

# Single-Dose versus Multiple-Dose Ciprofloxacin plus Metronidazole Prophylaxis in Transrectal Ultrasound-Guided Biopsy of the Prostate: a Randomized Controlled Trial

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**Abstract-** To investigate and compare the infectious and non-infectious complications of single-dose versus multiple-dose antibiotic therapy for trans-rectal ultrasound (TRUS)-guided biopsy of the prostate. Patients were enrolled in a prospective randomized study that was designed to investigate the effects of single-dose versus multiple-dose antimicrobial prophylaxis regimen mainly on asymptomatic bacteriuria, urinary tract infection (UTI) without fever, fever and urinary septicemia. The single-dose group received one ciprofloxacin 500 mg tablet and two metronidazole 250 mg tablets at 2 hours before the biopsy, while the multiple-doses group received those every 12 hours from 3 days before the biopsy. One-hundred and sixty patients were evaluated in two groups and bacteriuria in urinalysis was encountered in 12 patients (15%) in the single-dose group and four patients (5%) in the multiple-dose group, with a significant difference ( $P=0.035$ ). UTI without fever occurred in six patients (7.5%) in the single-dose group and one patient (1.25%) in the multiple-dose group, with no significant difference (borderline  $P=0.053$ ). After biopsy, three patients (3.75%) returned with fever due to UTI and bacteremia in the single-dose group and none in the multiple-dose group, but with no significant difference ( $P=0.08$ ). Regarding non-infectious complications, there were no significant differences between the two groups. Using prophylactic antibiotics for prostate biopsy in multiple doses, and at least 3 days before the procedure significantly reduces the rate of bacteriuria compared with a single-dose regimen.

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## Introduction

Transrectal ultrasound (TRUS)-guided biopsy of the prostate has become the gold standard for the detection and diagnosis of prostate cancer (1,2). The use of prostate-specific antigen (PSA) screening has increased the numbers of men undergoing prostate biopsy. Although infectious complications after TRUS-guided biopsy of the prostate are infrequent, many investigators suggest the use of prophylactic antibiotics (3-6).

Recently, most clinical trials and prospective studies have shown that single-dose antibiotic prophylaxis is comparable to multiple-dose prophylaxis before biopsy (7,8), but the optimum duration of antimicrobial

prophylaxis and the preparation for prostate biopsy remain debatable (9,10).

A few studies have mentioned a longer duration for antibiotic prophylaxis (11,12). There is also a current trend toward administration of single-agent antibiotics, especially fluoroquinolones, and recent reviews have shown that these agents are still good choices for prophylaxis selection because most of the frequently found organisms after TRUS-guided biopsies are susceptible to fluoroquinolones (8,12,13).

On the other hand, although anaerobic infections are rare after prostate biopsies, they can be lethal and life-threatening. In some studies for proper coverage of common microorganisms of the colorectal region,

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specific antibiotics have been used (3,14,15). In a trial, McArdle *et al.*, (16) reported that usage of ciprofloxacin and metronidazole for 3 days prior to colorectal surgery significantly decreased surgical site infections. Other studies investigating pre-biopsy and post-biopsy use of prophylactic antibiotics have indicated that the initiation timing and proper usage of prophylactic antibiotics play important roles in post-biopsy infectious complications, although agreement on this issue has not yet been reached (4,10,11,17,18).

In this prospective randomized controlled trial, we investigated the different effects of single-dose versus multiple-dose ciprofloxacin plus metronidazole as prophylactic antibiotics for prostate biopsy.

## Materials and Methods

Patients undergoing TRUS-guided biopsy of the prostate were enrolled into a prospective randomized study at Hasheminejad Urology Center (Tehran, Iran). The study was approved by the Pharmacy and Therapeutic Committee the (Tehran University of Medical Sciences) and the Ethical Committee of the Ministry of Health and Medical Education in 2010.

The patients enrolled in the study were aged from 40 to 85 years and had PSA of >4 ng/dL and suspicious digital rectal examination (DRE). Patients were excluded if they had poorly controlled diabetes, uncorrected bleeding tendency, indwelling catheter, unresolved urinary tract infection (UTI), immunosuppressant conditions, and hypersensitivity to ciprofloxacin or metronidazole, valvular heart disease or had received antibiotic treatment in the past 2 weeks.

The trial was designed to investigate the effect of single-dose versus multiple-dose antimicrobial prophylaxis regimens with ciprofloxacin and metronidazole on asymptomatic bacteriuria, UTI without fever, fever and urinary septicemia, as well as many other non-infectious complications, such as lower urinary tract symptoms, hematuria, hematospermia and rectal bleeding.

Written informed consent was obtained from all patients, and allocation to the study groups was conducted randomly by a central computerized system at 1:1 ratio to receive either single-dose or multiple-dose prophylaxis. The patients were registered at 2 weeks before the biopsy, and primary general physical examination was performed. Specifically, blood pressure, heart rate, body temperature and BMI were checked by a urology resident and a urine sample was obtained from each patient.

The drugs and general information on how to use these drugs, which was recorded in an envelope and blinded by the Pharmacy Department, were delivered to the patients. The single-dose group received one ciprofloxacin 500 mg tablet and two metronidazole 250 mg tablets at 2 hours before the biopsy, while the multiple-dose group received one ciprofloxacin 500 mg tablet and two metronidazole 250 mg tablets every 12 hours from 3 days before biopsy followed by a single dose at 2 hours before the biopsy like the first group.

A standard procedure was used for TRUS-guided biopsy for the patients. The prostate dimensions were determined by TRUS while the patient was in the left lateral decubitus position, and a biopsy was taken under local anesthesia with an 18 G needle fired by a spring-loaded biopsy gun. A total of 8 cores were obtained. Rectal enema was not performed for any of the patients.

All follow-up visits and documentation were performed by a urology resident. Information about chills, fever, hematuria, hematospermia and rectal bleeding was obtained at 4, and 10 days after biopsy and an International Prostate Symptom Scale (IPSS) questionnaire was completed. A baseline IPSS was obtained at 2 weeks before the biopsy. Data for urine analyses and urine cultures at 2 weeks before the biopsy and 4 and 10 days after biopsy were collected. Blood cultures were taken from patients fulfilling the criteria for septicemia, and proper treatment or hospitalization was considered for these patients. The definitions and endpoints of the study are shown in Table 1.

**Table 1. Definitions for follow-up**

<b>UTI</b>	Uropathogens Colony count > 10 <sup>5</sup> in urine culture + LUTS
<b>Bacteriuria</b>	Uropathogenic bacteria > 2-3 in each high-power field of urinalysis
<b>Significant fever</b>	>38.5°C
<b>Hematuria</b>	Many Red Blood Cells in urinalysis or gross hematuria more than 12 hour after the biopsy
<b>LUTS</b>	Using IPSS scale for lower urinary tract symptoms
<b>Rectal bleeding</b>	Visible blood in feces or gross bleeding from the rectum more than 12 hour after the biopsy
<b>Hematospermia</b>	Visible blood in the semen

All of the patients were contacted by telephone on the day after biopsy and asked about any discomfort or problems, or the need for consultation or referral to the clinic for further evaluations.

Using a bilateral test, the sample size of patients required to provide 80% power with an  $\alpha$  of 5% under a hypothesis of 15% for bacteriuria in the single-dose antibiotic regimen and 5% for bacteriuria in the multiple-dose antibiotic regimen was estimated to be

150 patients (75 patients in each group). We aimed to enroll >160 patients to take into account unusable cases. Data were presented as means and standard deviations, and statistical results were reported as p values. UTI rates and bacteriuria were compared between the study groups using intention-to-treat and as-per-protocol analyses by the chi-square test and two-tailed Fisher's exact test.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows Version 16.0 software (SPSS Inc., Chicago, IL).

## Results

A total of 180 patients were enrolled between September 2010 and March 2011. Nine patients were excluded because they met the exclusion criteria or did not meet the inclusion criteria, and three patients finally refused to participate in the study. Consequently, 168 patients were included in the intention-to-treat analysis and randomized to the single-dose group and multiple-dose group, respectively. Eight patients (four patients in each group) were lost to follow-up, and finally 160 patients were evaluated for the as-per-protocol analysis, including 80 patients in each group (Figure 1).

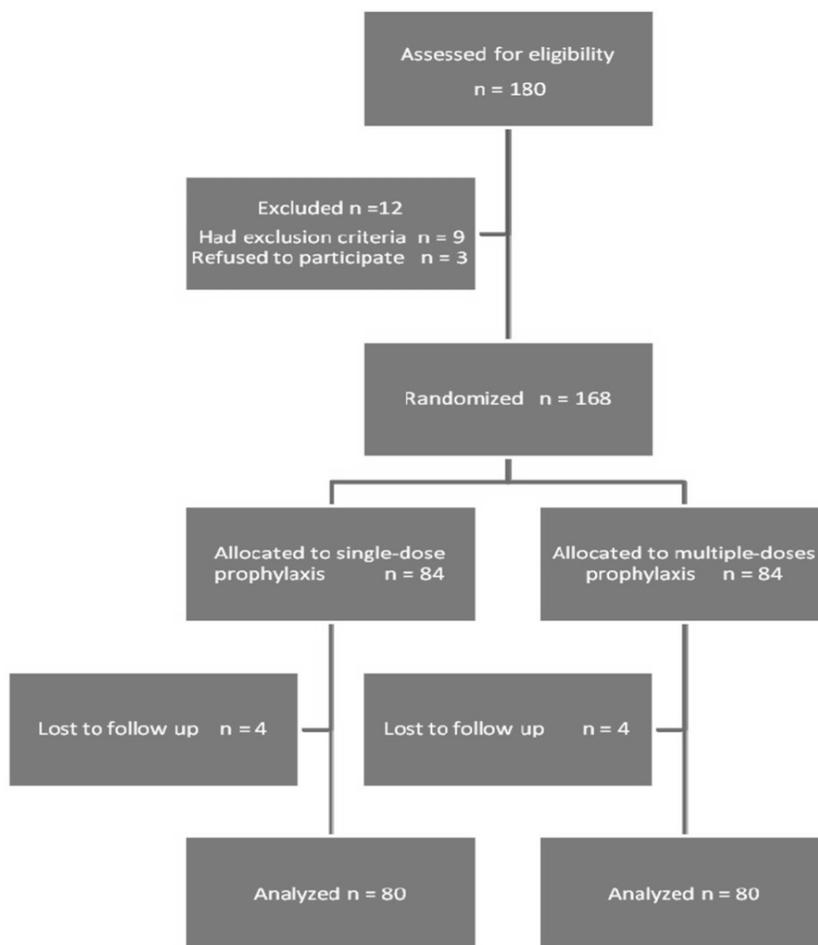


Figure 1. Trial profile which shows number of the included, excluded, randomized and lost to follow up cases.

The baseline characteristics were similar in the two groups (Table 2). The mean prostate volume was not significantly different between the single-dose group or the multiple-dose group (42.7±14.8 ml vs 41.6±16.1 ml *P*.value=0.02).

Bacteriuria in urinalysis was encountered in 12 patients (15%) in the single-dose group and four patients (5%) in the multiple-dose group, with a significant

difference between the two groups (*P*=0.035). UTI without fever occurred in six patients (7.5%) in the single-dose group and one patient (1.25%) in the multiple-dose group, but showed no significant difference with a borderline p value (*P*=0.053). After biopsy, three patients (3.75%) returned with fever caused by UTI and bacteremia in the single-dose group and no patients had fever in the multiple-dose group,

with no significant difference ( $P=0.08$ ) (Table 3).

**Table 2. Characteristics of the patients at follow-up on days 4 and 10**

Day 4	Single-dose	Multiple-dose	<i>P-value</i>	Day 10	Single-dose	Multiple-dose	<i>P-value</i>
IPSS	8.9±2.9	8.1±3.0	0.112	IPSS	8.7±2.8	8.1±3.3	0.170
Hematuria	15(18.75%)	12(15%)	0.527	Hematuria	9(11.25%)	8(10%)	0.798
Rectal bleeding	4(5%)	6(7.5%)	0.514	Rectal bleeding	2(2.5%)	3(3.75%)	0.650
hematospermia	7(8.75%)	8(10%)	0.786	hematospermia	4(5%)	6(7.5%)	0.514

On day 4 of follow-up after biopsy, hematuria was observed in 15 patients (18.75%) in the single-dose group and 12 patients (15%) in the multiple-dose group, with no significant difference between the two groups. On day 10 of follow-up, hematuria was present in nine (11.25%) and eight (8.75%) patients, respectively, also with no significant difference.

On day 4 of follow-up, four patients (5%) had rectal bleeding, and seven patients (8.75%) had hematospermia in the single-dose group compared with six patients (7.5%) and eight patients (10%),

respectively, in the multiple-dose group, with no significant differences between the two groups (rectal bleeding,  $P=0.514$ ; hematospermia,  $P=0.786$ ). On day 10, rectal bleeding was seen in two patients (2.5%) in the single-dose group and three patients (3.75%) in the multiple-dose group while hematospermia remained in four patients (5%) in the single-dose group and six patients (7.5%) in the multiple-dose group, also with no significant differences.

IPSS did not change significantly in either group on days 4 and 10 of follow-up (Table 4).

**Table 3. Infectious complication findings after the biopsy**

	Single-dose	Multiple-dose	<i>p-value</i>
<b>Bacteriuria</b>	12(15%)	4(5%)	0.035
<b>UTI without fever</b>	6(7.5%)	1(1.25%)	0.053
<b>Fever</b>	3(3.75%)	0(0%)	0.08

**Table 4. Characteristics of the patients at follow-up on days 4 and 10**

Day 4	Single-dose	Multiple-dose	<i>p-value</i>	Day 10	Single-dose	Multiple-dose	<i>p-value</i>
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Among the six patients who had symptomatic UTI without fever in the single-dose group, five had *Escherichia coli* in their urine culture, of which one showed ciprofloxacin resistance, and one had *Pseudomonas spp* that showed ciprofloxacin resistance. The one patient with symptomatic UTI without fever in the multiple-dose group had *Escherichia coli (E coli)* in their urine culture that was sensitive to ciprofloxacin. All of these patients were treated with 4 weeks of antibiotic therapy.

Among the three patients with fever after biopsy, two needed hospitalization owing to the severity of their problems. All three patients had urine cultures and blood cultures containing ciprofloxacin-resistant *E. coli*. These three patients achieved successful treatment at the end of 4 weeks of proper antibiotic therapy.

## Discussion

Prophylactic use of antibiotics in surgical procedures is always a debatable and challenging issue. Regarding prophylactic use of antibiotics in prostate biopsy, many different studies have been performed, and there is a broad consensus on the necessity of their use (3-9). However, the main concern for prophylaxis of prostate biopsy that makes it different from other situations is the number and variety of the investigations and regimens and their timings that have been used (17).

During the time of using prophylactic antibiotics for prostate biopsy, the important point is the tendency in recently published studies for comparisons of the single-dose versus multiple-dose antibiotics. In most of these studies, the differences, especially for severe infectious complications, were not significant between the two protocols, and, therefore, many authors have suggested

using a single-dose short course of prophylaxis rather than a multiple-dose long course (3,5,7,8,19-21).

Another important point is the type of antibiotic and the method of use. Since fluoroquinolones are one of the effective antibiotics for the genitourinary system and show excellent penetration into the prostate tissue, and because the vast majority of uropathogens and enteric species have proper susceptibility to these agents, most of the trials have focused on fluoroquinolones (22-24).

Although frequently encountered uropathogens and coliforms such as *E. coli* or *Klebsiella* spp are usually responsible for the incidence of infectious complications after prostate biopsy (9), some infrequently encountered enteric pathogens, especially anaerobes, were reported in fever and septicemia after prostate biopsy, and the effects in the majority of these cases were severe and devastating (14). Therefore, many studies have been conducted in the field of anaerobic coverage by prophylactic antibiotics during prostate biopsy (3,15). According to some reports about fluoroquinolone-induced pseudomembranous colitis (25,26) and based on the broad prescription of these antibiotics by urologists, we decided to use anaerobic coverage antibiotics, such as metronidazole with fluoroquinolones, at least for long-term durations.

In our center, we have used multiple-drug regimens in long-term courses for a long time, but have not reached a standard and evidence-based protocol. In this study, we compared the differences between single-dose and multiple-dose regimens of ciprofloxacin plus metronidazole for prostate biopsy in a prospective randomized trial. In a study by Aron *et al.*, (3). Using ciprofloxacin and tinidazole, the single-dose and multiple-dose regimens did not show a significant difference. However, some other studies have been published in support of multiple-dose regimens (11,28).

In our study, use of the multiple-dose regimen in the field of rate of bacteriuria after prostate biopsy showed significant superiority, whereas the differences for UTI without fever and septicemia after prostate biopsy between the single-dose and multiple-doses regimens were not significant. However, the obtained p values demonstrated that if we increased the power of our study and had more patients, we could have obtained other results, and the differences could have reached significance.

Another important problem is the timing of prophylactic antibiotics. Some authors believe that prophylaxis should be used a few hours before the biopsy and that it is better to continue for few days (3,7), whereas other authors prefer to start the antibiotics a few

days before biopsy until the day of the procedure (8). Since reaching a proper blood level is essential for oral antibiotics and the penetration of bacteria into tissues and circulation occurs in the first moments after biopsy, we decided to use antibiotics a few days before the biopsy. In a recent Cochrane review, the rates of fever and septicemia or acute prostatitis under prophylactic coverage with antibiotics reached approximately 1–3% in different studies, and the rate of bacteriuria after prostate biopsy was reported to be nearly 10% (27).

In our study, the rate of symptomatic UTI without fever in the multiple-dose group was 1.25%, and the rate of bacteriuria was 5%, which were nearly consistent with previously published articles (9-27). However, the corresponding data in the single-dose group were higher than the data in the literature. The most important aspect in our investigations was the presence of ciprofloxacin-resistant pathogens in infectious complications after prostate biopsy. This factor reached a rate of 33.3% of all positive urine cultures and 100% of the blood cultures.

The presence of ciprofloxacin-resistant uropathogens, especially ciprofloxacin-resistant *E. coli*, has been a disputed and challenging topic in recent studies, and occasionally severe and disastrous complications have been reported (29). In the matter of lower urinary tract symptoms (LUTS) and other parameters of non-infectious complications after prostate biopsy, our data were similar to previously published study by Rodriguez *et al.*, and showed no significant differences between the single-dose and multiple-dose groups (1).

The main limitation of our study was the small size of the groups and the small number of patients. Accordingly, although the statistical analyses were not significant for some of our endpoints, their values were near the point that could be changed by increasing the power of the study and the number of patients. However, one of our reasons for ending up with this size was the high rate of infectious complications in the single-dose group, and we gathered sufficient patients based on the estimated sample size required before starting the study.

Using prophylactic antibiotics for prostate biopsy in multiple doses, and at least 3 days before the procedure significantly reduces the rate of bacteriuria versus the single-dose regimen. We found a high incidence of ciprofloxacin resistance between the uropathogens that cause infectious complications.

The differences in the rates of UTI, fever and septicemia between the single-dose and multiple-doses regimens could be taken into consideration with larger

sample sizes. Using anaerobic coverage could be helpful in reducing the infectious complications after prostate biopsy.

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