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

Zhoobin Heidari Bateni[1], Hossein Shahrokh[1], Hormoz Salimi[1], Hossein Safari[1], Meghdad Tabatabai[1], and Dariush Saedi[2]

[1] *Department of Urology, Hasheminejad Hospital, Iran University of Medical Sciences, Tehran, Iran*

[2] *Department of Radiology, Hasheminejad Hospital, Iran University of Medical Sciences, Tehran, Iran*

Received: 7 Mar. 2013; Received in revised form: 2 Jul. 2013; Accepted: 8 Oct. 2013

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.

© 2014 Tehran University of Medical Sciences. All rights reserved.

Acta Medica Iranica, 2014;52(9):664-670.

Keywords: Transrectal Ultrasonographic Biopsy of Prostate; Antibiotic Prophylaxis; Prostate cancer

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,

Corresponding Author: Zh. Heidari Bateni
Department of Urology, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran
Tel: +98 21 81161, Fax: +98 21 88644441, E-mail address: zhoobin.h.bateni@gmail.com

Archive of SID

www.SID.ir

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

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

Archive of SID

www.SID.ir

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).

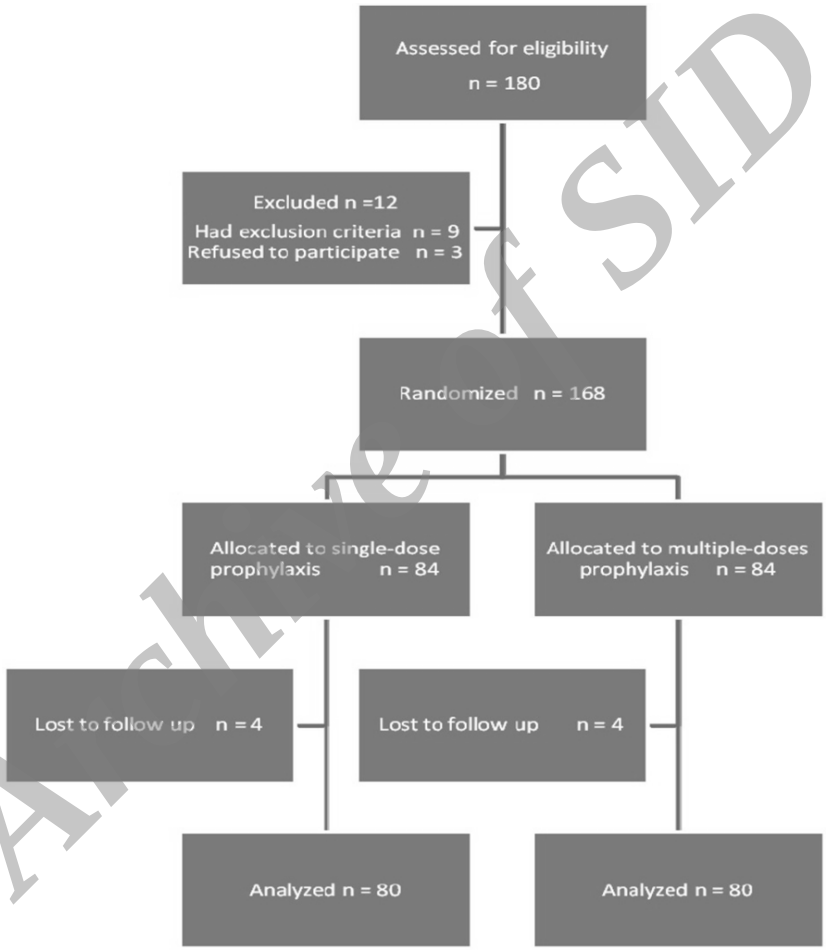

Figure 1. Trial profile which shows number of the included, excluded, randomized and lost to follow up cases.

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,

Archive of SID

www.SID.ir

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	*P-value*	Day 10	Single-dose	Multiple-dose	*P-value*
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	*p-value*
Bacteriuria	12(15%)	4(5%)	0.035
UTI without fever	6(7.5%)	1(1.25%)	0.053
Fever	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	*p-value*	Day 10	Single-dose	Multiple-dose	*p- value*
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

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

Archive of SID

www.SID.ir

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 regiments 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

Archive of SID

www.SID.ir

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

References

1. Rodriguez LV, Terris MK. Risks and complications of transrectal ultrasound guided biopsy or prostate needle biopsy: a prospective study and review of the literature. J Urol 1998;160(6 Pt 1):2115-20.
2. Djavan B, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided biopsy or prostate needle biopsies: results of a prospective European Prostate Cancer Detection Study. J Urol 2001;166(3):856-60.
3. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int 2000;85(6):682-5.
4. Sieber PR, Rommel FM, Agusta VE, et al. Antibiotic prophylaxis in ultrasound guided transrectal prostate biopsy. J Urol 1997;157(6):2199-200.
5. Kapoor DA, Klimberg IW, Malek GH, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology 1998;52(4):552-8.
6. Bootsma AM, Laguna Pes MP, Geerling SE, et al. Antibiotic prophylaxis in urologic procedures. A systematic review. Euro Urol 2008;54(6):1270-86.
7. Sabbagh R, McCormack M, Peloquin F, et al. A prospective randomized trial of 1-day versus 3-day antimicrobial prophylaxis for transrectal ultrasound guided prostate biopsy. Can J Urol 2004;11(2):2216-9
8. Briffaux R, Coloby P, Bruyere F, et al. One preoperative dose randomized against 3-day antibiotic prophylaxis for transrectal ultrasonography-guided prostate biopsy. BJU Int 2009;103(8):1069-73.
9. Webb NR, Woo HH. Antibiotic prophylaxis for prostate biopsy. BJU Int 2002;89(8):824-8.
10. Davis M, Sofer M, Kim SS, et al. The procedure of transrectal ultrasound guided transrectal prostate biopsy: a survey of patient preparation and biopsy technique. J Urol 2002;167(2 Pt 1):566-70.
11. Janoff DM, Skarecky DW, McLaren CE, et al. Prostate needle biopsy infection after four or six dose ciprofloxacin. Can J Urol 2000;7(4):1066-9.
12. Aus G, Ahlgren G, Bergdahl S, et al. Infection after transrectal core biopsies of the prostate- risk factors and antibiotic prophylaxis. Br J Urol 1996;77(6):851-5.
13. Shaeffer AJ, Montorsi F, Scattoni V, et al. Comparison of a 3-day with a 1-day regimen of an extended release formulation of ciprofloxacin as antimicrobial prophylaxis for patients undergoing transrectal needle biopsy of the prostate. BJU Int 2007;100(1):51-7.
14. Brewster SF, Rooney N, Kabala J, et al. Fatal anaerobic infection following transrectal biopsy of a rare prostatic tumour. Br J Urol 1993;72(6):977-8.
15. Breslin JA, Turner BI, Faber RB, et al. Anaerobic infection as a consequence of transrectal prostatic biopsy. J Urol 1978;120(4):502-3.
16. McArdle CS, Moran CG, Pettit L, et al. Value of oral antibiotic prophylaxis in colorectal surgery. Br J Surg 1995;82(8):1046-8.
17. Shandra KC, Thibault GP, Deshon GE Jr. Variability in patient preparation for prostate biopsy among American urologists. Urology 1998;52(4):644-6.
18. Crawford ED, Haynes AL Jr, Story MW, et al. Prevention of urinary tract infection and sepsis following transrectal prostate biopsy. J Urol 1982;127(3):449-51
19. Griffith BC, Morey AF, Ali-Khan MM, et al. Single dose levofloxacin prophylaxis for prostate biopsy in patients at low risk. J Urol 2002;168(3):1021-3.
20. Shigemura K, Tanaka K, Yasuda M, et al. Efficacy of 1-day prophylaxis medication with fluoroquinolone for prostate biopsy. World J Urol 2005;23(5):356-60.
21. Cam K, Kayikci A, Akman Y, et al. Prospective assessment of the efficacy of single dose versus traditional 3-day antimicrobial prophylaxis in 12-core transrectal prostate biopsy. Int J Urol 2008;15(11):997-1001.
22. Lugg J, Lettieri J, Stass H, et al. Determination of the concentration of ciprofloxacin in prostate tissue following administration of a single, 1000 mg, extended-release dose. J Chemother 2008;20(2):213-8.
23. Lindstedt S, Lindström U, Ljunggren E, et al. Single-dose antibiotic prophylaxis in core prostate biopsy: Impact of timing and identification of risk factors. Eur Urol 2006;50(4):832-7.
24. Naber KG, Sörgel F. Antibiotic therapy--rationale and evidence for optimal drug concentrations in prostatic and seminal fluid and in prostatic tissue. Andrologia 2003;35(5):331-5.
25. Gouliouris T, Brown NM, Aliyu SH. Prevention and treatment of Clostridium difficile infection. Clin Med 2011;11(1):75-9.
26. Deshpande A, Pant C, Jain A, et al. Do fluoroquinolones predispose patients to Clostridium difficile associated disease? A review of the evidence. Curr Med Res Opin 2008;24(2):329-33.
27. Zani EL, Clark OA, Rodrigues Netto N Jr. Antibiotic prophylaxis for transrectal prostate biopsy. Cochrane Database Syst Rev 2011;11(5):CD006576.
28. Petteffi L, Toniazzo GP, Sander GB, et al. Efficiency of short and long term antimicrobial therapy in transrectal ultrasound-guided prostate biopsies. Int Braz J Urol

Archive of SID

www.SID.ir

2002;28(6):526-32.

29. Ekici S, Cengiz M, Turan G, et al. Fluoroquinolone-resistant acute prostatitis requiring hospitalization after transrectal prostate biopsy: effect of previous fluoroquinolone use as prophylaxis or long-term treatment. Int Urol Nephrol 2012;44(1):19-27.

Archive of SID

www.SID.ir