ORIGINAL RESEARCH

Efficacy of a Single- Dose Fosfomycin as Antibiotic Prophylaxis Prior to Transrectal Ultrasound-Guided Prostate Biopsy

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Objectives: The goal to prevent increasing antibiotic resistance in urologic procedures has a significant impact on the choice of preoperative antibiotic prophylaxis. The efficacy of an old-new antibiotic-fosfomycin in TRUS-guided prostate biopsy was also evaluated.
Methods: Included were patients who underwent TRUS-guided prostate biopsy from August 1, 2015-July 31, 2016. Patients who satisfied the inclusion criteria were included. Patients were asked to take a single dose of 3g oral fosfomycin 1-3 hours prior to the procedure. Urinalysis was taken pre biopsy and post biopsy (at least 7-10 days). Occurrence of afebrile and febrile UTI were noted. Patients were informed of the signs and symptoms that need to be reported to the investigators.
Results: There were 74 patients enrolled in the study. The mean average age of patients was 66.5(±7). Majority of patients were having moderate lower urinary tract symptoms (40.5%) followed by patients with indwelling foley catheter (31.1%). Seventeen percent of patients had concomitant diseases like diabetes mellitus, cystolithiasis, nephrolithiasis, hypertension, etc. Pre biopsy, 51.4% of patients had asymptomatic urinary tract infection and 35% of these patients showed resolution of UTI post biopsy. The incidence of febrile UTI was 4%, 3.8% of patients with UTI pre biopsy and 50% of patients without UTI pre biopsy. Finally, the presence of afebrile and febrile UTI pre and post biopsy was statistically significant at 5% level of significance.
Conclusion: Single dose oral fosfomycin as prophylactic antibiotic in TRUS- guided prostate biopsy can be an alternative to reduce the rate of fluoroquinolone- resistant infections.

Key words: Prophylactic antibiotic, prostate biopsy, transrectal Ultrasonography, fosfomycin, urinary tract infection

Introduction

Transrectal ultasound-guided prostate biopsy is widely used and acceptable procedure to detect prostate cancer. This is done in patients with elevated prostate specific antigen, abnormal digital rectal exam such as presence of prostate nodules, hard and fix prostate and presence of prostatic nodules on ultrasound. This technique is usually safe and well-tolerated with a low incidence of serious complications. However, bacterial infection that can lead to life-threatening urosepsis can be one of its complications.

Urinary tract infection (UTI) is considered the second most frequently noted complication of prostate biopsy, after bleeding complications. It has been described as a minor or major complication, depending on its severity. Although

non-complicated or afebrile UTIs frequently occur after biopsy (1.2-11.3%), complicated or febrile UTIs are also not uncommon (1.4-4.5%).[1]

In other countries, the hospital admission rates for complications following TRUSPBx have increased dramatically during the last 10 years primarily due to an increasing rate of infection-related complications. The hospital admission rate for infection-related reasons within 30 days of the procedure increased from 1.0% in 1996 to 4.1% in 2005.[1] Perioperative antibiotic prophylaxis (PAP) is widely used to prevent this infectious complications.[2] The essential value of antimicrobial prophylaxis is to defend the patient undergoing invasive diagnostic procedures or surgery against infectious complications by reducing the bacterial load[3] and is recommended by the EAU guidelines and AUA best practice policy.[1] Prophylactic antibiotics used in urologic procedures are directed towards the most common uropathogens. Most postoperative infections are caused by enterococci of the Gram-positive strains and Enterobacteriaceae of the Gram-negative ones.[4] Escherichia coli still remains the predominant uropathogen (70-80%) isolated in acute community-acquired uncomplicated infections followed by Staphylococcus saprophyticus (10-15%). Klebsiella, Enterobacter, Proteus species and enterococci infrequently cause uncomplicated cystitis and pyelonephritis.[3]

Majority of urologists prescribe fluoroquinolone as antibiotic prophylaxis in TRUSPBx. The common practice is to use fluoroquinolones a day prior and after the procedure to complete 5 days of treatment. Since fluoroquinolones have a broad antimicrobial spectrum, the use or overuse of these drugs by physicians has led to increasing fluoroquinolone-resistant pathogens. Multiple reports describe an emergent trend of increasing bacterial resistance and infection-related complications after prostate biopsies. When patients present with post-prostate biopsy infective symptoms, almost 50% are associated with fluoroquinolone- resistant pathogens.[1] The increasing number of fluoroquinolone-resistant pathogens has led to investigations of alternative drugs- call for a new look at the therapeutic options. One of the alternative treatments for multidrug- resistant pathogens is fosfomycin.[5]

Fosfomycin, a phosphonic class antibiotic with broad spectrum antibacterial activity has been used outside the United States since the early 1970s for the treatment of a variety of infections. It was discovered in 1969 by Hendlin and colleagues in a Streptomyces fradiae culture.[6] It has broad antibacterial spectrum, coverage, targeting bacteria with mucopeptide synthesis by inactivation of UDP-N-acetylglucosamine-3-enolpyruvyltransferase, the first enzyme involved in the synthesis of peptidoglycan.[5,6] Through this mechanism of action, fosfomycin has a broad spectrum on in- vitro activity against a variety of clinically important Gram- positive pathogens, including methicillin-resistant Staphylococcus aureus and Gram- negative pathogens including extended-spectrum-β-lactamase (ESBL) - producing members of the family Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE).[6] It is a relatively small hydrophilic agent with negligible serum protein binding. It is excreted unchanged in urine, achieving high concentrations for prolonged period. It distributes well into the tissues, achieving clinically relevant concentrations in sites such as serum, soft tissues, lung, bone, CSF and heart valves. There is no cross-resistance hence fosfomycin can be administered in combination with a number of other antimicrobial agents.[5]

The objective of the study was to determine the efficacy of single dose Fosfomycin as a prophylactic antibiotic for patients undergoing transrectal ultrasound-guided prostate biopsy.

Materials and Methods

Inclusion Criteria

i. All patients who underwent transrectal UTZ-guided prostate biopsy from August 1, 2015-July 31, 2016.

ii. All patients who underwent transrectal UTZ-guided prostate biopsy who have a concomitant diseases like urolithiasis, diabetes mellitus, asymptomatic urinary tract

infection, treated prostatitis and those with indwelling Foley catheter.

Exclusion Criteria

i. All patients who have antibiotic intake of less than 7 days for treatment of on-going infections like prostatitis, UTI, pneumonia etc.

Prostate biopsy indications were an elevated prostate-specific antigen (PSA) level (>4 ng/ml), abnormal digital rectal examination like presence of nodules, hard and fix prostate, presence of nodules on prostate ultrasound and abnormal findings in the first prostate biopsy pathology that necessitate a repeat biopsy such as the presence of atypical glands. The latter was performed at least 6 weeks apart. All patients who underwent transrectal UTZ-guided biopsy was asked to have a baseline urinalysis at least 3-5 days before the procedure. All patients took Lactulose 30cc the night prior to the procedure. The patient was instructed to take light breakfast on the day of the procedure.

All patients were asked to take 3grams of Fosfomycin dissolve in 1 glass of water 1-3 hours prior to the procedure.[2,7,8]

With the patient in the left decubitus position, asepsis/antisepsis was done with betadinized gauze then 2% Lidocaine jelly (cathejell) was instilled intrarectally as local anesthesia. After 15 minutes, transrectal ultrasound was performed with a multi-planar multifrequency probe (75 MHz) attached to the ultrasound scanner. Prostate biopsy (12 cores) was taken using an automated biopsy gun with an 18 gauge, 30 cm biopsy needle. Prostate volume was calculated using the prostate ellipsoid formula: volume (V) = 0.52 (L x W x H) where L is the cephalocaudal diameter, W is the width and H is the antero-posterior diameter. Twelve cores were taken in the first biopsy and 24 cores in the repeat biopsy (saturation biopsy).

All patients were instructed to return to the hospital or report to the urologist if they developed fever of ≥38.0°C, chills or rigors, body weakness, severe irritative voiding symptoms like dysuria, frequency, urgency, gross hematuria, profuse bleeding per rectum, and suprapubic tenderness.

Patients were followed- up until 1 month after TRUSPBx as a cut-off to capture only infections that may have been related to prostate biopsy. Any events 1 month after prostate biopsy was considered unlikely to have been related to TRUSPBx.

Physical examination and repeat urinalysis were performed in all patients 7-10 days after biopsy. A repeat urinalysis was taken to note for occurrence of infections that have been related to prostate biopsy. Afebrile UTI was defined as a fever <38°C and dysuria accompanied by pyuria. Pyuria is defined as the presence of 10 white blood cells in 1 mm^3 of mid-stream urine. Febrile UTI is defined as a fever ≥38.0°C accompanied by one symptom of the lower urinary tract (i.e., urgency, frequency, dysuria, or suprapubic tenderness), with or without a positive urine culture. All patients with febrile UTI were hospitalized.

In patients that were hospitalized, non-urological causes of the symptoms were excluded. Physical examination included body temperature measurement, vital signs, signs of epididymo-orchitis and abdominal examination. The respiratory and cardiac systems were examined. Laboratory tests include complete blood count, urine culture and chest x-ray.

The patients were started on empirical intravenous Ceftriaxone 2grams as loading dose then 1gram every 12hours and was adjusted according to the culture results. When the fever subsided, the antibiotic was switched to an oral form and patients was discharged with 2 weeks of oral antibiotics based on the culture results.

Statistical Methods

All valid data from evaluable subjects satisfying the inclusion/exclusion criteria were included in the analysis. Missing values were not replaced or estimated during the statistical analysis of outcome variables. Summary statistics were presented in summary tables and reported as mean ± SD and median (IQR) for quantitative characteristics with normal distribution and skewed distribution, respectively or n (%) for qualitative characteristics. Comparison of pre- and

post-biopsy results was compared using McNemar test.

Statistical significance was based on p-values ≤ 0.05. SPSSv20 was used in data processing and analysis.

Results

A total of 74 patients underwent transrectal UTZ-guided prostate biopsy from August 2015 to July 2016 in a tertiary government hospital (Table 1). Average age was 66.5 years ± (SD=7.0), range from 49 to 83 years. Most common diagnosis was BPH with moderate LUTS (40.5%). Twenty-three percent of patients had concomitant disease among which were cystolithiasis (4), diabetes mellitus (4), hypertension (4), nephrolithiasis (2), external hemorrhoids (1), HCVD (1), and retroperitoneal mass spindle cell carcinoma (1). On the average, prostate-specific antigen was 9.7 ug/L (values from 1.6- 253) (IQR=24.2). Prostate sizes varied from 21.3 to 142.0 grams, average size was 57.5 grams (IQR=29.8).

Table 1. Baseline demographic and clinical characteristics.

Characteristics	n = 74
Age in years, mean ± SD	66.5 ± 7.0
Diagnosis, n (%)	
BPH with moderate LUTS	30 (40.5%)
BPH in retention	23 (31.1%)
BPH with mild LUTS	16 (21.6%)
BPH with severe LUTS	5 (6.8%)
Concomitant diseases, n (%)	
With	17 (23.0%)
Without	57 (77.0%)
Prostate-specific antigen, median (IQR)	9.7 (24.2)
Prostate size in grams, median (IQR)	57.5 (29.8)
Presence of UTI pre biopsy, n (%)	
With	40 (54.1%)
Without	34 (45.9%)

SD: standard deviation, IQR: interquartile range
Data presented as mean ± SD for characteristics with normal distribution, as median (IQR) for those with non-normal distribution and as n (%) for categorical variables

Symptoms such as fever (3), body malaise (1), dysuria (3), hypogastric pain (1), low back pain (1), gross hematuria (1), rectal bleeding and acute urinary retention (1) were observed in 5 patients (Table 2).

Majority had benign prostate (60.8%) while others had prostate adenocarcinoma (39.2%) and prostatitis (6.8%). Benign prostate and prostatitis were seen in 4 cases while one patient had prostate cancer and prostatitis (Table 2).

Table 2. Post-biopsy clinical characteristics.

Characteristics	n = 74
Post biopsy symptoms, n (%)	
With	5 (6.8%)
Without	69 (93.2%)
Biopsy results, n (%)	
Benign prostate	45 (60.8%)
Prostate cancer	29 (39.2%)
Prostatitis	5 (6.8%)

Data presented as n (%).

UTI was present in 40 cases pre biopsy. After the transrectal UTZ-guided prostate biopsy, 26 of these cases had UTI with resolution in 14 cases (65.0% and 35% respectively; p=0.000; Table 3). Twenty- five of these 26 cases had afebrile UTI (92.2%; 0.039; Table 4). On the other hand, 4 patients who did not present with UTI pre biopsy developed afebrile (2) and febrile UTI (2) (Table 4).

Table 3. Comparison of pre- and post-biopsy results.

Pre-biopsy U/A	Post-biopsy U/A		p-value
	With UTI	Without UTI	
With UTI	26 (65.0%)	14 (35.0%)	0.000*
Without UTI	4 (11.8%)	30 (88.2%)	

Data presented as n (%).
* Significant at 5% alpha level

Table 4. Comparison of pre- and post-biopsy results

Pre-biopsy U/A	Post-biopsy U/A		p-value
	With Afebrile UTI	With Febrile UTI	
With UTI	25 (92.2%)	1 (3.8%)	0.039*
Without UTI	2 (50.0%)	2 (50.0%)	

Data presented as n (%).
* Significant at 5% alpha level

Discussion

The detection and diagnosis of prostate cancer have benefited greatly from PSA screening efforts along with the introduction and refinement of systematic transrectal ultrasound-guided prostate biopsy techniques.[9] Prostate biopsy is the standardized diagnostic method for prostate cancer. However, although there is no standardized protocol, there are recommendations in order to reduce the incidence of complications.[10] An increasing frequency of complications has been recently noted with most postbiopsy hospitalization resulting from infectious causes. This has placed a renewed focus on antibiotic prophylaxis and other strategies to reduce postbiopsy infectious complications. Unlike other lower urinary tract procedures, antimicrobial prophylaxis is recommended for all patients undergoing prostate biopsy irrespective of risk factors.[9] According to Concia, et al. some of the invasive surgical procedures of the urinary tract can result in significant local or systemic infections such as fever, urosepsis, prostatitis and epididymitis due to uropathogens. These infectious complications are definitely more frequent in urological patients who are at risk, such as those of advanced age (>65 years), those who are diabetic, immunocompromised, malnourished, and obese, who have been recently hospitalized or with long preoperative hospitalization, those with pathogenic colonization of the surgical site, a history of recurrent urinary tract infection and home use of urinary catheter. Of all these risk factors, the most important ones for developing a postoperative infection are patients bearing a urinary tract infection and long preoperative hospitalization. Antibiotic prophylaxis is precisely indicated for prevention of infectious complications.[11]

The 2014 updated AUA Best Practice Policy-recommended antibiotics for prostate biopsy include fluoroquinolones; first-, second- and third- generation cephalosporines; and aminoglycoside. They added oral trimetophrim-sulfamethoxazole as a prophylactic agent, and when using IM/ IV aminoglycoside or aztreonam as an alternative agent, metronidazole or clindamycin is no longer required. A 2011 Cochrane review on prophylaxis for TRUS prostate biopsy demonstrated a reduction in bacteriuria, bacteremia, fever, UTI and hospitalization with antibiotics compared to placebo or no treatment. There was no definitive evidence demonstrating superiority of longer course or multiple doses compared to a shorter course or single any-dose protocols.[9]

Selection of the appropriate drug should be oriented to those molecules with spectrum of activity, which includes the primary uropathogens such as the Enterobacteriaceae, enterococci and less often, the staphylococci and Pseudomonas aeruginosa. Unfortunately, in recent years almost all of the afore-mentioned bacterial species have exhibited an unequivocal tendency to become resistant to numerous classes of antibiotics, making the choice of an efficacious drug for prophylaxis of therapy all that more difficult. The diffusion in both the hospital and community of extended-spectrum beta-lactamases (ESBLs) produced by enterobacteria are of especially critical importance. The presence of these enzymes causes not only resistance to the III and IV generation cephalosporins and monobactams but is also frequently associated with resistance to other classes of antimicrobial agents such as the fluoroquinolones, cotrimoxazole, tetracycline and aminoglycosides.[11] This alarming high resistance rates exhibited by contemporary uropathogens necessitate the re-evaluation of old antibiotics.[12] and change of prophylactic regimen to avoid bacterial mutations hence drug resistance. Fosfomycin trometamol can be a good potential choice due to its elevated activity against MDR Gram- negative bacteria, with pharmacokinetic

and pharmacodynamic properties that favor its use for the treatment of UTIs.[12,13] Ninety percent of Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs are susceptible to fosfomycin. Urinary concentrations may exceed 2,000 mg/L after administration of a single oral dose of 3g fosfomycin. Peak urinary concentrations occur within 4 hours of dosing, and urinary levels of fosfomycin remain for a prolonged period (over 24h); thus, these levels are sufficient to inhibit most urinary pathogens.[1] According to Michalopoulos et. al. Fosfomycin produces therapeutic concentration in the urine for 1-3 days. Comparative clinical trials suggest that a single 3-g dose of fosfomycin tromethamineis is as clinically effective as 7-to 10-day treatment regimens of standard agents such as nitrofurantoin, norfloxacin and trimethoprim/ sulfamethoxazole used to treat UTI.[13]

In the present study, the authors determined the presence of afebrile and febrile UTI after TRUS biopsy of prostate using single dose of fosfomycin as prophylactic antibiotic. Thirty five percent of patients having asymptomatic urinary tract infection before biopsy have resolved however, 11% of patients developed UTI after the procedure. The hospitalization rate was 5.4% somewhat similar to rates already reported in the literature.[1] The over-all incidence of febrile UTI post biopsy was 4% somewhat higher with previously reported rate of 0.9%.[1] The occurrence of febrile UTI in the patient may be attributed to the presence of comorbidities like urolithiasis, diabetes mellitus and indwelling foley catheter. The biopsy result of one patient showed prostatitis. On the other hand, comparison of prebiopsy and post biopsy occurrence of afebrile and febrile UTI showed statistical significance at 5% level of significance hence single-dose fosfomycin was effective as antibiotic prophylaxis prior to transrectal ultrasound-guided prostate biopsy.

Finally, the present study has several limitations which may be subjects of studies in the future. First, there was no comparison with other prophylactic antibiotics commonly used in TRUS biopsy of prostate. Second, the duration and sample size were limited. Third, the authors were not able to determine urine cultures on all patients prior and after biopsy to document presence of ESBL positive organisms which in some studies cause multiple antibiotic resistance and greater mortality.

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