitis. The infectious complication rate was 2.2%. Post-biopsy sepsis was reported in 2 patients (0.2%). In multivariable analysis predictors of post-biopsy sepsis included person performing biopsy (adjusted odds ratio [OR], 4.05; 95% confidence interval [CI], 1.31-12.5; p=0.015) and operation history within 6 months (adjusted OR, 5.65; 95% CI, 1.74-18.2; p=0.004).

Conclusions: The post-prostate biopsy infectious complication rate in this study was 2.2%. Person performing biopsy (non-urologists) and recent operation history were independent risk factors for infectious complications after trans-rectal prostate biopsy.

Keywords: Biopsy; *Escherichia coli*; Fluoroquinolones; Infection; Prostate

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INTRODUCTION

Prostate biopsy is currently an essential procedure for prostate cancer diagnosis. More than one million transrectal prostate biopsies are performed in Europe and the United States annually to determine whether patients have prostate cancer [1]. Fluoroquinolones (FQs) are particularly useful in this setting owing to their broad spectrum of activity against intestinal flora as well as their high prostatic tissue levels after oral administration [2,3].

Despite antibiotic prophylaxis, several recent studies have reported an increased rate of infective complications following transrectal prostate biopsy in both North America and Europe [4-8]. A recent review of the literature found that up to 6.3% of patients required hospitalization due to post-biopsy complications [4]. This has led to increased use of multiple broad-spectrum antibiotics for prophylaxis; however, this practice may accelerate the development of resistant bacteria [9,10]. The most common pathogen implicated in post-transrectal prostate biopsy sepsis is *Escherichia coli*, accounting for approximately 75-90% of infectious complications. Antimicrobial-resistant *E. coli* has been increasingly reported in post-biopsy sepsis over the past decade [8]. The link between prior FQ exposure, colonization with fluoroquinolone-resistant (FQ-R) *E. coli*, and subsequent post-biopsy infection with FQ-R *E. coli* was also recently demonstrated [11]. The risk of post-biopsy infection is increased by 7-fold in patients with FQ-R organisms in their rectal flora [12]. In an era of increasing rates of FQ-R *E. coli* in many countries, the role of prebiopsy screening for resistant pathogens, followed by culture-directed antimicrobial prophylaxis, was assessed in several recent studies [11,13]. Despite the emergence of FQ-R organisms, in practice, FQ remain the most commonly prescribed antibiotics [3]. In this context, knowledge of the incidence of infectious events requires comprehensive monitoring of patients undergoing biopsy with FQ prophylaxis. Unfortunately, only a few studies in Korea have been designed to ensure exhaustive analysis in this situation. Therefore, we evaluated the incidence of infective complications after trans-rectal prostate biopsy and identified risk factors in Koreans who received FQ.

MATERIALS AND METHODS

1. Data Collection

A prospective, multicenter study in Korea was conducted from January to December 2015. Groups at centers throughout Korea were recruited among members of the Korean Association of Urogenital Tract Infection and Inflammation (KAUTII) based on motivation and commitment to completeness. The study protocol was reviewed and approved by the institutional review board of Chonnam National University Hwasun Hospital (CNUHH-2014-154) and all study participants read and signed an informed consent form.

The indications for biopsy included elevated prostate-specific antigen levels or abnormal digital rectal examination findings. A 3-month recruitment period was planned, followed by 1 month of post-biopsy follow-up.

A prebiopsy questionnaire was used for identification of patient characteristics. Clinical variables including underlying disease, patient age, prostate-specific antigen levels, health care association, relation to healthcare worker, history of travel within the past 4 weeks, operation history, prostatitis within the previous 6 months, urinary tract infection (UTI) within the previous 6 months, recent antibiotic exposure, and previous prostate biopsy were recorded.

Patients who were residents of any nursing home or long-term care facility, were re-admitted within 90 days of discharge from a previous hospitalization for 2 or more days, or within 30 days prior to the onset of UTI, had indwelling urethral catheters, had undergone any invasive urinary procedure, had received hemodialysis or intravenous chemotherapy on an outpatient basis, or had received specialized nursing care at home by qualified healthcare providers were categorized as having health care association [14]. Peri-procedural data, the number of biopsy cores, duration of antibiotic use, use of local anesthesia, rectal enema use, povidone-iodine rectal cleansing, infectious complications after biopsy, and pathological results were obtained on all patients.

2. Antibiotic Prophylaxis before Prostate Biopsy

The American Urological Association Best Practice Policy Statement on Urologic Surgery and Antimicrobial Prophylaxis recommends <24 hours administration of a

FQ or alternative agent before transrectal prostate biopsy. In patients with risk factors, less than 4-day protocols are recommended in European countries and North America and in Japan among Asian countries [15].

In this study we recommend FQ protocols of less than 4 days and advise that physicians practice discretion in their use. This recommendation is not consistent with the American Urological Association statement. However, risk of infectious complications is higher in non-Caucasian people because of the potential for high exposure to antibiotics as a medicine or in meat, which may result in increased antibiotic resistance [15]. Therefore, we advise that physicians use discretion in the duration of antibiotic therapy. Patients administered antibiotics other than quinolones or for an extended duration were excluded.

3. Definition of Infectious Complications

Post-biopsy infectious complications were defined as follows: fever (37.8°C), febrile UTI, acute prostatitis, and bacteremia and sepsis within 3 to 5 days after the procedure [16]. Infectious complications and clinical and microbiological characteristics were recorded. The primary outcome was the post-biopsy infection rate. Risk factors for infectious complications were also determined.

4. Statistical Analysis

Baseline characteristics of the enrolled patients were analyzed using descriptive statistics. Univariable and multivariable logistic regression analyses (stepwise forward procedure) were performed to determine which factors influenced infectious complications. Among these factors, those with $p<0.25$ (in univariable analysis for infectious complication) were included in the multivariable logistic regression analysis, which was performed to obtain adjusted odds ratios (ORs) to determine risk factors for infectious complication. A 2-sided $p<0.05$ was considered statistically significant for all analyses. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Inc., Armonk, NY, USA).

RESULTS

1. Demographics

This study included 827 patients who received FQ prophylactic antibiotics; 12.6% received treatment for less than 3 days and 87.4% received treatment for more than 3 days, from the day of biopsy to the day after biopsy. The median patient age was 69 years (interquartile range [IQR], 63-74). The median prostate specific antigen levels and prostate volumes were 1.87 ng/dl (IQR, 1.51-2.43) and 37.2 ml (IQR, 27.0-51.7), respectively. Among all patients, 11.2% reported receiving antibiotics in the previous

Table 1. Baseline characteristics of enrolled patients

Variable	Value (n=827)
Age (y)	69 (63-74)
PSA[a] (ng/dl)	1.87 (1.51-2.43)
Prostate volume (ml)	37.2 (27.0-51.7)
Biopsy operators	
Urologist	423 (51.1)
Non-urologists	404 (48.9)
Biopsy results	
BPH	512 (61.9)
Prostate cancer	313 (37.8)
ASAP	2 (0.2)
Number of biopsy cores	
<12	345 (41.7)
≥12	482 (58.3)
Health care-associated patients	98 (11.9)
Health care workers	
Non-medical	806 (97.5)
Medical service provider	20 (2.4)
Medical service provider's family	1 (0.1)
Travel history within 4 wk	20 (2.4)
Diabetes mellitus	122 (14.8)
Operation history within 6 mo	48 (5.8)
Prostatitis history within 6 mo	21 (2.5)
UTI history within 6 mo	12 (1.5)
Prior prostate biopsy	
No	794 (96.0)
<12 mo	23 (2.8)
≥12 mo	10 (1.2)
Antibiotics exposure history	93 (11.2)
Duration of Antibiotics	
<3 d	104 (12.6)
≥3 d	723 (87.4)
Local anesthesia used	252 (30.5)
Povidone iodine used	827 (100)
Enema	
No	21 (2.5)
Rectal	789 (95.4)
Oral	17 (2.1)
Infectious complication	18 (2.2)
Hospitalization due to infectious complications	16 (1.9)
Fever	17 (2.1)
UTI, acute prostatitis	15 (1.8)
Bacteremia	8 (1.0)
Sepsis	2 (0.2)

Values are presented as median (interquartile range) or number (%).
PSA: prostate specific antigen, BPH: benign prostate hyperplasia, ASAP: atypical small acinar proliferation, UTI: urinary tract infection.
[a]Logarithmically adjusted.

6 months and 2.5% had a history of prostatitis. The rate of health care-associated patients was 11.9%. Most patients underwent enema with rectal (95.4%) or oral agents (2.1%), and all patients underwent povidone-iodine rectal cleansing despite the lack of official recommendation for this treatment prior to this study. Urologists performed 51.1% of the biopsies, and radiologists performed 48.9% of the biopsies, respectively. The pathological results of the biopsies were benign in 61.9% of patients (Table 1).

2. Rates and Risk Factors of Infectious Complications

The overall rate of infectious complication was 2.2%. Post-biopsy sepsis was detected in 2 patients (0.2%) (Table 1), and there were no infection-related deaths.

In univariable analysis person performing biopsy (non-urologists vs. urologists) (OR, 3.76; 95% confidence interval (CI), 1.22-11.5; p=0.020), the number of biopsy cores (vs. <12 cores) (OR, 2.85; 95% CI, 1.06-7.69; p=0.038), health care association (OR, 2.96; 95% CI, 1.03-8.49; p=0.043), operation history within 6 months (OR, 4.96; 95% CI, 1.57-15.7; p=0.006), and history of antibiotic exposure (OR, 4.14; 95% CI, 1.51-11.3; p=0.006) were associated with infectious complications (Table 2). In multivariable analysis the risk factors for post-biopsy infectious complications included person performing biopsy

Table 2. Univariable and multivariable analysis of clinical parameters affecting infectious complications after prostate biopsy

Variable	Odds ratio	p-value	Adjusted odds ratio	p-value
Age	0.96 (0.91-1.01)	0.088		
Person performing biopsy (non-urologists vs. urologists)	3.76 (1.22-11.5)	0.020	4.05 (1.31-12.5)	0.015
Number of biopsy cores (vs. <12)	2.85 (1.06-7.69)	0.038		
Health care-associated	2.96 (1.03-8.49)	0.043		
Health care workers				
Medical service provider	NA	0.998		
Medical service provider's family	NA	1		
Travel history within 4 wk	NA	0.998		
Diabetes mellitus	1.67 (0.54-5.17)	0.371		
Operation history within 6 mo	4.96 (1.57-15.7)	0.006	5.65 (1.74-18.2)	0.004
Prostatitis history within 6 mo	2.32 (0.29-18.2)	0.424		
UTI history within 6 mo	4.26 (0.52-34.9)	0.176		
Prior prostate biopsy (vs. no)				
<12 mo	NA	0.998		
≥12 mo	NA	0.999		
Antibiotics exposure history	4.14 (1.51-11.3)	0.006		
Duration of antibiotic use (vs. ≥3 d)	2.48 (0.32-18.8)	0.380		
Local anesthesia used	0.28 (0.06-1.22)	0.091		
Enema				
Rectal	NA	0.998		
Oral	NA	1		

UTI: urinary tract infection, NA: not available.

Table 3. Culture results

Culture	Pathogens	ESBL positivity	Fluoroquinolone resistance
Urine (n=2)	*E. coli*	-	+
	E. coli	-	+
Blood (n=3)	*E. coli*	+	+
	E. coli	-	+
	Staphylococcus aureus	-	-
Blood and urine (n=5)	*E. coli*	+	+
	E. coli	+	+
	Citrobacter freundii	-	-
	E. coli	+	+
	E. coli	-	+

ESBL: extended-spectrum beta lactamase, *E. coli*: *Escherichia coli*.

Table 4. *Escherichia coli* resistance patterns

Antibiotics	Urine (n=2)		Blood (n=2)		Blood and urine (n=4)			
Amoxicillin/clavulanate	Resistance	Sensitive	Sensitive	Sensitive	Intermediate	Resistance	Resistance	Sensitive
Piperacillin/tazobactam	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Trimethoprim-sulfamethoxazole	Resistance	Sensitive	Sensitive	Resistance	Sensitive	Resistance	Resistance	Resistance
Levofloxacin	Not tested	Intermediate	Not tested	Not tested	Not tested	Resistance	Not tested	Not tested
Ciprofloxacin	Resistance	Resistance	Intermediate	Resistance	Resistance	Resistance	Resistance	Resistance
Gentamicin	Resistance	Resistance	Sensitive	Not tested	Resistance	Sensitive	Sensitive	Sensitive
Amikacin	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Imipenem	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Meropenem	Not tested	Sensitive	Sensitive	Sensitive	Not tested	Sensitive	Not tested	Not tested

(non-urologists vs. urologists) (adjusted OR, 4.05; 95% CI, 1.31-12.5; p=0.015) and operation history within 6 months (adjusted OR, 5.65; 95% CI, 1.74-18.2; p=0.004) (Table 2).

Only 10 bacterial isolates were obtained from blood and urine specimens. The most common pathogen was *E. coli* (8 of 10) (Table 3). The FQ-R *E. coli* rate was 100% (8 of 8), and the extended-spectrum beta lactamase positivity rate was 50 % (4 of 8). The resistance pattern of *E. coli* showed that all cultured *E. coli* were sensitive to amikacin, piperacillin/tazobactam, and imipenem (Table 4). The antimicrobial susceptibility test for fosfomycin and nitrofurantoin was not performed.

DISCUSSION

Although FQ have most commonly been used for prostate biopsy, infectious complications after the procedure have increased in recent years. In Korea, the reported incidence of infectious complications after transrectal ultrasound prostate biopsy ranges from 0.65% to 3.1% [17,18]. In another global multi-institutional study including Korea, the reported incidence of febrile UTI was 3.5%, and the incidence of infections requiring admission was 3.1% [19]. The main cause of this situation is the rise in antibiotic resistance, particularly to FQ. Carignan et al. [20] reported that infectious complications increased from 0.52% to 2.15% between 2002-2009 and 2010-2011, respectively, with significant increases in FQ-R among the isolated bacteria. Feliciano et al. [21] reported that the incidence of infective complications after prostate biopsy was 3 times higher in 2006 compared with that observed in the 2 previous years, with the incidence of FQ-resistant UTIs 4.3 times higher in 2006 compared with that in 2004. Bang et al. [22] reported occurrence of acute bacterial prostatitis after prostate biopsy in 1.36% of patients and the prevalence of FQ-R strains was 23.8%. Overall, in recently published series, FQ resistance was detected in 24-100% of the bacterial isolates from patients with post biopsy infections [20-22].

In this study, consistent with previous studies, 80% of the isolates were FQ-R, but the infectious complication rate was 2.2%. Despite the high prevalence of FQ-R in Asian countries, the overall infectious complication rate was not higher than the rates in Europe and North America. This observation may be explained by use of rectal enemas and povidone-iodine rectal cleansing. Most patients in this multicenter study underwent both procedures in addition to antibiotic prophylaxis. Other methods to reduce the complications of prostate biopsy are currently being investigated, including alternative or targeted prophylactic agents such as rectal swabbing and adjunctive measures (e.g., enema, rectal cleansing with povidone-iodine) to antimicrobial prophylaxis. However, the role of adjunct measures in prevention of post biopsy infections remains controversial [23,24]. Zani et al. [23] reported no significant differences in total infectious complication rates between "antibiotic" and "antibiotic+enema" groups, and in a prospective randomized trial, rectal cleansing with povidone-iodine before transrectal ultrasound guided prostate biopsy did not result in a statistically significant reduction in the risk of infectious complications [25]. However, contradictory findings were also reported. In a meta-analysis, regardless of mono-prophylaxis and combined-prophylaxis with antibiotics, rectal disinfection with povidone-iodine reduced the risk of infectious complications after prostate biopsy [24], and Hwang et al. [16] reported that rectal cleansing with povidone-iodine reduced severe infectious complication including bacteremia and sepsis (p=0.001). Thus, large, multicenter, and prospective randomized controlled trials of good quality are required to assess the preventive efficacy of povidone-iodine and rectal enema on infectious

complications. However, we suggest that in this era of quinolone resistance, rectal cleansing with povidone-iodine and rectal enemas may reduce infectious complication rates by reducing bacterial burden and thereby decreasing the bacterial inoculum introduced during the biopsy procedure.

Procedure-specific factors that increase the risk of infective complications after prostate biopsy are still not well defined. The suggested risk factors for post-biopsy infectious complications include diabetes mellitus, immunosuppressive treatment, history of FQ use, endocarditis or artificial cardiac valves, chronic obstructive pulmonary disease, and biopsy within the previous several months [1,20,26]. Additional potential risks include age >80 years, indwelling catheter, former pyuria, history of prostatitis, and prostatic enlargement. Responsible use of extended or targeted prophylaxis requires better understanding of the risk factors of infectious complications. In this study, operation history within 6 months prior to prostate biopsy and person performing biopsy (biopsy performed by radiologist) were risk factors for infectious complications. Concordant with the results of previous studies, operation history may be related to exposure to antibiotics, which may lead to antibiotic resistance. We cannot explain the reasons for the statistically significant association with person performing biopsy, thus the precise effect of person performing biopsy on infectious complications should be elucidated in future studies.

Early empirical antibiotic treatment of infectious complications is important for prevention of progression to severe sepsis. Selection of antibiotics for this empirical treatment depends on results of local antibiograms. According to the results of this Korean multicenter study, the antibiotic resistance pattern of *E. coli* indicated that all cultured *E. coli* isolates were 100% sensitive to amikacin, piperacillin/tazobactam, imipenem, and 100% resistant to FQ. Despite their sensitivity to piperacillin/tazobactam, the inoculum effect of antibiotics should also be considered because there was also 50% extended-spectrum beta lactamase positivity in the *E. coli* pathogens.

To the best of our knowledge, ours is the first large Korean multicenter prospective analysis of infectious post-prostate biopsy complications. Although 24 institutions participated in this study, we believe that they are nationally representative.

However, our study has several important limitations. We acknowledge that our protocol which included administration of antibiotics for more than 1 day is not consistent with the American Urological Association statement. The American Urological Association guidelines generally recommend prophylaxis for <24 hours [15]. Similarly, the European Association of Urology guidelines recommend single-dose prophylaxis for low-risk patients and prolonged courses of prophylaxis only in high-risk patients [27]. However, according to a recent prospective multicenter study, in cases of guideline noncompliance, quinolones were administered for durations not in accordance with the recommended 1-day treatment by 75% of investigators [28]. Asian men are at risk for infectious complications because of possible high exposure to antibiotics as a medicine or in meat [15,26]. Therefore, many Korean urologists are hesitant to reduce antibiotic prophylaxis regimens to single or 1-day regimens.

In addition, there is no consensus on the optimal duration of antibiotic prophylaxis for prostate biopsy [19]. Second, only cases of FQ prophylaxis were included and other antibiotics, as well as extended and targeted prophylaxis were excluded. Heterogeneity of antibiotics might prevent identification of the risk factors for infectious complications. For example, the Global Prevalence Study of Infections in Urology, a prospective, multinational, multicenter study, included 702 men who underwent prostate biopsy. Outcome data were available on only 521 men, and no patient subgroups at significantly higher risk for infection were identified in multivariate analysis [19]. The current study on FQ prophylaxis might have a selection bias and some patients at risk might have been omitted. Additional prospective studies are required to further evaluate the performance of culture-directed therapy or extended prophylaxis and for comparison of their cost-effectiveness to empiric therapy based on local susceptibility patterns and risk factors.

CONCLUSIONS

In this prospective study, 2.2% of patients developed infectious complications after prostate biopsy and no deaths were reported. The risk factors identified by multivariable analysis included person performing biopsy and recent operation history. The results of this study suggest that use of enema and povidone-iodine rectal cleansing could decrease complications despite FQ-only prophylaxis.

CONFLICT OF INTEREST

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

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