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Research Article

Clinical Utility of Stool Culture in Targeting Antibiotic Prophylaxis for Transrectal Ultrasonography-Guided Prostate Biopsy

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Abstract

Escherichia coli is the pathogen most commonly associated with infections after transrectal ultrasonography-guided prostate biopsy, and the prevalence of fluoroquinolone-resistant E. coli is increasing. This study prospectively analyzed stool cultures, determined the presence of fluoroquinolone-sensitive (i.e., normal) and resistant E. coli, administered appropriate prophylactic antibiotics accordingly, and analyzed the rates of infectious complications following transrectal ultrasonography-guided prostate biopsy. The data from 150 consecutive patients who underwent transrectal ultrasonography-guided prostate biopsy between May 2013 and October 2014 were analyzed. A stool culture was obtained at least 7 but no more than 35 days before prostate biopsy. All patients received 500 mg levofloxacin orally once daily for 3 days, beginning 2 hours before prostate biopsy; patients who proved to be fluoroquinolone-resistant E. coli carriers according to stool culture results were supplemented with targeted intravenous prophylactic antibiotics. All biopsies were performed as outpatient procedures. Among the 150 patients, 18 (12%) had a stool culture positive for fluoroquinolone-resistant E. coli; 15 and 3 received intravenous ceftazidime and minocycline, respectively, in addition to levofloxacin. The 132 (88%) patients who were fluoroquinolone-sensitive E. coli carriers received only levofloxacin orally before transrectal ultrasonography-guided prostate biopsy. No patients developed acute bacterial prostatitis after prostate biopsy. Obtaining stool cultures and administering a targeted prophylactic antimicrobial agent may control the onset of acute prostatitis after transrectal ultrasonography-guided prostate biopsy.

Keywords: Prostate; Biopsy; Drug Resistance; Fluoroquinolones; Stool Culture

Abbreviations:

AMK: Amikacin;
CAZ: Ceftazidime;
CFPM: Cefepime;
CZOP: Cefozopran;
ESBL: Extended-Spectrum Beta-Lactamase-Producing;
IPM: Imipenem;
LVFX: Levofloxacin;
MINO: Minocycline;
TRUS biopsy: Transrectal Ultrasonography-Guided Prostate Biopsy;
PSA: Prostate-Specific Antigen

Introduction

Transrectal ultrasonography-guided prostate biopsy (TRUS biopsy) is generally accepted as the standard procedure for diagnosing prostate cancer. Complications of this procedure, such as hematuria and hemospermia, are minor, but others including infection are clinically significant. Infectious complications of TRUS biopsy are not unexpected and include fever, urinary tract infection, acute bacterial prostatitis, orchiepididymitis, and sepsis [1,2]. Many studies demonstrate the advantages of using fluoroquinolones (new quinolones), especially levofloxacin (LVFX), prophylactically to significantly decrease infectious complications of prostate biopsy [3,4]. However, some patients develop acute prostatitis caused by fluoroquinolone-resistant Escherichia coli (E.coli) after TRUS biopsy [5,6]. Because fluoroquinolones have broad-spectrum activity, their use has increased, leading to resistance [7,8]. We investigated the prevalence of fluoroquinolone-resistant E. coli before TRUS biopsy in our center and found it to be 13%. In 31% of these fluoroquinolone-resistant E. coli carriers, acute bacterial prostatitis was detected after TRUS biopsy [8]. These results prompted us to review our prophylactic antibiotic regimen in patients undergoing this procedure. Many studies recommend administering prophylactic antibiotics with an intravenous antibiotic. There are many recommendations for intravenous antibiotics, and most of these studies reported significantly decreased cases of detected acute bacterial prostatitis after TRUS biopsy [9-11]. However, these methods may not administer antibiotics suitable for E. coli of each and may increase the rate of multiresistant E. coli in the future.

Therefore, in this study, we prospectively analyzed stool cultures, determined the presence of fluoroquinolone-sensitive (i.e., normal) and resistant E. coli, administered appropriate prophylactic antibiotics accordingly, and analyzed the rates of infectious complications following TRUS biopsy.

Material and Methods

We prospectively evaluated the records of 150 consecutive patients who underwent TRUS biopsy at Kitasato University Medical Center, Saitama, Japan, between May 2013 and October 2014. Informed consent was obtained from each patient. Authorization for the use of patient samples for research purposes was obtained from the Institutional Review Board of Kitasato University Medical Center. This study conformed to the principles outlined in the Declaration of Helsinki (2008).

The indications for TRUS biopsy were elevated prostate-specific antigen (PSA) levels, abnormal digital rectal examination findings, or both. Before prostate TRUS biopsy, all patients underwent urinalysis and prostate examination to confirm the absence of urinary infection. If TRUS biopsy was indicated, stool samples were collected, preferably at least 7 days before the TRUS biopsy to allow adequate time for results but no more than 35 days before the TRUS biopsy. The stool samples for aerobic culture were obtained using a rectal swab. The stool samples were cultured onto deoxycholate-hydrogen sulfide-lactose agar and incubated aerobically at 35°C for 24 hours. After incubation, colonies thought to be those of E. coli were identified and cultured onto brain-heart infusion broth for re-culturing. The bacilli colonies were confirmed as those of E. coli using differential media, including lysine indole motility medium, Simmons citrate agar, and triple sugar iron medium. The isolated E. coli was re-cultured onto blood agar to reconfirm appropriate bacterial contamination. The isolated E. coli was identified to the strain level for reconfirmation and tested for antibiotic susceptibility by using the MicroScan WalkAway 96 plus System (Siemens Healthcare Diagnostics, Tokyo, Japan) in conjunction with a Neg Combo 6.11J Panel (Siemens Healthcare Diagnostics) [12,13]. The minimal inhibitory concentration was determined using the broth microdilution method with the MicroScan Neg Combo 6.11J panels, following guidelines from the Clinical and Laboratory Standards Institute [14].

All TRUS biopsies were performed as outpatient procedures. Patients received 500 mg LVFX orally once daily for 3 days, beginning 2 hours before TRUS biopsy [15]. Patients who proved to be fluoroquinolone-resistant E. coli carriers, according to the results of the stool culture were supplemented with intravenous antibiotics selected from the following: ceftazidime (CAZ, 1 g), cefepime (CFPM, 1 g), cefozopran (CZOP, 1 g), minocycline (MINO, 200 mg), amikacin (AMK, 200 mg), and imipenem (IPM, 0.5 g). If the strain was sensitive to multiple antibiotics, additional intravenous antibiotics were selected in the following order: CAZ, CFPM, CZOP, MINO, AMK, and IPM. If the strain was resistant to all planned antibiotics, we planned to use an antimicrobial drug (that was not in the above list) to which the strain was sensitive. Fluoroquinolone-resistant E. coli carriers received a single-dose instillation of selected intravenous antibiotics 30 minutes before TRUS biopsy in addition to LVFX. An automatic biopsy gun with an 18-gauge needle was used to obtain 12-core biopsies; the same protocol was used for all patients [15].

A clinical diagnosis of acute bacterial prostatitis was made when the following criteria were met: body temperature >38°C, leukocytes in the urine sediment, and clinical findings on digital rectal examination within 7 days after TRUS biopsy. Statistical analysis was performed using the Fisher exact test; $p < 0.05$ was considered significant.

Results

A total of 150 men underwent stool culture and TRUS biopsy during the study period and were included in the analysis. Elevated PSA level was the indication for prostate biopsy in all pa-

tients. Of the 150 patients, we detected fluoroquinolone-resistant E. coli in 18 (12%) and normal E. coli in 132 (88%) (Table 1). The 132 patients who were normal E. coli carriers received only LVFX orally, whereas the 18 patients who were fluoroquinolone-resistant E. coli carriers received LVFX orally combined with targeted antimicrobial prophylactic intravenous antibiotics before biopsy. Of 18 administrations of intravenous antibiotics, CAZ (15 of 18) and MINO (3 of 18) were used as additional intravenous antibiotics. No patients developed acute bacterial prostatitis after biopsy. Age, PSA levels, prostate volume, pathology, and prior biopsies were not associated with type of E. coli carried (p = 0.374, p = 0.42, p = 0.7, p = 1, and p = 0.54, respectively).

Table 1. Patient demographics

Variable	Total	Fluoroquinolone-resistant *E. coli* patients	Normal *E. coli* patients	*p* value*
n (%)	150	18 (12%)	132 (88%)	
Median age (range)	68.5 (45–90)	67 (52–75)	69 (45-90)	0.37
Median PSA (range) ng/mL	7.403 (3.06–1167)	5.988 (3.80–26.90)	7.477 (3.060–1167)	0.41
Prostate volume (range) mL	36.56 (7.83–150)	35.27 (19-94)	36.71 (7.83–150)	0.7
Pathology (%)				1
normal tissue and benign prostatic hyperplasia	60 (40)	11 (18)	49 (82)	
prostate adenocarcinoma	90 (60)	7 (7)	83 (92)	
Prior biopsy (%)				0.54
None	144 (96)	17 (12)	127 (88)	
One or more	6 (4)	1 (17)	5 (83)	

Normal *E. coli*: fluoroquinolone-sensitive *Escherichia coli*

PSA: prostate-specific antigen.

* Fisher's exact test.

Table 2. Drug susceptibility of fluoroquinolone-resistant and normal Escherichia coli isolated from feces.

Antimicrobial agent	Fluoroquinolone -resistant *E. coli* (*n* = 18)	Normal *E. coli* (*n* = 132)	*p* value*
Ampicillin	15 (83%)	43 (33%)	<0.01
Piperacillin	11 (61%)	14 (11%)	<0.01
Cefazolin	6 (33%)	1 (<1%)	<0.01
Cefotaxime	3 (16%)	1 (<1%)	<0.01
Ceftazidime	3 (16%)	1 (<1%)	<0.01
Cefepime	3 (16%)	1 (<1%)	<0.01
Cefozopran	3 (16%)	1 (<1%)	<0.01
Cefditoren-pivoxil	5 (28%)	10 (8%)	0.02
Cefcapene pivoxil	5 (28%)	6 (5%)	<0.01
Flomoxef	0	0	-
Imipenem	0	0	-
Tazobactam/piperacillin	0	0	-
Clavulanic acid/amoxicillin	5 (28%)	25 (19%)	0.36
Amikacin	2 (11%)	1 (<1%)	0.38
Gentamicin	0	1 (<1%)	1
Minocycline	5 (28%)	9 (7%)	0.01
Trimethoprim-sulfamethoxazole	9 (50%)	4 (3%)	<0.01

Normal *E. coli*: fluoroquinolone-sensitive *E. coli*

* Fisher's exact test.

E. coli isolated from feces were tested for susceptibility to a wide range of antimicrobial agents, and resistance patterns observed for E. coli were variable (Table 2). More than 50% of E. coli samples exhibited resistance to ampicillin, piperacillin, and trimethoprim-sulfamethoxazole (83%, 61%, and 50%, respectively). Of the 18 samples, 7 (39%), E. coli strains were resistant only to fluoroquinolone. On the other hand, of the 132 normal E. coli isolates, 43 (33%) were resistant to ampicillin, 14 (11%) were resistant to piperacillin, and 4 (3%) were resistant to trimethoprim-sulfamethoxazole. Fluoroquinolone-resistant E. coli isolates had higher multiple drug resistance ratios than did normal E. coli isolates.

Of the 150 stool cultures, 4 extended-spectrum beta-lactamase-producing (ESBL) E. coli strains were present. Of the 4 ESBL E. coli strains, 3 also showed resistance to fluoroquinolone; therefore, MINO was used as an additional intravenous antibiotic for these 3 patients with ESBL E. coli strains. Of the 4 ESBL E. coli, 1 was sensitive to fluoroquinolone; therefore, this ESBL E. coli carrier received only LVFX orally.

Discussion

TRUS biopsy remains a common urological procedure for the detection of prostate cancer. One of the most common risks of TRUS biopsy is infectious complications, among which sepsis is the most serious. Infectious complications ranging from bacteriuria to sepsis occur in 1–4% of patients [16]. Antibiotic prophylaxis has significantly decreased the rate of infectious complications associated with this procedure [16,17]. Fluoroquinolones have been the prophylactic antibiotics of choice since the 1980s mostly because of their potent activity against a large spectrum of clinically relevant pathogens in the urogenital tract [4,17]. The American Urological Association Best Practice Statement on Antibacterial Prophylaxis and the European Association of Urology guideline recommend using fluoroquinolones to prevent infection after transrectal prostate biopsy [18,19]. Despite these recommendations, fluoroquinolone-resistant E. coli isolates are increasing yearly in most countries [7,8]. Liss et al. reported that the prevalence of fluoroquinolone-resistant E. coli before prostate biopsy was 23%, and we found prevalence to be 13% in our previous study [8,20]. As the prevalence of fluoroquinolone-resistant E. coli increases, the incidence of acute prostatitis after TRUS biopsy increases [8]. One possible cause of increasing resistance to fluoroquinolones is the previous widespread use of these drugs; in fact, prior fluoroquinolone use has been reported to be an independent risk factor for the acquisition of fluoroquinolone-resistant E. coli [8,21]. Because we cannot forbid using fluoroquinolone, developing countermeasures to combat the increasing prevalence of fluoroquinolone-resistant E. coli is important. To decrease acute prostatitis incidence after TRUS biopsy, many studies recommend administering any one of various prophylactic antibiotics combined with an

intravenous antibiotic. While most of these studies reported significantly decreased cases of detected acute bacterial prostatitis after TRUS biopsy, these methods may increase the rate of further multiresistant E. coli in the future [9-11]. To prevent the development of multiresistant E. coli while preventing development of acute prostatitis by fluoroquinolone-resistant E. coli, it is necessary to minimize the use of antibiotics for TRUS biopsy with a targeted approach tailored to the patient.

In this study, we selected prophylactic antibiotics for patients according to results of their stool culture before biopsy. Normal E. coli carriers received only LVFX orally before biopsy, whereas fluoroquinolone-resistant E. coli carriers received LVFX orally combined with intravenous antibiotics. We considered the importance of diffusion of the antibiotic into the prostate when selecting effective additional antibiotics. Among the antibiotics available in our institution, the 6 antibiotics that could diffuse to prostatic tissue included for consideration were AMK, CAZ, CFPM, CZOP, MINO, and IPM [22-27]. The most effective antibiotic for sepsis following TRUS biopsy is IMP [28,29]; however, we decided to use IMP as a last resort, as it may increase the rate of multiresistant E. coli including specifically IMP-resistant E. coli. Our penultimate antibiotic choice was AMK, as AMK-sensitive E. coli can result in sepsis development after TRUS biopsy even in patients who used AMK as prophylactic antibiotics [9]. Of the cephem antibiotics (CAZ, CFPM, and CZOP) and MINO, we prioritized use by fewer side effects and lower generations. Both CFPM and CZOP are fourth-generation cephem antibiotics; CAZ is a third-generation antibiotic. Thus, antibiotics were preferentially administered in the following sequence: CAZ, CFPM, CZOP, MINO, AMK, and IPM. As a result, CAZ (15 of 18 patients) and MINO (3 of 18 patients) were the additional intravenous antibiotics used for the fluoroquinolone-resistant E. coli carriers. The 3 patients who received MINO did so because they carried ESBL E. coli that showed resistance to LVFX and all cephem antibiotics. Fortunately, E. coli resistant to all antimicrobial drugs was not detected.

In this study, we were able to control the onset of acute prostatitis after TRUS biopsy by administering an adequate, specific, prophylactic intravenous antibiotic to a fluoroquinolone-resistant E. coli carrier. This proved the importance of identifying carriers of fluoroquinolone-resistant E. coli and selecting prophylactic antimicrobial agents individually for these patients. To identify carriers of fluoroquinolone-resistant E. coli, stool cultures should be obtained before TRUS biopsy, and a prophylactic antimicrobial agent can then be selected based on these results. Prescribing prophylactic antimicrobial agents according to resistance profiles from cultures would not only eliminate prostatitis development, but also reduce additional bacterial resistance potential, as the patient will not receive superfluous antibiotic treatment. Furthermore, because none of our patients who were normal E. coli carriers developed acute bacterial prostatitis, we believe that fluoroquinolones are still potent and effective prophylactic antimicrobial agents for TRUS biopsy in patients with known normal E. coli.

Our study has potential limitations. First, the number of patients in this study was relatively small, necessitating further studies with larger samples. Second, we prophylactically administered oral LVFX and an intravenous antibiotic to fluoroquinolone-resistant E. coli carriers. Using LVFX could be problematic for patients who are administered intravenous antibiotics, but we continued administration based on the following experience. We previously administered MINO in conjunction with LVFX as prophylactic antibiotics before TRUS biopsy. Some patients developed acute prostatitis after TRUS biopsy. In 1 patient, blood culture revealed LVFX-sensitive Klebsiella sp. Because of this experience, we have continued to administer LVFX orally specifically to suppress any prostatitis onset except as a result of E. coli proliferation. However, this approach is not supported by large-scale statistics or evidence and therefore requires future investigation and inspection. Third, the reported rate of fluoroquinolone-resistant E. coli depends on methods used to identify reculture colonies, because the patient may have multiple E. coli colonies, both resistant and sensitive to fluoroquinolone. When fluoroquinolone-resistant E. coli is present but undetectable in culture, the patient may develop acute bacterial prostatitis after biopsy because of failure to administer adequate prophylaxis. Further studies to refine the stool culture method may be needed to prevent overlooking the detection of resistant bacteria.

Multidrug-resistant pathogens will continue to emerge, and the need for research directed toward development of new antibiotics has never been greater. Actions against producing multidrug-resistant bacteria are essential. Our method of selecting prophylactic antibiotics for patients based on stool culture results before biopsy controlled the onset of acute prostatitis. This method may also decrease the emergence of multidrug-resistant bacteria and ultimately reduce medical costs.

Conclusion

While prophylactic fluoroquinolone is still effective in preventing acute bacterial prostatitis after TRUS biopsy in patients with normal E. coli, the prevalence of fluoroquinolone-resistant E. coli continues to increase. Obtaining stool cultures before TRUS biopsy and administering an adequate, specific prophylactic antimicrobial agent may control the onset of acute prostatitis after TRUS biopsy.

Conflicts of Interest

The authors declare no conflicts of interest.

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