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

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OBJECTIVE

To compare the clinical and bacteriological efficacy and the clinical safety of a 1-day with a 3-day regimen of an extended-release formulation of ciprofloxacin (ciprofloxacin XR) given as antimicrobial prophylaxis to men undergoing transrectal needle biopsy of the prostate (TRNBP).

PATIENTS AND METHODS

This was a multicentre, prospective, international, double-blind study in patients who required TRNBP. Patients were randomized to receive oral ciprofloxacin XR 1000 mg as either a 1-day or a 3-day regimen. Single doses were given at 24 h before, 2–3 h before, and 24 h after TRNBP. Patients in the 1-day regimen had placebo instead of the first and third doses of ciprofloxacin.

RESULTS

Of 497 patients enrolled, 247 were randomized to 1-day ciprofloxacin XR and 250 to the 3-day regimen. In the population valid for microbiological efficacy, the final assessment identified bacteriological success (primary efficacy endpoint) in more patients who had the 3-day regimen (98%) than in those who received the 1-day regimen (94.8%, 95% confidence interval, CI, −6.1%, 0.8%), although the difference was not statistically significant. In this population, the clinical response at the final visit was 98.5% and 96.7% for patients receiving the 3-day and the 1-day regimens, respectively (95% CI −5.2%, 0.8%). However, in the clinical efficacy population the clinical success rate was significantly greater for the 3-day (99.0%) than for the 1-day regimen (95.8%; 95% CI −6.4%, −0.3%). In a multivariate analysis, patients with diabetes mellitus and patients with a history of prostatitis had higher microbiological and clinical failure rates, respectively, than those without such conditions. For these patients, all failures occurred among those treated with the 1-day regimen.

CONCLUSION

As defined by bacteriological success in the population assessed for microbiological efficacy, prophylaxis with one dose of ciprofloxacin XR was statistically no worse than a 3-day regimen. However, in all efficacy analyses, bacteriological and clinical success rates were consistently lower for the 1-day than for the 3-day treatment. Thus, for selected patients undergoing TRNBP, there might be a role for 3-day preventive therapy with ciprofloxacin XR.

KEYWORDS

prostate biopsy, infection, antimicrobial prophylaxis, ciprofloxacin, extended release

INTRODUCTION

The use of prostate biopsy has increased dramatically with the use of PSA screening for prostate cancer. Transrectal needle biopsy of the prostate (TRNBP) is generally considered a safe procedure, but there are complications associated with the technique, including infection, acute urinary retention and rectal bleeding [1,2]. However, in general serious complications develop infrequently after TRNBP.

The reported incidence of complications after TRNBP varies substantially. Subclinical transient bacteraemia has been reported after TRNBP in most patients not receiving antibacterial prophylaxis [3,4]; prophylaxis can decrease the incidence of infections, including fever, positive urine cultures and bacteraemia, that are associated with TRNBP [4]. Although consultants for the *Medical Letter* recommend prophylaxis for patients undergoing TRNBP because of the risk of urosepsis [5], and many urologists accept the need for and administer prophylaxis [6–8], some think the need for antibacterial prophylaxis has not been clearly shown [4].

Although a recent retrospective study showed that TRNBP with no antibacterial prophylaxis had a statistically significantly higher risk of infectious complications [9], generalizations cannot be made from most published studies because patient preparation is not standardized, the antibacterial regimens vary considerably, and there are wide ranges in the proportion of patients who developed infectious complications [4]. In addition, although the incidence of positive cultures after TRNBP can be high, the low clinical significance of some of the infections and the low incidence of serious complications

argue against the routine use of antibacterial prophylaxis [4,10].

The choice of antibacterial agent and the duration of dosing vary widely among urologists [6–8,11]. In one survey of American urologists, >98% of the respondents prescribed antibacterial prophylaxis [8]. Ciprofloxacin was prescribed by ≈60% of the responding urologists and was the most common antibacterial of the 11 different agents used. About half of the respondents reported using ≥3 days of prophylaxis.

Although the reported duration of prophylaxis is not consistent with the published recommendations (one dose by mouth or i.v. before surgery, with additional doses given for prolonged procedures) [5], incidences of infectious complications associated with TRNBP were lower with a longer duration of therapy in some but not all studies [12–16]. In at least three studies, the first dose was given the day before the procedure [12,17,18].

The most frequently isolated organisms after TRNBP appear to be Enterobacteriaceae, including *Escherichia coli*, *Enterobacter* spp., *Proteus* spp. and *Klebsiella* spp. [3,4,16]. Other pathogens include *Enterococcus* spp. and *Staphylococcus saprophyticus* [16]. Although severe infections caused by *Bacteroides* spp., *Peptococcus* spp., *Peptostreptococcus* spp. and *Clostridium perfringens* have been reported, the frequency of anaerobic infections appears to be low [10,19,20].

Ciprofloxacin extended-release (XR), is a once-daily, oral formulation that is active *in vitro* against a broad range of organisms, including *E. coli*, *Enterobacter cloacae*, *Pr. vulgaris*, *K. pneumoniae*, *S. saprophyticus* and some strains of *Ent. faecalis* [21]. The present study was designed to evaluate the efficacy and safety of oral ciprofloxacin XR 1000 mg once daily, given as a 1-day or 3-day regimen for preventing infectious complications after TRNBP. Active study drug in the 3-day regimen was started the day before the procedure.

PATIENTS AND METHODS

Men aged ≥18 years and who required a TRNBP were enrolled; patients were included if their midstream urine (MSU) sample was negative (<10^4 colony-forming units, cfu/mL) for possible uropathogens at the visit before therapy and before TRNBP. Exclusion criteria were hypersensitivity to quinolone antibacterial agents, valvular heart disease, renal or hepatic insufficiency, or a CNS disorder that might predispose to seizures. Patients should not have had endoscopic manipulation of the urinary tract within 7 days before study entry nor had an indwelling catheter within 48 h or antibacterial treatment within 7 days before TRNBP. They should also have had no signs or symptoms of any underlying infection that might have required antimicrobial therapy.

The 'enrolled' population consisted of all patients enrolled in the study, including those who received no study medication. The 'safety' population consisted of all patients who received at least one dose of the study medication, within which an 'intention-to-treat' (ITT) population, who actually had TRNBP, was identified. The 'clinical efficacy' (CE) population was defined as all patients who met all key inclusion and exclusion criteria; took all study medication; had TRNBP; had their clinical outcome determined at the final visit; received no other antimicrobial therapy during the study unless they were classified as failing prophylaxis; and had no protocol violation that could affect efficacy.

The 'microbiologically valid' (MV) population was defined as all patients who met the criteria for inclusion in the CE population and who had a negative MSU sample at the visit before therapy and had a valid MSU culture at the final visit. However, a valid clinical outcome was not necessary. The MV population was used for the primary bacteriological efficacy analysis. The four most common reasons for invalidity were not adhering to the dosing regimen, no culture after treatment, no study medication taken or given, and no surgery. Others included inadequate dosing, antimicrobials after therapy (unless assessed as failing prophylaxis based on previous culture results), no pretreatment culture, positive pretreatment culture, lost to follow-up and concomitant antimicrobials.

This multicentre study, conducted at 46 centres in Brazil, Canada, Italy, Mexico, Spain and the USA, was prospective and double-blind, in which patients were randomized to receive oral ciprofloxacin XR 1000 mg once daily (Bayer HealthCare Pharmaceuticals, West Haven, CT, USA) given as a 1-day or a 3-day regimen. The first dose was given 24 h before, the second 2–3 h before and the third 24 h after TRNBP. For patients in the 1-day arm the first and third doses of ciprofloxacin XR were replaced with placebo.

The specific type of TRNBP was at the discretion of the surgeon, but all procedures were done under TRUS guidance, and all patients had a cleansing enema before TRNBP. The number of core samples obtained was recorded.

The primary efficacy variable was the result of urine cultures at all assessments including the final visit (bacteriological response). The secondary efficacy variable was clinical evidence of a genitourinary infection or procedure-related non-genitourinary infection at all assessments including the final visit (clinical response). Bacteriological success was defined as a negative urine culture (<10^4 cfu/mL) at the final visit with all other urine cultures obtained after the TRNBP negative. Clinical success was the absence of a genitourinary or procedure-related non-genitourinary infection at the final visit or at any time during the study period after the TRNBP. A genitourinary infection was defined as the presence of at least one of the following symptoms or signs after the TRNBP: leukocytosis, elevated temperature, chills, dysuria, urgency, frequency, flank pain, suprapubic pain or heaviness, haematuria, or pyuria. In addition, the symptom or sign had to be assessed by the investigator as caused by a genitourinary infection. Bacteriological and clinical failures occurring before the final visit were carried forward. Bacteriological and clinical responses were assessed as indeterminate if the patient received antibacterial therapy other than study drug at any time during the study period (unless the patient had been assessed as a prophylaxis failure), or if any required evaluations were missing or could not be interpreted.

Patients were assessed at a visit 2–5 days before TRNBP, a procedure visit at the time of TRNBP, a visit 1–6 days after the last dose of study drug, and a final visit 7–21 days after the final dose of study drug. A medical history and physical examination were conducted at the pre-therapy visit and a brief physical examination at the procedure visit. Blood chemistry, haematology and urine analysis tests and MSU cultures were obtained at all visits except for the procedure visit. Blood

TABLE 1 Patient disposition, n (%)

Population	Key criteria	1-day	3-day
Enrolled	Randomized	247 (100)	250 (100)
Safety	Took ≥1 dose of study drug	241 (97.6)	244 (97.6)
ITT	Took ≥1 dose of study drug and had TRNBP	239 (96.8)	238 (95.2)
CE	Took all doses of study drug, had TRNBP, and clinical response assessed	216 (87.4)	205 (82.0)
MV	Took all doses of study drug, had TRNBP, and bacteriological response assessed	210 (85.0)	201 (80.4)

TABLE 2 Demographics of patients undergoing TRNBP in the MV population

Variable	1-day	3-day	P
Number of patients	210	201	
Mean (SD):			
Age, years	65.0 (8.4)	64.7 (7.9)	0.726
Weight, kg	81.8 (16.3)	80.7 (16.0)	0.481
Height, cm	171.3 (8.6)	171.3 (7.9)	0.969
Body mass index, kg/m^2	27.7 (5.0)	27.3 (4.5)	0.363
Temperature, °C	36.5 (0.7)	36.5 (0.6)	0.565
Patient general health status, n (%)			0.800
Excellent	66 (31.4)	68 (33.8)	
Good	130 (61.9)	122 (60.7)	
Fair	14 (6.7)	11 (5.5)	
Race, n (%)			0.700
White	173 (82.4)	156 (77.6)	
Black	14 (6.7)	20 (10.0)	
Asian	3 (1.4)	2 (1.0)	
Hispanic	3 (1.4)	4 (2.0)	
Uncodeable	17 (8.1)	19 (9.5)	

cultures were obtained for any patient with a fever likely to be caused by an infection. Susceptibility thresholds of cultured micro-organisms were determined using broth microdilution. Safety assessments were conducted from the pre-therapy visit to the final visit.

The study was designed to show that a 1-day regimen was no worse than a 3-day regimen of ciprofloxacin XR 1000 mg in preventing infections after TRNBP. Significance tests were two-sided, with $\alpha = 0.05$ (unless otherwise indicated). The primary and secondary efficacy variables were analysed using 95% CIs for the difference in the success rates, calculated using Mantel–Haenszel statistics weighted by centre size. Lack of inferiority was defined statistically as the lower limit of the CI being >−7%; this value was chosen based on an assessment that differences of this magnitude or greater would be considered clinically significant, and because of the low predicted rate of bacteriuria. Additional definitions of prophylaxis failure were explored retrospectively. Fisher's exact test was used to compare these rates between treatment groups. As these comparisons were retrospective, *P* values should be considered descriptive. Statistical summaries were provided for demographic and baseline characteristics. Categorical variables were analysed using chi-square tests. For continuous variables, a one-way ANOVA model was used to compare the treatment groups. Logistic regression analyses were used to determine whether certain risk factors influenced the microbiological and clinical success rates. Univariate analyses used independent variables considered to be possible risk factors for failure [22]. These variables included age, race, treatment group, centre location, number of core samples obtained during surgery, history of diabetes mellitus, baseline serum glucose level ≥200 mg/dL, previous UTI or prostatitis, presence of BPH, neurogenic bladder, urinary retention, ischaemic heart disease, peripheral vascular disease, and cerebrovascular disease. Multivariate analyses were then used which included in the model only those variables with $P \leq 0.3$.

RESULTS

Of 497 patients enrolled, 247 were randomized to receive a 1-day regimen and 250 to receive a 3-day regimen of ciprofloxacin XR. The disposition of patients in the different populations is shown in Table 1. For patients in the MV population (the population used for the primary bacteriological efficacy analysis), the treatment groups were well balanced for baseline demographic data (Table 2). The number of core samples obtained during surgery was similar for the 1-day (9.3) and the 3-day regimen (9.5; $P = 0.491$).

Results for the primary efficacy variable of bacteriological response (the MV population) at the final visit are shown in Table 3. The bacteriological success rates at the final visit were 94.8% (199/210) and 98.0% (197/201) for the 1-day and 3-day regimens, respectively (95% CI −6.1%, 0.8%). Although it could be concluded that the 1-day was no worse than the 3-day regimen, because the lower limit of the CI for the difference in success rates was >−7.0%, there was a trend to greater efficacy with the 3-day regimen.

In all, 15 MV patients were assessed as bacteriological failures (11 had received the 1-day and four the 3-day regimen), from whom 18 organisms were isolated (Table 4). Of the 15 bacteriological failures, six were also clinical failures, with two having at least one resistant organism, two having only susceptible organisms, one having an intermediate organism, and one having no minimal inhibitory concentration (MIC) available. Nine of the 15 bacteriological failures were assessed as clinical successes, among whom three patients had at least one resistant organism, five had only susceptible organisms, and one had no MIC available. All five resistant organisms were isolated from

patients receiving the 1-day regimen (2.4% vs none; $P = 0.061$).

The clinical response at the final visit in the patients valid for microbiological efficacy is shown in Table 3. The clinical success rates at the final visit were 96.7% (203/210) and 98.5% (198/201) for the 1-day and 3-day regimens, respectively (95% CI −5.2%, 0.8%). It could be concluded that the 1-day regimen was no worse than the 3-day regimen, but again there was a trend to greater efficacy with the 3-day regimen. For 96.8% of the patients, the clinical and bacteriological outcomes were the same.

In all, nine MV patients were assessed as clinical failures (seven on the 1-day and two on the 3-day regimen). Among patients receiving the 1-day regimen, six assessed as clinical successes were bacteriological failures, while two assessed as clinical failures were bacteriological successes. Among patients receiving the 3-day regimen, three assessed as clinical successes were bacteriological failures while one assessed as a clinical failure and one as clinically indeterminate were bacteriological successes. In all, six of nine patients assessed as clinical failures were also bacteriological failures, and the remaining three were assessed as bacteriological successes.

The definitions of bacteriological and clinical failure did not require the subsequent use of antibacterial therapy. Seven of the 15 patients assessed as bacteriological failures in the MV population were treated with an antibacterial agent (six received the 1-day regimen and one the 3-day regimen) while six of the nine assessed as clinical failures were treated with an antibacterial agent after being assessed as clinical failures (five received the 1-day and one the 3-day regimen). Among the six patients assessed as both bacteriological and clinical failures, five were treated with an antibacterial agent (four had received the 1-day and one the 3-day regimen). In all, eight of 18 patients assessed as bacteriological or clinical failures were treated with an antibacterial agent. The overall treatment rates were 3.3% (7/210) and 0.5% (1/201) for the 1-day and 3-day regimens, respectively ($P = 0.068$).

Patients assessed as clinical failures were grouped into those with localized (presence of dysuria, urgency, frequency, suprapubic pain or heaviness, or pyuria) or systemic symptoms and signs (leukocytosis, elevated temperature, chills, or flank pain). For this analysis, two patients whose only symptom or sign was haematuria were not counted as clinical failures. Among those patients with localized symptoms or signs, the clinical failure rates were 2.9% (6/210) and none for the 1-day and 3-day regimens, respectively ($P = 0.030$). Among those with systemic symptoms or signs, the rates were 2.4% (5/210) and 0.5% (1/201) for the 1-day and 3-day regimens, respectively ($P = 0.216$).

The most commonly identified organism causing bacteriological failure at the final visit with both regimens was *E. coli* (Table 4). At the visit after therapy, it was possible to identify 8 of the 13 infecting organisms from the 1-day group, but none of the organisms from the 3-day group. Notably, most patients

TABLE 3 Bacteriological and clinical responses in the MV and ITT populations at final visit

	Response			
	Bacteriological		Clinical	
Variable	1-day	3-day	1-day	3-day
MV				
Number of patients	210	201	210	201
Success, n (%)	199 (94.8)	197 (98.0)	203 (96.7)	198 (98.5)
95% CI	−6.1, 0.8		−5.2, 0.8	
Failure, n (%)	11 (5.2)	4 (2.0)	7 (3.3)	2 (1.0)
Indeterminate, n (%)	NA	NA	0	1 (0.5)
ITT				
Number of patients	239	238	239	238
Success, n (%)	213 (89.1)	215 (90.3)	218 (91.2)	225 (94.5)
95% CI	−7.1, 4.7		−8.5, 0.6	
Failure, n (%)	11 (4.6)	6 (2.5)	13 (5.4)	5 (2.1)
Indeterminate, n (%)	0	0	2 (0.8)	1 (0.4)
Missing, n (%)	15 (6.3)	17 (7.1)	6 (2.5)	7 (2.9)

NA, not applicable.

TABLE 4 Organisms causing bacteriological failure in the MV population

	1-day, n	MIC*, μg/mL	3-day, n	MIC*, μg/mL
Total N	210		201	
E. coli	5	32.0	2	0.023
		32.0		ND
		32.0		
		32.0		
		ND		
Ent. faecalis	2	1.0	1	0.5
		1.0		
Enterococcus spp.	1	0.75	2	0.5
				3.0
Klebsiella pneumoniae	2	0.047	0	NA
		0.008		
Staph. aureus	1	32.0	0	NA
Proteus mirabilis	1	0.032	0	NA
Streptococcus spp.†	1	1.0	0	NA

**MIC susceptibility thresholds (broth microdilution) were: sensitive (≤1 μg/mL) and resistant (≥4 μg/mL). †Isolated from a blood culture at visit after therapy; the patient also had* E. coli *isolated from a urine culture after therapy. ND, not determined; NA, not applicable.*

Event	1-day	3-day
Number of patients	241	244
Any event	31 (12.9)	37 (15.2)
Dizziness	6 (2.5)	2 (0.8)
Nausea	3 (1.2)	3 (1.2)
Blood glucose increased	2 (0.8)	4 (1.6)
Lipase increased	2 (0.8)	3 (1.2)
Headache	3 (1.2)	1 (0.4)
Nasopharyngitis	0	3 (1.2)

TABLE 5
Incidence of adverse events, as n (%), occurring in ≥1% patients in the safety population

(85.7%) in the 1-day group had the visit 3 or 4 days after the last dose of active drug, while most (85.6%) in the 3-day group had this visit 2 or 3 days after the last dose of active drug.

Three of the five patients from whom an *E. coli* isolate resistant to ciprofloxacin was obtained received antibacterial therapy, as did the one with an *Enterococcus* spp. of intermediate susceptibility. One patient in the 1-day group had α-haemolytic *Streptococcus* spp. susceptible to ciprofloxacin and $\geq 10^5$ cfu/mL of *E. coli* resistant to ciprofloxacin isolated from blood and urine cultures after therapy, respectively. This patient was assessed as a clinical failure, and was one of four patients who received antibacterial therapy.

In a multiple logistic regression model we used potential predictors of microbiological failure identified by univariate analyses, including race, treatment group, centre location, history of diabetes mellitus, previous UTI or prostatitis, and presence of BPH. Patients with a history of diabetes mellitus ($P = 0.050$) and those enrolled in USA centres ($P = 0.031$) had significantly higher failure rates than those without diabetes and those enrolled in centres in other countries, respectively. Among diabetic patients, microbiological failure occurred in four of 16 of those treated with the 1-day regimen and none of 12 of those treated with the 3-day regimen. However, adjusting for these factors did not influence the results of the comparison between the 1-day and 3-day treatment regimens. On univariate analysis, the number of core samples obtained during surgery was not associated with microbiological failure ($P = 0.973$).

CE population: the clinical success rate for patients treated with the 3-day regimen was significantly higher than that for patients treated with the 1-day regimen. The success rates at the final visit were 95.8% (207/216) and 99.0% (203/205) for the 1-day and 3-day regimens, respectively (95% CI −6.4%, −0.3%).

In a multiple logistic regression model we used potential predictors of clinical failure identified by univariate analyses, including treatment group, history of diabetes mellitus, previous UTI or prostatitis, and presence of BPH. Patients with a history of prostatitis ($P = 0.021$) had a significantly higher failure rate than those with no previous prostatitis, while treatment with the 1-day regimen approached statistical significance ($P = 0.060$). Among patients with previous prostatitis, there was clinical failure in two of eight of those treated with the 1-day and none of seven with the 3-day regimen. The number of core samples obtained during surgery was not associated with clinical failure on univariate analysis ($P = 0.973$)

ITT population: all patients who received at least one dose of study drug and had TRNBP were included in this group. The bacteriological and clinical responses in the ITT population at the final visit are also shown in Table 3. The bacteriological success rates for the 1-day and 3-day regimens were 89.1% and 90.3%, respectively (95% CI: −7.1%, 4.7%). However, it could not be concluded that the 1-day regimen was no worse, because the lower limit of the 95% CI was <−7.0%. The clinical success rates for patients treated with the 3-day (94.5%) was slightly higher than the rate for those treated with the 1-day regimen (91.2%), but the difference was not statistically significant (95% CI −8.5%, 0.6%).

Seven of the 17 patients assessed as bacteriological failures were treated with an antibacterial agent (six received the 1-day and one the 3-day regimen). Fourteen of the 18 patients assessed as clinical failures were treated with an antibacterial agent (10 had received the 1-day and four the 3-day regimen). In all, 16 of 29 patients assessed as bacteriological or clinical failures in the ITT population were treated with an antibacterial agent. The overall treatment rates were 5.0% (12/239) and 1.7% (4/238) for the 1-day and 3-day regimens, respectively ($P = 0.072$).

Among those patients with localized symptoms or signs, the clinical failure rates were 3.3% (8/239) and 0.5% (1/238) for the 1-day and 3-day regimens, respectively ($P = 0.037$). Among those with systemic symptoms or signs, the rates were 4.6% (11/239) and 1.7% (4/238) for the 1-day and 3-day regimens, respectively ($P = 0.113$).

All patients who received at least one dose of study drug were included in the safety population. Adverse events occurred in 12.9% of the safety population who received the 1-day and in 15.2% who received the 3-day regimen, and at least one event was assessed to be drug-related in 2.5% and 3.7% of patients, respectively, in the two groups. Serious adverse events occurred in four patients (two in each group), but there were only two discontinuations due to adverse events (in the 3-day group) and no deaths. The overall event rates were low and the small differences between groups were not clinically relevant. The incidences of adverse events occurring in at least 1% of either treatment group are shown in Table 5. Again, there were no differences in event rates between the groups, with only dizziness and nasopharyngitis having a >1% difference between the groups.

DISCUSSION

This double-blind prospective study was designed to show that a 1-day regimen was no worse than a 3-day regimen of oral ciprofloxacin XR 1000 mg for preventing infectious complications in men undergoing TRNBP. The microbiological and clinical analyses in the MV population showed that the 1-day regimen was statistically no worse than the 3-day regimen. However, patients in the CE population receiving the 3-day regimen had a statistically better clinical success rate than those receiving the 1-day regimen. Moreover, with all efficacy analyses in all populations, there were slightly lower success rates for the 1-day than for the 3-day regimen.

The clinical significance of many of the bacteriological failures is unclear because 58.8% of patients with positive urine cultures in the ITT and 53.3% in the MV population received no antimicrobial therapy. For patients with positive urine cultures but no evidence of a clinical failure, 81.8% and 77.8% in the ITT and MV populations, respectively, did not receive antimicrobial therapy. In addition, although there were more patients with localized symptoms or signs of failure among those receiving 1 day than among those receiving 3 days of ciprofloxacin XR (2.9% vs none, $P = 0.030$), there was no statistically significant difference between the treatment groups in the number of patients with systemic symptoms or signs of failure (2.4% vs 0.5%; $P = 0.216$).

This current study is consistent with two prospective randomized studies that concluded that there is no clinical advantage to a longer course of antimicrobials to prevent infections associated with TRNBP. The incidences of infectious complications were similar in 79 patients receiving one dose of ciprofloxacin 500 mg and tinidazole 600 mg, and in 77 receiving the same combination twice daily for 3 days [14]. In a slightly larger study, patients were randomized to receive 1 day or 3 days of ciprofloxacin or levofloxacin starting at least 1 h before TRNBP [13]. At the telephone follow-up after 7 days, there was no difference in infectious complications. These outcomes are supported by pharmacokinetic data showing that prostate levels of ciprofloxacin at 1 and 3 h after an oral dose of ciprofloxacin XR 1000 mg generally exceed corresponding serum levels [23].

The suggestion that a 3-day regimen started the day before the procedure is no more effective in preventing TRNBP-related infectious complications than a 1-day regimen contrasts with the findings of other studies. In a retrospective study of 625 TRNBP procedures [12], fewer symptomatic UTIs with a positive urine analysis, culture or both, developed in patients who received six doses of ciprofloxacin 500 mg twice daily (two doses 24 and 12 h before the TRNBP and four doses after) than in patients who received four doses (one dose 12 h before and three doses after TRNBP). In another large, retrospective study, the UTI rate after TRNBP was 0.1% among 4439 patients who received ciprofloxacin 500 mg twice daily (three doses before TRNBP and five doses after) [17], which is lower than in the present study, and again suggests that longer antimicrobial prophylaxis, starting 24 h before TRNBP, might be more effective than shorter prophylaxis in patients undergoing TRNBP.

Two prospective studies also indicate that a longer duration of antimicrobial prophylaxis might be more effective than a shorter one. In a randomized comparison of two different dose regimens of ciprofloxacin in 257 patients undergoing TRNBP, complications occurred in 3.1% of those receiving a single dose of ciprofloxacin and in 2.1% of those receiving three daily doses, although this difference was not statistically significant [15]. Both ciprofloxacin regimens were better than 3 days of prophylaxis with chloramphenicol or norfloxacin (18.3% and 10.5% complication rates, respectively). In another randomized study in 491 patients undergoing TRNBP, prophylaxis with norfloxacin 400 mg twice daily for 1 week was significantly more effective than prophylaxis for 1 day (infection rate of 4.9% vs 11%; $P < 0.05$) [16].

Based on the present results a longer course of antimicrobial prophylaxis, starting the day before TRNBP, might be more beneficial than a shorter course for some patients. Patients with diabetes mellitus and a history of prostatitis had higher microbiological and clinical failure rates, respectively, than those with no such conditions. Among diabetic patients and those with previous prostatitis, all failures were among those treated with the 1-day regimen.

The conclusion that a longer course of antimicrobial prophylaxis might be more beneficial should be considered with some caution. First, the primary efficacy analysis showed that the 1-day regimen was no worse than the 3-day regimen in preventing bacteriological failure. Second, most patients in the 1-day group were assessed 3–4 days after receiving active drug, while patients in the 3-day group were assessed 2–3 days after receiving active study drug, which might have had an impact on the findings. Third, the utility of dosing ciprofloxacin XR 12–24 h before TRNBP is not supported by pharmacokinetic data. Prostate levels of ciprofloxacin at 1 and 3 h after an oral dose of ciprofloxacin XR 1000 mg generally exceed corresponding serum levels [23].

The safety findings raised no new or unexpected issues for the safety of either 1-day or 3-day treatment with ciprofloxacin XR 1000 mg in antimicrobial prophylaxis in patients undergoing TRNBP. The findings were consistent with previous clinical experience with ciprofloxacin. No treatment-related serious adverse events or treatment-related adverse events leading to withdrawal occurred in either treatment group.

In conclusion, the results of the present study show that ciprofloxacin XR 1000 mg is well tolerated when given for 1 or 3 days to prevent infectious complications associated with TRNBP. Antimicrobial prophylaxis using a 1-day regimen of ciprofloxacin XR 1000 mg was statistically no worse than a 3-day regimen, as defined by the primary efficacy endpoint of bacteriological success in the CE population. However, in all efficacy analyses, bacteriological and clinical success rates were consistently lower for 1-day than for 3-day treatment, and there were more bacteriological failures among patients receiving the 1-day (5.4%) than the 3-day regimen (2.1%). Thus, for patients undergoing TRNBP, there might be a role for 3-day preventive therapy with ciprofloxacin XR, possibly for those with diabetes or a history of prostatitis.

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CONFLICT OF INTEREST

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Abbreviations: **TRNBP**, transrectal needle biopsy of the prostate; **TRUS**, transrectal ultrasound; **XR**, extended-release; **MSU**, midstream urine; **cfu**, colony-forming units; **ITT**, intention-to-treat; **CE**, clinical efficacy; **MV**, microbiologically valid; **MIC**, minimal inhibitory concentration.