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Fosfomycin antimicrobial prophylaxis for transrectal ultrasound-guided biopsy of the prostate: A prospective randomised study

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KEYWORDS

Fosfomycin;
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ABBREVIATIONS

ESBL, extended-spectrum β-lactamase;
FQ, fluoroquinolone;
MDR, multidrug-resistant;
TRUSBx, TRUS-guided biopsy of the prostate

Abstract ***Objectives:*** To compare the incidence of infectious complications after single-dose fosfomycin vs. standard fluoroquinolone (FQ)-based prophylaxis in patients undergoing transrectal ultrasound-guided biopsy of the prostate (TRUSBx), as there is an alarming trend worldwide of increasing resistance to FQs limiting their suitability as appropriate prophylaxis for TRUSBx.

Patients and methods: A prospective study was conducted in 412 consecutive patients undergoing TRUSBx between February 2012 and June 2015. Patients were randomly divided into two groups; Group 1 (202 patients) who received single-dose fosfomycin (3 g, orally) 1–2 h before TRUSBx and Group 2 (210 patients) who received routine empirical prophylaxis in the form of oral ciprofloxacin 500 mg and metronidazole 500 mg at least 1 h before TRUSBx and continued this twice daily for 3 days before TRUSBx. We recorded all febrile and afebrile urinary tract infections (UTIs) within the 4 weeks after the procedure.

Results: There was no difference in baseline demographics between the two groups. Total infectious complications occurred in four (1.9%) and 18 (8.5%) patients in Groups 1 and 2, respectively, which was statistically significant ($P = 0.001$). *Escherichia coli* was the most common isolated pathogen from urine cultures in all patients with infectious complications (68%). The other isolated bacterium, *Klebsiella pneumoniae*, was detected in four patients (18%). Urine

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cultures revealed FQ-resistant strains (73%), all of which were extended-spectrum β-lactamase-producing *E. coli* and *K. pneumoniae*.

Conclusions: Single-dose fosfomycin before TRUSBx significantly reduces infectious complications when compared with standard therapy. Fosfomycin is an effective agent for antimicrobial prophylaxis in patients undergoing TRUSBx, particularly in populations where FQ resistance is common.

Introduction

The risk of infection-related complications after TRUS-guided prostate biopsy (TRUSBx) has increased. Clinically significant infectious complications include UTI, acute bacterial prostatitis, epididymo-orchitis, and even life-threatening sepsis [1]. There is no currently accepted optimal prophylactic antibiotic regimen before TRUSBx. The value of antibiotic prophylaxis in reducing the incidence of such complications have been documented in several studies; however, there are wide variations in antibiotic regimens and administration among different centres, with none clearly better than another [2,3].

Fluoroquinolone (FQ) antibiotics, which reach high concentrations in the prostate after oral administration, are routinely used to reduce the risk of infectious complication after TRUSBx because of broad spectrum activity against Gram-positive and Gram-negative organisms [2,4,5]. Unfortunately, many recent studies have identified an alarming trend of increasing resistance to FQs worldwide, limiting their suitability as appropriate prophylaxis [6–8]. In the wake of the increased FQ resistance in *Escherichia coli* strains, several interventional studies have compared different antibiotic prophylactic regimens before TRUSBx [9–12].

Fosfomycin is an oral, bactericidal, broad-spectrum antibiotic with favourable pharmacokinetic and pharmacodynamics profile that promotes its effectiveness against UTIs. Specifically, after a single 3-g oral dose of fosfomycin tromethamine, high urinary and prostatic tissue concentrations are achieved above the minimal inhibitory concentrations of the common uropathogens within 4 h and persist for 48 h [13,14].

The present prospective randomised study aimed at comparing the incidence of infectious complications after TRUSBx using single-dose fosfomycin (3 g) vs. standard FQ-based prophylaxis.

Patients and methods

Patients undergoing TRUSBx were enrolled into a prospective randomised study at the Alexandria University Department of Urology. Indications were an elevated PSA level and/or an abnormal finding on DRE. The study was approved by our Local Research and Ethics Committee.

The urine analysis and urine cultures, conducted 5 days before the TRUSBx, were negative for infection in all the study patients. The patients with a history of allergy or intolerance to anyone of the study drugs, UTI with positive urine culture, indwelling urinary catheters, and antibiotic use during the previous 4 weeks were excluded.

Patients were randomly divided into two groups: Group 1, received single-dose fosfomycin (3 g, orally) 1–2 h before TRUSBx and Group 2 received routine empirical prophylaxis in the form of oral ciprofloxacin 500 mg and metronidazole 500 mg at least 1 h before TRUSBx and continued this twice daily for 3 days before TRUSBx. Randomisation was performed using sealed opaque envelopes; sealed envelopes were placed into a box and mixed. Allocation concealment was achieved by using an independent person 'biopsy nurse' who blindly selected one of the sealed opaque envelopes. Thus patients were randomly allocated to Group 1 or Group 2 before the procedure. We recorded all febrile and afebrile UTIs within 4 weeks of TRUSBx.

Technique of TRUSBx

Informed consent was obtained from all patients before TRUSBx, after they had been instructed by the physician regarding all possible complications. Patients were strictly advised not to take non-steroidal anti-inflammatories and anticoagulant medications for a week before the TRUSBx, to minimise the risk of bleeding and associated complications with continuation.

All TRUSBx were performed in an outpatient clinic setting using a 7-MHz probe. After prophylactic antibiotic administration, biopsies were taken with the patient in the left decubital position using an automated biopsy gun with a disposable 18-G biopsy needle. No rectal cleansing enema was used. A standardised template-based series of TRUSBx was taken through a systematic approach (a standard 12-core biopsy taken from the base, mid-gland, apex of the right and left sides of the lateral and far-lateral peripheral zone). Two transitional

zone biopsies were added in case of a previous history of negative biopsies.

We prospectively recorded the following variables in all patients: age, PSA level, prostate volume, diabetic status, and prior history of TRUSBx. Urine cultures were conducted 2 weeks after the TRUSBx in all patients. Urine and blood cultures were obtained from patients admitted with a suspicion of a post-TRUSBx febrile UTI.

UTI, defined as the association of leucocyturia (> 5 cells/high-power field) and significant bacteriuria (> 105/mL) within 4 weeks of the procedure and the antimicrobial-resistance pattern of the strains were noted. Sepsis was defined as a fever of > 38 °C in the presence of constitutional symptoms.

The primary endpoint was the occurrence of post-TRUSBx infectious complications as evidenced by fever (> 38 °C) in any patient who underwent TRUSBx within the proceeding 4 weeks and presenting with rigours and/or any one of the following LUTS e.g. dysuria, frequency, urgency or suprapubic pain.

Statistical analysis

This study was designed to detect a 10% difference between the incidence of infectious complications after TRUSBx using single-dose fosfomycin vs. standard FQ-based prophylaxis with 80% power assuming a significant difference level of 0.05 and two-sided statistical testing. The sample size was estimated to be 400 patients (200 patients in each group). We aimed to enrol 440 patients to take into account withdrawals. Statistical analyses were performed with SPSS version 21.0 (Chicago, IL, USA) statistical software package. The two groups were compared with the independent samples *t*-test and chi-squared test. Statistical significance was set as a $P < 0.05$.

Results

In all, 440 patients were randomly divided into the two groups (220 patients/group) between February 2012 and June 2015. We had 28 withdrawals (18 patients in Group 1 and 10 in Group 2). Consequently, 412 patients completed the entire treatment protocol (Fig. 1); Group 1 (202 patients) who received single-dose fosfomycin (3 g, orally) and Group 2 (210) who received routine empirical prophylaxis in the form of oral ciprofloxacin 500 mg and metronidazole 500 mg.

There was no significant difference between the two groups in baseline demographics, except for there being more patients with a prior history of TRUSBx in Group 1.

Total infectious complications occurred in four (1.9%) and 18 (8.5%) patients in Groups 1 and 2, respectively, which was statistically significant ($P = 0.001$).

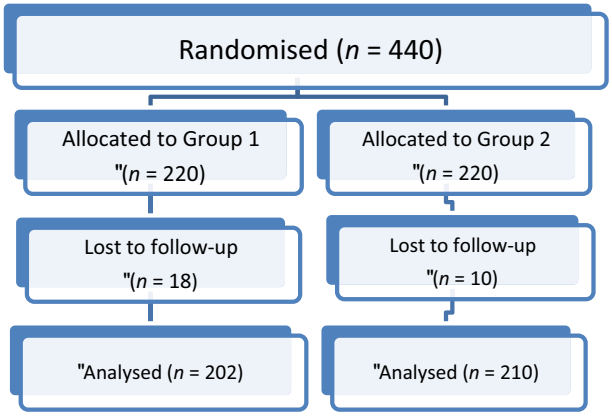

Figure 1 Study flow diagram.

There were no cases of septic shock and no deaths. Of the four patients in Group 1 with infectious complications, three developed afebrile UTI after TRUSBx and one had febrile UTI in the form of prostatitis including bacteriuria, leucocyturia, general and urinary symptoms. Of the 18 patients in Group 2 with infectious complications, 14 (78%) developed afebrile UTI, whilst four (22%) presented with febrile UTI in the form of pyelonephritis (two) and prostatitis (two). Antibiotic regimens were adjusted according to the antimicrobial susceptibility testing results of urine cultures. All patients with febrile UTI were considered cured after 4 weeks of antibiotics (Table 1).

Culture results

Post-TRUSBx blood cultures were negative in all patients who presented with febrile UTI. Organisms identified in the urine cultures in Group 1 were *E. coli* (two), *Streptococcus* (one) and *Pseudomonas* (one), of which three of the four patients were FQ resistant. In Group 2, the organisms identified were *E. coli* (13), *Klebsiella pneumoniae* (four) and *Staphylococcus epidermidis* (one), of which 13 of the 18 patients (72%) were FQ resistant (Table 2).

Table 1 Patient characteristics and infectious complications of the two groups.

Variable	Group 1 Fosfomycin	Group 2 Standard FQ	*P*
Number of patients	202	210	
Mean (SD):			
Age, years	68.8 (4.2)	62.5 (2.8)	0.62
Prostate volume, mL	67.3 (31.2)	59.8 (28.5)	0.08
Mean (SE) PSA level, ng/mL	23.9 (5.8)	17.8 (3.2)	0.06
Prior TRUSBx, *n*	13	5	0.03*
N (%):			
Afebrile UTI	3 (75)	14 (78)	0.001
Febrile UTI	1 (25)	4 (22)	

* Statistically significant.

Table 2 Antimicrobial susceptibility of the urine isolates of patients with afebrile and febrile UTIs.

Variable	Group 1 Fosfomycin	Group 2 Standard FQ	*P*
Number of patients	4	18	0.001*
Afebrile UTI, *n*	3	14	
FQ-sensitive	1	5	
FQ-resistant	2	9	
Febrile UTI, *n*	1	4	
FQ-sensitive	–	–	
FQ-resistant	1	4	

* Statistically significant.

Patients with infectious complications (22/412, 5.3%)

E. coli was the most common isolated pathogen in the urine cultures in all patients with infectious complications (68%). The other isolated bacterium, *K. pneumoniae*, was detected in four of the 22 patients (18%). Urine cultures revealed FQ-resistant strains (16 of 22; 73%), all of which were extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae*.

There were no side-effects due to the antibiotic regimen in either group. Antimicrobial susceptibility of the urine isolates of patients with afebrile and febrile UTIs are shown in Table 2. Minor haematuria and bleeding per rectum were recorded in 46 patients (25 in Group 1 vs. 21 in Group 2) after TRUSBx, with no case of significant bleeding requiring hospitalisation or blood transfusion.

Discussion

The increasing prevalence of multidrug-resistant (MDR) infections is a major worldwide concern. This is especially true for Gram-negative organisms, for which increasing resistance to currently available antibiotics is particularly apparent. FQ-resistant Gram-negative bacilli are currently reported with increasing frequency throughout the world and are currently responsible for increased infectious complications after TRUSBx [15].

One of the MDR mechanisms that have emerged is the ESBLs, primarily in *E. coli*, *Klebsiella* and *Proteus mirabilis*. Bacteria that produce these enzymes are able to inactivate extended-spectrum cephalosporins and monobactams; furthermore, the plasmids that transmit ESBLs also carry resistance determinants for trimetho prim/sulphamethoxazole, FQs, and aminoglycosides [16]. Carbapenems were considered the antimicrobials of choice for these organisms, although this was complicated by the development of carbapenemase-producing *K. pneumoniae* the following decade [17].

Recently, there has been renewed interest in the somewhat historical antibiotics such as fosfomycin, in view of the limited choices of antibiotics available to treat infections associated with these pathogens. Fosfomycin formulations are relatively safe and non-allergenic [18]. Fosfomycin is a natural phosphonic antibiotic that acts by blocking bacterial cell wall synthesis by inhibiting phosphoenolpyruvate transferase, an enzyme involved in the initial stage of peptidoglycan synthesis [18]. This inhibition is bactericidal and occurs at an earlier step than the action of β-lactams or glycopeptides [19]. In addition, fosfomycin decreases bacterial adhesion to uroepithelial cells, and has the ability to penetrate biofilms, which may contribute to its effectiveness in the treatment of UTIs. Fosfomycin formulations do not appear to exhibit cross-resistance with other antimicrobials, perhaps because of their unique mechanism of action and lack of structural relationship to other known antibiotics, allowing it to retain activity against MDR organisms [20,21]. Fosfomycin has a broad-spectrum activity against a wide variety of aerobic and anaerobic bacteria including Gram-positive and Gram-negative bacteria and has shown excellent results in the treatment of uncomplicated UTIs.

Fosfomycin, administered as a single oral dose, has been shown to be well tolerated and have a favourable safety profile in multiple studies. The primary adverse effects of the oral formulations are mild gastrointestinal distress, fatigue, and headache. A potential concern that may be associated with fosfomycin treatment is the emergence of resistance [22]. Despite its clinical use, emergence of uropathogens resistant to fosfomycin has been reported in few studies; therefore, fosfomycin could also be recommended as a prophylactic before endourological procedures [23].

A prospective study by Gardiner et al. [24] studied the penetration of fosfomycin into benign prostatic tissue in a large cohort of otherwise healthy men undergoing TURP. They detected that fosfomycin achieved reasonable intraprostatic concentrations in the inflamed prostate after a single 3-g oral dose and pointed out that fosfomycin may be a potential alternative for pre-TRUSBx antibiotic prophylaxis and possibly for the treatment of multidrug-resistant Gram-negative bacterial prostatitis.

Clinical data about the prophylactic use fosfomycin before TRUSBx is relatively limited. A recent prospective randomised study by Volkan et al. [25] reported that single-dose fosfomycin is as effective and safe as single-dose 500 mg oral ciprofloxacin for antibiotic prophylaxis before TRUSBx. Fosfomycin was also found to be as safe and effective as ciprofloxacin and levofloxacin in two studies: in the retrospective study by Ongün et al. [26], who compared single-dose fosfomycin with single-dose levofloxacin and 500 mg oral ciprofloxacin twice daily administered for 5 days starting 1 day before the procedure; and Lista et al. [27], who compared double doses of fosfomycin with 500 mg oral ciprofloxacin

twice daily administered for 5 days starting 1 day before the procedure in a prospective randomised study.

The findings of the present study are similar to other published reports on the efficacy of fosfomycin for TRUSBx antimicrobial prophylaxis, moreover, our results revealed that fosfomycin was associated with a significant reduction in infectious complications when compared with standard FQ therapy in patients undergoing TRUSBx ($P = 0.001$). In all patients with infectious complications (22 patients), *E. coli* was the most common isolated pathogen from urine cultures (15/22, 68%), with FQ-resistant strains reaching 73% (16/22), all of which were ESBL-producing *E. coli* and *K. pneumoniae*. This might explain the superiority of fosfomycin over FQ in preventing post-TRUSBx infectious complications.

We have recently reconsidered the routine empirical administration of FQs before TRUSBx, especially after we observed an increase in post-TRUSBx infectious complications, particularly in patients who had used FQs in the 6 months before the TRUSBx. We chose fosfomycin as an alternative prophylactic antibiotic to the standard FQ regimen because of its convenience as an oral single-dose therapy with expected enhanced compliance, lower cost, and possibly fewer adverse events, in comparison with longer antibiotic regimens. In addition, a high concentration of fosfomycin is achieved in urine and prostatic tissue after a single dose. Fosfomycin has a broad spectrum of activity and is well tolerated. Yet, considerations regarding the achievement of microbiological eradication, as well as the emergence of microbiological relapse or re-infection, may arise. Further study of this promising agent, on a larger scale with a longer follow-up, seems warranted in the current climate of increasing resistance to current standard prophylactic antibiotic regimens.

We acknowledge several limitations of the present study. First, there might be a recall bias, relying on patient recall for past histories of TRUSBx, it is possible that some patients might have forgotten these past events, therefore, underestimating the total number of patients with a past history of TRUSBx. Second, a prior history of TRUSBx was significantly higher in Group 1, which could make the sample not comparable regarding repeated infection and prostatitis. Finally, lack of culture standardisation in microbiological laboratories may represent a limiting factor.

Conclusion

Single-dose fosfomycin before TRUSBx significantly reduces infectious complications when compared with standard FQ-based therapy. Fosfomycin is an effective agent for antimicrobial prophylaxis in patients undergoing TRUSBx, particularly in populations where FQ resistance is common.

Conflict of interest

None to declare.

Source of funding

None.

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