



Comparison of levofloxacin-based prophylaxis regimens for transrectal prostate biopsy: a prospective randomized single-center study

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Abstract

To develop an optimal prophylactic regimen among Chinese patients who accept transrectal prostate biopsy. We enrolled 420 patients who accepted transrectal prostate biopsy. They were randomly classified into three groups ($n = 140$ for each): Group A received a single 500-mg tablet of levofloxacin without enema; group B received a single 500-mg tablet of levofloxacin plus enema; group C received 3-day levofloxacin orally plus enema. Patients were assessed if they had a febrile urinary tract infection (FUTI). The incidence of FUTI was compared among groups. Subgroup analysis was performed between patients at high and low risk of infection in each group. There were 15 cases developed FUTI: 7 (5%), 6 (4.3%), and 2 (1.4%), respectively, in groups A, B, and C. Of the 15 patients who developed FUTI, *Escherichia coli* was detected in blood culture in two cases. Urine culture results were all negative. FUTI patients (73.3% (11/15)) had at least one high risk factor. Subgroup analysis showed that the incidence of FUTI in group A was significantly higher than that in group C among high-risk patients. There was no statistical difference between group A and group B among both high- and low-risk patients. A single 500-mg dose of levofloxacin without enema represents excellent prophylaxis for transrectal prostate biopsy in Chinese patients at low risk of infection. For those at high risk, 3-day levofloxacin prophylaxis is the optimal regimen. Prebiopsy enema provides no clinically significant outcome advantage and is unnecessary.

Keywords Fluoroquinolone · Prophylaxis · Enema · Prostate biopsy

Introduction

Prostate cancer (PCa) is the most common malignant tumor in adult males and the second leading cause of cancer-related death in men in western world [1]. Meanwhile, in recent years, the incidence of PCa is also quickly increasing in China. Transrectal prostate biopsy (TPB) guided by ultrasound is

generally accepted as the standard diagnostic tool for PCa. Generally, it is a safe procedure with low morbidity. However, a variety of infective complications may occur post biopsy, and some are serious and potentially life-threatening which require clinical intervention, such as febrile urinary tract infection (FUTI) and sepsis [2]. Therefore, some precautions are taken to reduce infection-related complications, usually including antibiotic prophylaxis and cleansing enema [3]. Most urologists agree that antibiotic prophylaxis is necessary [4, 5]. However, there is no consensus on the choices of antibacterial agents, administration route, and course of treatment [6]. Enema is recommended by some studies and is widely used in China, but its role in TPB is still controversial worldwide [7–9].

According to previous studies, single-dose levofloxacin orally without enema has been used as prophylaxis before biopsy with excellent results and low costs in European and American countries [10–12]. It was also demonstrated that 1-day and 3-day antibiotic prophylaxis regimens for patients undergoing TPB were equally effective [13, 14]. One

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multicenter trial in China recommended 3-day levofloxacin plus bowel preparation as precaution [15]. The study showed that compared with clinically common prophylactic regimens of various intravenous antibacterial agents, levofloxacin 500 mg, po, qd, for three consecutive days showed the same protective effect, with lower cost and economic advantage.

In our opinion, an excellent prophylactic regimen should include the following advantages: high efficiency, low cost, convenient for practice, comfortable, and acceptable for patients. Referring to this standard, on the premise of guaranteeing the efficacy, we believe that oral administration with shorter course of treatment is a better choice. Cleansing enema may potentially increase patient cost and discomfort [9] and also increase the workload of nurses. Therefore, we propose that single-dose levofloxacin orally without enema may be an ideal strategy. However, the effectiveness of this prophylactic regimen has not yet been evaluated in China. Although it has already been validated in western countries [10–12], the impact of ethnic and regional differences on efficacy remains uncertain.

Based on the above, in order to develop an optimal prophylactic regimen among Chinese patients who accepted TPB, we conducted a prospective randomized study to evaluate the effectiveness of single-dose levofloxacin-based prophylaxis regimens for preventing serious infective complications of TPB.

Materials and methods

From May 2015 to September 2018, a total of 420 patients were enrolled and underwent TPB at Ningbo First Hospital. After obtaining consent, patients were randomly classified into three groups: Group A ($n = 140$) received a single 500-mg tablet of levofloxacin 60 min before biopsy and was asked to relieve the bowel by himself before the procedure instead of enema; group B ($n = 140$) received a single 500-mg tablet of levofloxacin, 60 min before biopsy, plus enema as prophylaxis before biopsy; group C ($n = 140$) received 3-day levofloxacin orally since the day of biopsy plus enema as prophylaxis (60 min before biopsy in the first day). The solution used for enema is soapy water. Groups A and B are test groups, while group C is a control group because the regimen of 3-day levofloxacin + enema has proved effective in China.

The indications for biopsy were an elevated PSA level (> 4 ng/ml) and/or an abnormal digital rectal examination and/or abnormal TRUS/MR imaging results. Six to twelve core biopsies were performed by a same operator using 18-gauge biopsy needles. Patients were informed to return to our clinic if they developed a fever of ≥ 38.0 °C, chills, or severe irritative voiding symptoms. They would be assessed by an experienced urologist to determine whether they had a FUTI. FUTI was defined as fever ≥ 38.0 °C within 2 weeks after biopsy,

accompanied by at least one symptom of urinary tract (urgency, frequency, dysuria, and pain suprapubic) and positive urine test with the absence of other sources of infection [16]. Confirmed patients were hospitalized and complemented with urine and blood culture studies. The incidence of FUTI would be compared as a major indicator among groups, because FUTI requires clinical intervention and may lead to sepsis. Subgroup analysis was performed between patients at high and low risk of infection in each group. High risk factors include diabetes mellitus, preoperative catheterization, recent steroid use, and concomitant urinary tract infection in this study.

All data were analyzed using SPSS version 20.0 software. Nonparametric numerical data were analyzed using the Mann-Whitney U test. Categorical data were analyzed by Pearson's chi-squared test or Fisher's exact test. In order to avoid increasing the probability of type I error, the test level was adjusted with $P < 0.017$ as statistical significance.

Results

A total of 420 patients were eventually enrolled and divided into three groups randomly, with 140 cases in each group. Of the whole cohort, the age range was 26–89 years (median, 67 years), serum PSA levels ranged from 0.92 to 818 ng/ml (median, 11.2 ng/ml), and prostate volumes ranged from 15 to 218 ml (median, 50.0 ml).

Patient characteristics and clinical results in each group are shown in Table 1. There was no statistically significant difference among the three groups for ages, PSA levels, prostate volumes, and the number of biopsy cores taken. Number of patients at high risk of infection was also similar in each group. Of the 420 biopsies performed, there were 15 cases that developed FUTI: 7 (5%), 6 (4.3%), and 2 (1.4%), respectively, in groups A, B, and C. No statistical differences were found between any two groups. Of the 15 patients who developed FUTI, *Escherichia coli* was detected in blood culture in two cases, one of which was fluoroquinolone-sensitive in group A, while the other was fluoroquinolone-resistant and extended-spectrum β -lactamase-producing in group B. Urine culture results were all negative.

In addition, high risk factors of infection were analyzed among the patients with FUTI (Table 2). It was found that 73.3% (11/15) FUTI patients had at least one high risk factor. Therefore, a subgroup analysis was further performed, which compared the FUTI rates among groups of patients at high or low risk factors of infection (Table 3). The results showed that the incidence of FUTI in group A was significantly higher than that in group C among high-risk patients ($P < 0.017$). There was no statistical difference between group A and group B among both high- and low-risk patients.

Table 1 Patient characteristics and clinical results

Group	A (n = 140)	B (n = 140)	C (n = 140)	P value		
				AvsB	AvsC	BvsC
Age (years), median (range)	68.0 (26–89)	66.0 (48–84)	67.5 (46–88)	0.29	0.82	0.36
PSA (ng/ml), median (range)	12.48 (1.08–150)	10.27 (0.92–818)	11.37 (1.10–300)	0.13	0.35	0.55
Prostate volume (cm ³), median (range)	50 (18–160)	49 (15–218)	51 (21–200)	0.31	0.19	0.81
Biopsy cores (n), median (range)	10 (6–12)	10 (6–12)	10 (6–12)	0.90	0.73	0.64
Patients at high risk of infection						
Total (n)	17	15	21	0.71	0.49	0.28
Diabetes mellitus (n)	8	5	8	–	–	–
Preoperative catheterization (n)	4	2	6	–	–	–
Recent steroid use (n)	0	0	1	–	–	–
Urinary tract infection (n)	6	8	7	–	–	–
FUTI (%)	5 (7/140)	4.3 (6/140)	1.4 (2/140)	0.78	0.18	0.28
Positive urine culture (n)	0	0	0	–	–	–
Positive blood culture (n)	1	1	0	–	–	–

Discussion

Different studies have shown that prophylactic use of fluoroquinolone can reduce the infection complications of TPB [17–19]. Levofloxacin is well absorbed orally and has excellent bioavailability in the prostate tissue. It was proved that the concentration of levofloxacin in prostate fragments obtained by transurethral resection is sufficient to effectively treat the most common pathogens [20]. In 2002, Griffith et al. demonstrated that a single 500-mg dose of levofloxacin represents excellent prophylaxis for TPB in patients at low risk [10]. After that, though a trend of increasing resistance to

fluoroquinolones was observed, preventive use of single-dose levofloxacin was confirmed by numerous studies. An 8-year single-center study enrolled 3694 cases suggested that levofloxacin 500 mg in a single dose 1 h before biopsy remained effective and was superior to piperimide acid-based prophylactic antibiotics [15]. Sabbagh et al. [13] and Linden-Castro et al. [14] both reported that 1-day fluoroquinolone prophylaxis regimen was sufficient and 3-day prophylaxis had no additional clinical advantages.

According to previous reports, the incidence of infectious complications after TPB is 1–6% [21]. Wagenlehner et al. [22] reported that 3.5% of patients had febrile urinary infections and 3.1% required hospitalization after TPB. In this study, the number of FUTI cases was 7 (5%), 6 (4.3%), and 2 (1.4%) in groups A, B, and C, respectively. There was no significant difference between any two groups (Table 1), which suggested that single-dose prophylaxis was as effective as 3-day prophylaxis in general. However, further investigation among high-risk patients showed that the incidence of FUTI in groups A and B was significantly higher than that in group C, while there was no significant difference in the number of high infection risk cases among each group (Table 3). This result indicates that although a single 500-mg tablet of levofloxacin is generally safe and effective, 3-day prophylaxis is a better option for patients at high risk of infection.

In addition to antibiotic prophylaxis, prebiopsy enema also plays an important role in most hospitals of China. However, a preventive effect on infectious complications of bowel preparation or enema before biopsy is controversial. None of the current guidelines found sufficient evidence to recommend the routine use of preprocedural rectal enemas [23]. Some investigators indicated that prebiopsy enemas increase the infectious complications, patient cost, and discomfort [9, 12].

Table 2 Infection risk factors of patients with FUTI

Patients	Group	Infection risk factors
1	A	DM
2	A	DM + PC
3	A	–
4	A	PC
5	A	–
6	A	DM
7	A	UTI
8	B	PC
9	B	–
10	B	DM
11	B	DM
12	B	UTI
13	B	UTI
14	C	–
15	C	PC + UTI

DM diabetes mellitus, PC preoperative catheterization, UTI urinary tract infection

Table 3 Comparison of FUTI incidence among groups of patients at high and low risk

Group	A	B	C	P value		
				AvsB	AvsC	BvsC
High risk (<i>n</i>)	17	15	21			
FUTI (%)	35.3 (6/17)	33.3 (5/15)	5 (1/21)	1.00	0.015	0.026
Low risk (<i>n</i>)	123	125	119			
FUTI (%)	0.81 (1/123)	0.80 (1/125)	0.84 (1/119)	1.00	1.00	1.00

Despite this, one meta-analysis suggested that the risk of bacteremia was diminished in an antibiotic + enema group as compared with an antibiotic-only group [24]. In China, there are few randomized controlled literatures on the necessity of enema and most urologists choose prebiopsy enema to ensure the procedure safer. In this study, no matter in high-risk or low-risk patients, there was no significant difference in the incidence of FUTI between group A and group B. This result suggests that the value of cleansing enema may be limited.

To the best of our knowledge, this is the first prospective randomized study to evaluate the prophylactic use of single-dose levofloxacin with or without enema in Chinese patients accepted TPB. However, there are several limitations in our study. First, the sample size of high-risk patients in each group is not large enough; further studies are needed to be conducted in a larger sample of high infection risk cohort. In addition, the risk factors for infectious complications remain controversial; some author reported that obesity, recent hospitalization, history of antibiotic use, and year of biopsy were also significantly associated with rates of infectious complications after TPB [25, 26]. Nevertheless, we only referred to the high-risk factors mentioned in the 2011 EAU guidelines for prostate biopsy. Second, we mainly counted the incidence of FUTI requiring clinical intervention, which may carry the risk for missing cases with minor infectious complications such as asymptomatic bacteriuria or pyuria, although the clinical significance of these complications may be limited. Third, it is a single-center trial in eastern China; further multicenter studies are needed to be conducted in other regions of China to confirm our results.

Conclusions

Based on the results of this study, a single 500-mg dose of levofloxacin without enema represents excellent prophylaxis for transrectal prostate biopsy in Chinese patients at low risk of infection. For those at high risk, 3-day levofloxacin prophylaxis is the optimal regimen. Prebiopsy enema provides no clinically significant outcome advantage and is unnecessary.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical approval was obtained from the Ningbo First Hospital Research Ethics Committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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