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Original Article

Efficacy of combined prophylactic use of levofloxacin and isepamicin for transrectal prostate needle biopsy: A retrospective single-center study☆

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ABSTRACT

Purpose: To assess the efficacy of a combined regimen of levofloxacin (LVFX) plus isepamicin (ISP) as prophylaxis for transrectal ultrasound-guided needle biopsy of the prostate (TRUSP-Bx).
Materials and methods: Overall, 562 patients undergoing TRUSP-Bx were included in the present study. All patients were administered a single-dose of oral LVFX (500 mg) in the morning and intravenous ISP (400 mg) 60 min before biopsy. All biopsies were performed via TRUSP-Bx with an 18-gauge needle, and 12-core specimens were routinely obtained. Before initiating antibiotic treatment, urine and blood bacterial cultures were tested to determine the causative microorganisms in the patients with acute bacterial prostatitis.
Results: Acute bacterial prostatitis developed in three (0.53%) participants. The incidence rates of acute bacterial prostatitis in the low- and high-risk groups were 0.79% and 0.46%, respectively. These patients showed clinical symptoms of acute bacterial prostatitis 12–24 h after their biopsy. *Escherichia coli* (*E. coli*) was isolated in the urine or bladder cultures of all of patients. All three isolates were determined to be LVFX-resistant *E. coli*, although they had good sensitivity to aminoglycosides, cephalosporins, and carbapenems. All patients were administered antibiotic treatment (cephalosporin or carbapenem) immediately and were treated successfully with no evidence of further disease progression.
Conclusion: Antibiotic prophylaxis with LVFX plus ISP was effective, resulting in a lower incidence of acute bacterial prostatitis after TRUSP-Bx in both low- and high-risk patients.

1. Introduction

Performing transrectal ultrasound-guided needle biopsy of the prostate (TRUSP-Bx) is necessary to diagnose prostate cancer. However, TRUSP-Bx can result in several complications, such as hematuria, urinary retention, and anal bleeding. One of the most serious complications of TRUSP-Bx is acute bacterial prostatitis, which has a reported incidence rate of 1%–5% [1–3]. Furthermore, there have been reports of fatal septic shock in some patients after TRUSP-Bx [4–6].

Antibiotic prophylaxis is recommended before TRUSP-Bx, and its efficacy is accepted worldwide. Fluoroquinolones (FQs) are widely used for antibiotic prophylaxis in TRUSP-Bx because of their outstanding prostatic tissue bioavailability and broad spectrum against bacteria [7,8]. However, FQ-resistant *Escherichia coli* (*E. coli*) has increasingly been isolated worldwide in recent times [9], and there have been reports of cases with acute bacterial prostatitis after TRUSP-Bx with prophylactic FQ administration [4,5,10]. Therefore, the establishment of more effective antibiotic regimens is a priority to reduce the incidence of acute bacterial prostatitis after TRUSP-Bx. Periodic monitoring of causative microorganisms and their drug susceptibility in cases with acute bacterial prostatitis is likely to be important.

Currently, the Japanese Urological Association (JUA)/Japanese Research Group for Urinary Tract Infection (JRGU) guidelines have recommended combined use of an aminoglycoside with

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single-dose levofloxacin (LVFX) as one option of prophylaxis to decrease incidence of bacterial complications caused by FQ-resistant microorganisms after TRUSP-Bx. Aminoglycosides have a concentration-dependent antimicrobial effect, and once daily usage is recommended. Therefore, single-dose administration of aminoglycoside is also likely to be suitable for prophylaxis. Hence, we combined an aminoglycoside with a single-dose of LVFX in our prophylactic regimen. In the present study, we assessed the efficacy of a combined regimen of LVFX plus isepamicin (ISP) as prophylaxis for TRUSP-Bx.

2. Materials and methods

2.1. Subjects

Overall, 562 patients undergoing TRUSP-Bx in Ishikawa Prefectural Central Hospital between January 2015 and March 2018 were included in the present study. The indications for TRUSP-Bx were based on the following criteria: rising serum prostate-specific antigen levels and/or abnormal findings on digital rectal examination (DRE), TRUS, and magnetic resonance imaging.

2.2. Protocols

All patients underwent urinalysis and prostatic examination to confirm the absence of any signs of urinary infection before TRUSP-Bx. All patients were administered a single-dose of oral LVFX (500 mg) in the morning and intravenous ISP (400 mg) 60 min before biopsy. None of the patients received an enema before the biopsy. Sterilization of the rectum with an iodic swab was performed by each physician. All biopsies were performed via TRUSP-Bx with an 18-gauge needle, and 12-core specimens were routinely obtained. All patients were hospitalized at our institution overnight to allow observation for any complications, such as hematuria, urinary retention, fever, or anal bleeding. Patients without complications were discharged the following morning.

Diagnosis of acute bacterial prostatitis was made based on the following criteria: body temperature >38 °C, leukocytes in the urine sediment (white blood cells >4/high-power field), and clinical findings on DRE, within 7 days of the biopsy. Before the initiation of antibiotic treatment, urine and blood bacterial cultures were tested to determine the causative microorganisms in all patients. The minimum inhibitory concentration (MIC) was measured using the broth microdilution method, and the drug susceptibility of the isolated microorganisms was determined based on the criteria of the Clinical and Laboratory Standards Institute.

We recorded the clinical characteristics, backgrounds, treatment, and bacterial culture results for the patients with acute bacterial prostatitis. Risk of acute bacterial complications after TRUSP-Bx was judged based on criteria suggested in the JUA/JRGU guidelines [11]. High-risk factors are as follows: prostate volume >75 ml, diabetes mellitus, steroid administration, severe urination disorders (International Prostate Symptom Score ≥20, maximum flow rate <12 ml/min, residual urine volume >100 ml). We then assessed the efficacy of the LVFX plus ISP prophylactic regimen. The study protocol was approved by Ishikawa Prefectural Central Hospital Institutional Review Board.

3. Results

The clinical characteristics of the patients are shown in Table 1. Of the study subjects, 22.4% had at least one high-risk factor. Acute bacterial prostatitis was found in three (0.53%) participants. The mean age of these three patients was 66.4 years (range, 59–71 years) (Table 2). Two of these patients belonged to the low-risk group, and the other had any high-risk factors based on the JUA/JRGU guidelines. The incidence rates of acute bacterial prostatitis in the low- and high-risk groups were 0.79% and 0.46%, respectively.

Table 1
Patient characteristics.

Number of patients	562
Median age (range) (years)	70 (65–74)
Median PSA value (range) (ng/ml)	6.5 (4.6–10.7)
Median prostate volume (range) (ml)	30.6 (21.9–40.3)
Median residual urine volume (range) (ml)	14 (0–65)
Number of re-biopsies (%)	132 (23.4)
Number with diabetes mellitus (%)	64 (11.3)
Number with pyuria (%)	6 (4.0)
Number with prostatitis history (%)	5 (0.8)
Risk: low-risk/high-risk	126/436
Frequency of prostatitis (%)	3 (0.53)

PSA, Prostate-specific antigen.

These three patients showed clinical symptoms of acute bacterial prostatitis 12–24 h after biopsy. *E. coli* was isolated in the urine culture of the three patients (Table 3). Only one microorganism (*E. coli*) was isolated from the blood culture. The isolates from all three patients were determined to be LVFX-resistant *E. coli*. On the other hand, all isolates had good sensitivity to aminoglycosides, cephalosporins, and carbapenems. All patients were administered antibiotic treatment (cephalosporin or carbapenem) immediately. The median duration of treatment was 7 days. All patients were treated successfully, with no evidence of further disease progression.

4. Discussion

With the LVFX plus ISP prophylactic regimen, the incidence rate of acute bacterial prostatitis was 0.53%, which appears to be slightly lower than those (0.6–1.5%) given FQ prophylaxis alone, as reported previously [11–14]. Togo et al. reported that the prophylactic efficacy of single-dose LVFX (500 mg) for 365 patients undergoing TRUSP-Bx was acceptable, with an incidence rate of 0.82% in terms of acute bacterial complications [12]. However, this previous study also described some cases of acute bacterial prostatitis caused by FQ-resistant *E. coli* and suggested that the increase in FQ-resistant *E. coli* is an emerging problem that needs to be monitored. Indeed, in this era of widespread FQ-resistant microorganisms, the incidence of acute bacterial complications caused by FQ-resistant microorganisms after TRUSP-Bx is on the rise. Carignan et al. reported that bacterial complications after TRUSP-Bx with prophylactic ciprofloxacin administration increased from 0.52% in 2002–2009 to 2.15% in 2010–2011 [13]. Kamei et al. demonstrated that FQ-resistant and/or extended-spectrum β-lactamase–producing *E. coli* could be detected in the fecal cultures of 48 patients out of 376 (13%) [14]. In our study, all isolates were LVFX-resistant *E. coli*. FQs are currently recommended as prophylaxis for TRUSP-Bx in many guidelines [11,15–17], although the use of an additional antibiotic against FQ-resistant microorganisms is also required to further prevent acute bacterial prostatitis.

Some previous studies have demonstrated the efficacy of combined usage of aminoglycosides, cephalosporin, and tazobactam/piperacillin (TAZ/PIPC) with FQs. The prophylactic use of amikacin plus ciprofloxacin resulted in significantly reduced bacterial complications caused by FQ-resistant microorganisms after TRUSP-Bx (from 3.9% to 1.4%) [18]. Shigemura et al. reported that the incidence rate of acute bacterial prostatitis was 0.53% (3/568) in patients given intravenous ISP (400 mg) combined with oral LVFX (300 mg) for 3 days [19]. In another study in which patients were administered intravenous TAZ/PIPC plus LVFX (300 mg) daily for 3 days as prophylaxis, only one patient (0.50%) in 201 cases had bacterial complications [20]. Furthermore, a combined protocol of

Table 2
Clinical details of patients with acute bacterial prostatitis after transrectal prostate biopsy.

Patient no.	Age (years)	Risk[a]	Interval[b] (h)	Therapy	Culture		Isolated organisms
				Antibiotics (g/day) × days	Urine	Blood	
1	59	Low	29	MEPM 1.5 g × 6	+	+	*Escherichia coli*
2	71	High[c]	24	MEPM 1.5 g × 6	+	−	*Escherichia coli*
3	66	Low	24	CTRX 2 g × 7	+	−	*Escherichia coli*

PSA, Prostate-specific antigen; MEPM, meropenem; CTRX, ceftriaxone.
[a] High-risk factors: prostate volume >75 ml; diabetes mellitus; steroid administration; severe urination disorder (International Prostate Symptom Score ≥20, Qmax <12 ml/min, residual urine >100 ml).
[b] Interval between biopsy and appearance of acute prostatitis.
[c] High-risk factors: residual urine >100 ml.

single-dose ciprofloxacin (500 mg) plus single-dose intramuscular ceftriaxone (1 g) significantly reduced the postoperative bacterial complication rates compared with oral ciprofloxacin alone [21]. The overall efficacy of our protocol is likely to be comparable to that of previously reported combined antibiotic regimens.

In general, aminoglycosides do not penetrate prostatic tissue and prostate fluid well, and the local concentration in this tissue cannot be maintained for long periods of time [22]. However, of the various aminoglycosides, amikacin (AMK) has been found to have some degree of effective diffusion into the prostatic tissue and fluid [23]. The pharmacokinetic profiles of ISP and AMK are similar, and these drugs have almost equal efficacy in the treatment of urinary tract infections [24]. Additionally, aminoglycosides have a concentration-dependent antimicrobial effect, and once daily usage is recommended. However, only single-dose administration of aminoglycoside is likely to be dubious as a prophylaxis for TRUSP-Bx because of its lower bioavailability in the prostate compared to FQs which are the widely accepted antibiotics [23]. Indeed, combined use of an aminoglycoside with single-dose LVFX as prophylaxis for TRUSP-Bx is recommended in the JUA/JRGU guidelines [11]. Therefore, we combined an aminoglycoside with a single-dose of LVFX in our prophylactic regimen.

In our institute, another prophylactic protocol of LVFX (200 mg) orally twice daily for 4 days plus intravenous ISP (200 mg) was used between 2003 and 2006, and acute bacterial prostatitis developed in 1.3% of the 457 patients [10]. In the results of this previous study, all the isolated microorganisms also showed resistance to LVFX and sensitivity to aminoglycosides. Therefore, in the present study, we increased the dose of intravenous ISP from 200 mg to 400 mg to minimize the incidence rate of acute bacterial prostatitis following TRUSP-Bx. The incidence rate (0.5%) of acute bacterial prostatitis when using the present regimen was lower than that (1.3%) when using our previous regimen. These findings suggest that increasing the ISP dose could reduce the development of postoperative acute bacterial prostatitis.

Table 3
Drug susceptibility of the bacterial isolates from urine and/or blood cultures.

Antibiotic	Patient 1	Patient 2	Patient 3
ABPC	S	R	S
PIPC	S	R	S
SBT/ABPC	S	R	S
CEZ	S	S	S
CTRX	S	S	S
CFPM	S	S	S
MEPM	S	S	S
GM[a]	S	S	S
AMK[a]	S	S	S
LVFX	R	R	R
MINO	S	S	S
IPM	S	S	S

S, sensitive; R, resistant; ABPC, ampicillin; PIPC, piperacillin; SBT/ABPC, sulbactam/ampicillin; CEZ, cefazolin; CTRX, ceftriaxone; CFPM, cefepime; MEPM, meropenem; GM, gentamicin; AMK, amikacin; LVFX, levofloxacin; MINO, minocycline; IPM, imipenem.
[a] We used the drug susceptibility of aminoglycosides for GM and AMK.

Furthermore, we found that the incidence rates of acute bacterial prostatitis in the low- and high-risk groups as judged by the JUA/JRGU guidelines were 0.79% and 0.46%, respectively. The efficacy of the present regimen does not appear to differ between the risk groups. However, single-dose administration of LVFX alone as prophylaxis is likely to be insufficient in high-risk patients. Indeed, the JUA/JRGU guidelines recommend PIPC/TAZ (4.5 g) administration twice a day for one day in high-risk patients [11]; postoperative bacterial complications occurred in 2.3% of high-risk patients who received PIPC/TAZ twice for one day [25]. Another recent study suggested the efficacy of intravenous cephamycin administration combined with a single-dose of oral LVFX, which resulted in decreased rates of bacterial complications in high-risk patients [26]. Therefore, the efficacy of the present regimen is likely to be remarkable, especially in high-risk patients.

Recently, cost-effectiveness and utility of a targeted antimicrobial regimen following rectal culture have been reported [11,27,28]. A recent meta-analysis from 15 studies representing 12,320 participants, incidence of acute bacterial prostatitis incidence was 3.4% in patients with empiric regimens and 0.8% in ones with target prophylaxis following rectal culture [28]. The overall efficacy of the present empiric regimen is likely to be similar to ones of the target regimens reported previously. In the present study, combined empiric regimen was applied to all patients according to clinical pathway of TRUSP-Bx in clinical practice. It has been widely accepted that implementation of clinical pathway reduces the variability in clinical practice, and then improves clinical outcomes for medical staff and patients. On the other hand, use of antimicrobials have been recently recommended to be getting stricter to prevent increase in antimicrobial resistance. Therefore, proper use of some prophylactic regimens according to risk factors should be also assessed.

There were some limitations in the present study. Initially, this was a single-arm, retrospective study. The add-on effects of ISP to the single-dose of LVFX could not be accurately evaluated. The isolates from all three cases with acute bacterial prostatitis were aminoglycoside-sensitive *E. coli*, which indicates that the addition of ISP was not effective in these cases. However, we could not determine the risk factors for the development of acute bacterial prostatitis using the present prophylactic regimen because only three patients developed acute bacterial prostatitis after TRUSP-Bx. In addition, accurate MIC for ISP in these isolates was not measured. Further analysis of these cases is required to improve the prophylactic regimen for TRUSP-Bx, and randomized control studies involving many subjects are likely to be needed to reach a more definite conclusion.

In conclusion, antibiotic prophylaxis using intravenous ISP (400 mg) plus a single-dose of oral LVFX (500 mg) effectively lowered the incidence of acute bacterial prostatitis after TRUSP-Bx in both low- and high-risk patients.

Conflicts of interest

None.

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