ORIGINAL RESEARCH

The Use of Fosfomycin as Preoperative Antibiotic Prophylactic for Transrectal Ultrasound-Guided Prostate Needle Biopsy: A Randomized, Controlled Clinical Study in Veterans Memorial Medical Center

Sid C. Sergio, MD; Karl Marvin M. Tan, MD, FPUA and Sherwin N. Reyes, RMT, MSc

Section of Urology, Department of Surgery, Veterans Memorial Medical Center

Introduction

Transrectal ultrasound guided prostate needle biopsy (TRUS-PNB) is one of the most common urological modalities used in the detection and diagnosis of prostate cancer. However, despite its common use, complications like bleeding, pain, lower urinary tract symptoms, and infection are encountered. It has been found, based on EAU guidelines that there is a 0.1% to 5% chance of sepsis for post TRUS-PNB patients. These infectious complications are also the most common reasons for post TRUS-PNB hospitalization.

With these, perioperative antibiotic prophylaxis is used widely to prevent these infectious complications. However, there exists a wide variety of antibiotic prophylaxis used by many urologists. One of the most commonly used is Fluoroquinolone. However, prolonged use of fluoroquinolones has resulted in increasing microbial resistance. Fosfomycin has been widely recommended and used in the management of uncomplicated UTI because of its safety, efficiency, and ease-of-administration. This promising quality of Fosfomycin appears as a good alternative in various endourological procedures and even TRUS-PNB.

This study aims to demonstrate the efficacy, safety, and ease of-use of Fosfomycin 3gm, 60 mins prior to TRUS-PNB and compare it with Ciprofloxin 500mg/tab 60 mins prior to TRUS-PNB in a randomized, controlled clinical study.

Literature Review

Transrectal ultrasound-guided prostate needle biopsy (TRUS-PNB) is the standard procedure in the diagnosis of prostate cancer. The need for doing such is based on PSA level and/or suspicious DRE. Although TRUS-guided prostate biopsy is a safe method, it is an invasive procedure that is not free from complications.

Efesoy, et al. cited the following complications following TRUS-PNB: macroscopic hematuria, hematospermia, rectal bleeding, vasovagal symptoms, and infectious complications such as genitourinary system infection, fever, persistent dysuria, and cases of serious complications such as urosepsis.[1] With these, preventable measures are done in order to avoid complications. Pre-procedural antimicrobial prophylaxis remains a standard of care for urological surgery in order to reduce the risk of infectious complications. In an article by Puig, et al. Ciprofloxacin 500mg/tablet

was used 1 hour prior to procedure as antibiotic prophylaxis in 614 cases in a series of 1018 patients in whom they performed TRUS-guided antibiotic prophylaxis, while 404 patients did not receive antibiotic prophylaxis. Infectious complication rates in groups who received or didn't receive prophylactic post-biopsy antibiotic therapy were 3.7% vs. 10.3%, respectively (p=0.0001). While the authors reported that serious infectious complications were seen at a lower incidence (24%) in the prophylaxis group when compared with the untreated patients (75.6%) (p=0.0410).[2] Although a consensus has been almost reached about the requirement of preprocedural antibiotic prophylaxis, uncertainty exists concerning choice of appropriate antibiotics, and duration of prophylactic antibiotic therapy.

Though contrary opinions were asserted in some publications, necessity of prophylactic antibiotic use has been revealed in prospective, randomized, controlled studies.[3] The American Urological Association and the European Association of Urology currently recommend prophylactic antimicrobials prior to transrectal ultrasound-guided prostate needle biopsy with an oral fluoroquinolone-based, 1 hour prior to biopsy as single dose.[4] This consensus is supported by a research done by Rajeev, et al. where Ciprofloxacin 500mg/tablet single dose, 1 hour prior to biopsy was used and that continuing the antibiotic prophylaxis for 3 days offered no benefit over single dose prophylaxis.

Since fluoroquinolones have a broad spectrum of activity against most Gram-negative organisms and a good prostatic tissue penetration, they are widely used for antibiotic prophylaxis in TRUS-PNB. However, prolonged use of fluoroquinolones has resulted in increasing microbial resistance;[6,7] recent years have shown an increase in resistant *E. coli*. Further, alternative prophylactic regimens, such as Fosfomycin single- or double dose have come into use. The study done by Sen, et al. used single-dose 3gm Fosfomycin 1 hour prior to TRUS PNB.[8]

Fosfomycin is a phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid). It acts by inhibiting pyruvyltransferase, a cytoplasmic enzyme that catalyzes the first step in the biosynthesis of peptidoglycans and was initially described and isolated in 1969 from cultures of Streptomyces species.[9] Fosfomycin has a broad-spectrum activity against Gram-positive and Gram-negative bacteria and was approved for the treatment of uncomplicated UTIs. Previous studies showed that Fosfomycin, administered as a single oral dose, is generally safe and well-tolerated. The most frequent adverse events of Fosfomycin are diarrhea, headache, nausea, and abdominal pain. The resistance rates against Fosfomycin are still low, despite its clinical use; therefore, Fosfomycin could also be recommended in endourological procedures if preoperative antibiotic prophylaxis is indicated.[10] Gardiner, et al. prospectively assessed the penetration of fosfomycin into benign prostatic tissue in a large cohort of otherwise healthy men undergoing TURP.[11] They detected that oral Fosfomycin achieved sufficient concentrations in most cases and pointed out that fosfomycin may be a potential option for prophylaxis pre-TRUS-PNB and possibly for the treatment of multi drug-resistant Gram-negative bacterial prostatitis.

There are few reports about the use of Fosfomycin as a preoperative antibiotic prophylaxis in TRUS-PNB. Ongun, et al. compared single-dose Fosfomycin with single-dose 500 mg oral Ciprofloxacin in a retrospective study and Lista, et al. compared double doses of fosfomycin with 500mg oral Ciprofloxacin twice daily administered for five days starting one day before the procedure in a prospective randomized study.[12,13] Fosfomycin was found to be as safe and as effective as Ciprofloxacin in these two studies.

Optimal timing in giving Fosfomycin is defined in the study done by Rhodes, et al. who recommended that Fosfomycin prophylaxis be given 1-4 hours prior to prostate biopsy. Their findings indicate that 3g of oral Fosfomycin is most likely to achieve adequate plasma and prostatic concentrations for highly susceptible organisms (MIC≤4 mg/L) when surgery is performed between 1 and 4 hours post-dose. The interim recommendation is to wait at least 1 hour after Fosfomycin is administered to initiate surgery or biopsy. Their analysis suggests that attaining therapeutic concentrations in the prostate may be delayed and blunted compared with

plasma. Therefore, the recommended administration of prophylaxis is between hours 1 and 4.[14]

Materials and Methods

This study was conducted on an outpatient basis at the Veterans Memorial Medical Center, Section of Urology from May 2016 to September 2017. All cases were fully informed about the procedure and were required to fill up an informed consent form.

Inclusion Criteria:

- An elevated prostate-specific antigen (PSA) level (>4 ng/ml)
- Abnormal digital rectal examination
- Previous prostate pathologies (such as high-grade prostate intraepithelial neoplasia [HGPIN]).
- Normal urinalysis and urine cultures yielding no growth prior to biopsy

Exclusion Criteria:

- History of UTI, indwelling urinary catheters, and antibiotic use within a month of study initiation
- Severe coagulopathy, severe immuno-suppression and acute prostatitis
- Painful anorectal conditions or anal stenosis

Special Cases:

- Patients who received anticoagulant therapy were referred to appropriate specialists, and acetylsalicylic acid, anticoagulants (low-molecular weight heparin, and warfarin) were advised to be discontinued 7 and 3 days respectively before biopsy.

In order to eliminate bias, simple trial randomization by single blinding was done. Patients were randomly divided into 2 groups. Randomization was performed using envelopes placed in a box, mixed and handpicked blindly. Group 1 consisted of the Ciprofloxacin group where patients were given 500 mg oral ciprofloxacin twice daily administered for five days starting one day before the procedure. Group 2 consisted of the Fosfomycin group where patients were given Fosfomycin 3gm sachet dissolved in 1 glass water 60 mins prior to biopsy.

In order to produce a superior acoustic window for imaging[16], patients were advised to place a small cleansing enema (Fleet Enema) night before the scheduled biopsy. Transrectal ultrasound was performed under the guidance of a standard gray-scale ultrasound, and 7.5 MHz rectal probe in the left lateral decubitus position. Following evaluation of the prostatic anatomy, a periprostatic nerve blockade was performed using 2% Lidocaine and injecting 4ml in each lobe. Biopsy specimens were obtained 1 minute after induction of local aesthesia by using a disposable BARD biopsy gun with an 18-gauge biopsy needle. Twelve core biopsy specimens were obtained from the base of the right, and left prostate lobes, lateral, and far remote lateral to the midline, medial, and lateral parts of the apex.[16] This includes areas which are suspicious (hypoechoic on ultrasound). All biopsy specimens were marked according to laterality, and sent to the pathology laboratory for examination.

All patients prior to biopsy were informed of the possible complications of TRUS-PNB. Emergency admission was recommended when patients developed fever of >38.0°C, severe irritative voiding symptoms, and gross hematuria. All patients were then asked to attend a follow-up visit in the first week and first month after biopsy. Physical examination, urinalysis, and culture if necessary were done in follow-up visits.

Afebrile UTI is defined as a temperature <38°C and dysuria accompanied by pyuria.[15] Pyuria is defined as the presence of >5 white blood cells per high power field of midstream urine. Febrile UTI is defined as a temperature >38°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.[15] Patients with febrile UTI were hospitalized and treated with empirical intravenous antibiotics then culture-guided and were switched to an oral form once they were discharged. All patients with afebrile UTI were treated by oral antibiotics Ciprofloxacin 500mg/

tablet 2x/day for 7 days with repeat urinalysis post regimen.

Post-procedural febrile and afebrile infectious complications and pathological characteristics of two groups were then compared prospectively. Statistical analyses was performed with SPSS version 21 statistical software package. The two groups were then compared with independent samples t-test and chi square test. Statistical significance set as a p value of <0.05.

Results

With an average of 6 patients per week, and roughly 240 patients per year undergoing TRUS PNB in this institution, sample size was calculated based on the incidence of urinary tract infection among patients given Fosfomycin versus those given Ciprofloxacin by means of post procedural infectious complications. Assuming that the incidence of UTI among those given Ciprofloxacin is 10.3% and those given fosfomycin, 3.7%, with an alpha error of 10% and a power of 80% with 1 tailed alternative hypothesis, sample size is 134 per group or 268 for 2 groups.

All of the data included for analysis fit the inclusion criteria. The respective patient characteristics are seen in Table 1. There were no significant differences between the two groups in terms of age and PSA levels with p values of 0.458 and 0.140, respectively. With the prostate size, a significant difference among the population was noted, (p-value of 0.012).

Table 2 shows the comparison of incidence of afebrile and febrile UTI in between groups. Note that the incidence of afebrile UTI was higher in Group 1, 13/134 at 9.7% compared to that of Group 2, 3/134 at 2.2%. The same is true with Febrile UTI with Group 1 having 3/134 at 2.2% and Group 2, 1/134 at 0.7%. Using the Pearson chi square test, the results for both comparisons were noted to be statistically significant, with a p value of 0.010 and 0.006 for afebrile and febrile UTI respectively in between groups, thus showing Fosfomycin as having a much lower rate in terms of infectious complications.

Table 1. Comparison of patient characteristics.

	Treatment		
Patient Characteristics	Group 1	Group 2	P value (95% CI)
Patients (N)	134	134	
Age (years)	65.8 +/-SD 5.70	66.3 +/-SD 6.20	0.458
Total PSA (ng/mL)	20.8	25.9	0.140
Prostate Size (g)	37.7 +/-SD 14.34	34.9 +/-SD 10.25	0.012

PSA: prostate-specific antigen;

Table 2. Comparison of afebrile and febrile UTI in between groups.

		Group 1		Group 2		Sig.
		n	%	n	%	
Afebrile UTI (N)	Present	13	9.7%	3	2.2%	0.010
	Absent	121	90.3%	131	97.8%	
Febrile UTI (N)	Present	3	2.2%	1	0.7%	0.006
	Absent	131	97.8%	133	99.3%	

Discussion

In this single center prospective, randomized, controlled study comparing single-dose Fosfomycin with 500 mg oral Ciprofloxacin twice daily administered for five days as a preoperative antibiotic prophylaxis of TRUS-PNB, febrile UTI was observed in only one patient and afebrile UTI was identified in three patients in the Fosfomycin group. Both febrile and afebrile UTI rates were significantly higher in the Ciprofloxacin group.

This study revealed that single-dose Fosfomycin is as effective and as safe as 500 mg oral Ciprofloxacin twice daily administered for five days in the antibiotic prophylaxis for prostate biopsy. The very main advantage of Fosfomycin is its simple oral use as a single dose.

Conclusion

The study showed that with its single dose, easy to use antibiotic and lower rates of infectious complications, make Fosfomycin a strong alternative for antibiotic prophylaxis for TRUS-PNB.

Limitations and Recommendations

Further studies including a larger sample size, multi center and culture studies including the rate of resistance to each antibiotic can further strengthen the results of this study.

References

1. Ozan Efesoy, Murat Bozlu, Selahittin Çayan, Erdem Akbay. Complications of transrectal ultrasound-guided 12-core prostate biopsy: a single center experience with 2049 patients. Turkish J Urol 2013; 39(1): 6-11 o DOI:10.5152/tud.2013.002

2. Puig J, Darnell A, Bermúdez P, Malet A, Serrate G, Baré M, et al. Transrectal ultrasound-guided prostate biopsy: is antibiotic prophylaxis necessary? Eur Radiol 2006; 16: 939-43.

3. Enlund AL, Varenhorst E. Morbidity of ultrasound-guided transrectal core biopsy of the prostate without prophylactic antibiotic therapy. A prospective study in 415 cases. Br J Urol 1997;79:777-80.

4. Grabe M. Perioperative antibiotic prophylaxis in urology. Curr Opin Urol 2001;11:81-5. http://dx.doi.org/10.1097/00042307-200101000-00012

5. 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. Carmignani L, Picozzi S, Spinelli M, et al. Bacterial sepsis following prostatic biopsy. Int Urol Nephrol 2012;44:1055-63. http://dx.doi.org/10.1007/s11255-012-0145-9

6. Zervos MJ, Hershberger E, Nicolau DP, et al. Relationship between fluoroquinolone use and changes in susceptibility to fluoroquinolones of selected pathogens in 10 U.S. teaching hospitals, 1991-2000. Clin Infect Dis 2003; 37: 1643-8. http://dx.doi.org/10.1086/379709

7. Sen, et al. The use of prophylactic single-dose fosfomycin in patients who undergo transrectal ultrasound-guided prostate biopsy:A prospective, randomized, and controlled clinical study. Can Urol Assoc J 2015; 9 (11-12):E863-7. http://dx.doi.org/10.5489/cuaj.3068 December 14, 2015

8. Hendlin D, Stapley EO, Jackson M, et al. Phosphonomycin, a new antibiotic produced by strains of streptomyces. Science 1969;166:122-3. http://dx.doi.org/10.1126/science.166.3901.122

9. Falagas ME, Giannopoulou KP, Kokolakis GN, et al. Fosfomycin: Use beyond urinary tract and gastrointestinal infections. Clin Infect Dis 2008;46:1069-77. http://dx.doi.org/10.1086/527442

10. Gardiner BJ, Mahony AA, Ellis AG, et al. Is fosfomycin a potential treatment alternative for multidrugresistant Gram-negative prostatitis? Clin Infect Dis 2014;58:e101-05. http://dx.doi.org/10.1093/ cid/cit704

11. Ongün S, Aslan G, Avkan-Oguz V. The effectiveness of single-dose fosfomycin as antimicrobial prophylaxis for patients undergoing transrectal ultrasound-guided biopsy of the prostate. Urol Int 2012;89:439-44. http://dx.doi.org/10.1159/000342370

12. Lista F, Redondo C, Meilán E, et al. Efficacy and safety of fosfomycin-trometamol in the prophylaxis for transrectal prostate biopsy. Prospective randomized comparison with ciprofloxacin. Actas Urol Esp 2014;38:391http://dx.doi.org/10.1016/j.acuro.2014.01.002

13. Rhodes, et al. Optimal timing of oral fosfomycin administration for pre-prostate biopsy prophylaxis. J Antimicrob Chemother 2015; 70: 2068-73 doi:10.1093/jac/dkv067 Advance Access publication 22 March 2015

14. Grabe M, Bartoletti R, Bjerklund-Johansen TE, et al. Guidelines on urological infections. EAU 2015 guidelines. http://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf. Accessed Dec. 3, 2015.

15. Whittam BM, Thomasch JR, Makari JH, et al. Febrile urinary tract infection after ureteroneocystostomy: A contemporary assessment at a single institution. J Urol 2010; 183: 688-92. http://dx.doi. org/10.1016/ j.juro.2009.10.039

16. Transrectal Ultrasound Guided Prostate Needle Biopsy. Campbell and Walsh Urology, 11th edition, page 2585