e-ISSN: 0975-1556, p-ISSN:2820-2643
Available online on www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2023; 15(10); 1566-1570

Original Research Article

A Randomized Study to Compare the Efficacy of Single Dose versus Three-Day Course Prophylactic Ciprofloxacin with Transrectal Prostate Biopsy

Saket Singh[1], Nitish Kumar[2], Parvez Ahmad[3]

[1]Assistant Professor, Department of Urology, A.I.I.M.S., Patna, Bihar, India
[2]Assistant Professor, Department of Urology, A.I.I.M.S., Patna, Bihar, India
[3]Senior Resident, Department of Urology, A.I.I.M.S., Patna, Bihar, India

Received: 25-07-2023 / Revised: 23-08-2023 / Accepted: 18-09-2023
Corresponding Author: Dr. Saket Singh
Conflict of interest: Nil

Abstract:

Objective: To evaluate and compare the efficacy of single dose versus three-day course prophylactic ciprofloxacin (CF) therapy following transrectal prostate needle biopsy (TRPB).

Methods: The study included a randomized parallel group of select patients in whom TRPB was indicated as per protocol. Eligible patients were randomized to receive either Tab. CF 500mg (single dose, n=30) in group I or Tab CF 500mg (one tab twice a day for three days, n=30) in group II. Primary outcome measures for infective complications were compared in both groups by urine culture and secondary outcome measures (hematuria, pain, hematochezia) were evaluated along with rectal swab cultures at day 1,2 and 5.

Results: Three-day CF significantly (p=0.021) lowered infective complications as documented by lower pyuria / positive urine cultures 9 (30%) vs 2 (6.67%) in groups I and II respectively. There was no significant difference in the hematuria/VAS score post TRPB. While there was no hospitalization due to infectious complications, two patients (3.3%) were hospitalized due to abnormal rectal bleeding (1) and hematuria (1) in groups I and II respectively.

Conclusions: A three-day course of CF was significantly better and efficacious in reducing urine culture positivity (UTI/pyuria) versus single dose CF prophylaxis following TRPB. While *E. coli* was the commonest isolate in urine/rectal culture, no correlation could be established between rectal swab and urine culture. The frequency of hematuria and post prostate biopsy pain was comparable in both groups.

Recommendations: The study suggests using a three-day ciprofloxacin (CF) regimen for transrectal prostate needle biopsy (TRPB) as it effectively reduces infective complications, including pyuria and positive urine cultures. There's no clear correlation between rectal swab and urine cultures. Hematuria and post-biopsy pain frequencies were similar in both groups. Thus, the three-day CF regimen is recommended for improved infection prevention during TRPB.

Keywords: Prostate, Trans-Rectal Prostate Biopsy, Needle Biopsy Prostate, Prostate Biopsy Complication, Hematuria, UTI.

Introduction

Prostate cancer is the second most frequently diagnosed cancer and sixth leading cause of cancer death in men [1]. Transrectal prostate biopsy (TRPB) has emerged as the reference standard [2] for diagnosing prostate carcinoma with age-specific guidelines for prostate cancer screening [3]. TRPB is a safe procedure, but complications secondary to biopsy can occur, which may be infective (UTI, asymptomatic bacteriuria, transitory bacteremia, prostatitis, cystitis, epididymoorchitis, urosepsis) or non-infective (rectal bleeding, hematospermia, erectile dysfunction, urinary retention, vasovagal response, hematuria and pain). The rate of infection is variably reported to be 0.1-15.0% [4, 5] in the English literature, with lack of clarity regarding the need, optimum duration of antibiotic prophylaxis for TRPB. Though a single dose oral fluoroquinolone (FQ) administered prior to TRPB has been followed [6], the precise duration/ need for antibiotics remains unresolved as conflicting studies suggest that 3-day oral FQ may be more effective [7].

The current study aims to evaluate and compare the efficacy of single dose versus three-day course prophylactic ciprofloxacin (CF) therapy following transrectal prostate needle biopsy (TRPB).

Methods

Study Design: A randomized parallel study design.

Study Setting: The study was conducted at All India Institute of Medical Sciences, Patna, Bihar,

between April 2022 to January 2023.

Participants: A total of 60 patients participated and completed the study without any withdrawal (study flow diagram is depicted in figure 1).

Inclusion Criteria: Patients aged 40-80 years in whom TRPB was indicated were enrolled as per protocol.

Exclusion Criteria: Patients not consenting, with active untreated genitourinary tract infection/ anorectal conditions/patients allergic to FQ and mental disorders who failed to comply with our protocol were excluded.

Data Collection and Analysis: Eligible patients were screened, and computer randomized from www.randomization.com and included in this randomized parallel study design with the primary intent to treat and were randomized into two groups of 30 each (single dose group I vs. 3 days group II). Enrolled patients were worked up with detailed history, examination, digital rectal examination (DRE), urine analysis/culture (UC), rectal culture (RC), blood biochemistry (hemogram, RFT, serum PSA) and randomized to receive ciprofloxacin (CF) either as single dose or 1BD for 3days. Patients were assessed for pyuria/UTI by urine (routine/culture) on day1, 2, 5 and for pain/hematuria by VAS/urine routine after 6, 24 ,48 hrs of TRPB. Additional visits were made as per patient need.

Methodology

Eligible patients were advised; (i) Bowel preparation/soap water enema on the night and coming morning, (ii) Group I patients were prescribed single dose of oral Tab CF(500mg) at 6 AM prior to TRPB, post biopsy they were prescribed cap lactobacillus 1BD given for three days, (iii) Group II patients were prescribed only Tab CF(500 mg) BID at 6 AM continued for 3 days after TRPB performed under aseptic precautions using the sextant TRPB technique [8], prior 10% povidone iodine prep was used to paint the perianal area and a 18 G trucut™ needle using the technique described by Issa et al [9], the biopsy cores were preserved in 10% formalin for histopathology.

Outcome Measures: Primary outcome measures included (positive UC/ hospitalization) and secondary outcome measures included (VAS score, duration of hematuria, antimicrobial sensitivity pattern of rectal flora and side effects of CF).

Sample Size Calculation: Considering proportion of complications as 0.1% in the three-day course and 15% in a single dose, to estimate a difference of 14.9% a sample size of 30 cases was required per group at α=5% and power of study 80%.

Statistical Analysis: SPSS software was employed. Analysis of quantitative data (VAS scores and serum PSA) was done using NPar Tests and Mann-Whitney Test, and t-test for equality of means (for age). Qualitative data (pyuria, urine culture positivity, hematuria and detection of carcinoma) were analyzed by using Pearson Chi-Square test and Fisher's Exact Test.

Ethical Considerations: The study protocol was approved by IEC-HR, and written informed consent was administered.

Results

Table 1: Showing a summary of the salient patient demographic and base line parameters in both the patient groups.

Parameter	Group I	Group II	P-Value
Total	30	30	-
Age (Mean ±SD)	67.80 ±12.178	64.4 ±10.139	0.245
Median PSA (ng/dl)	8.835	6.970	0.128
Cancer Prostate	4/30(13.33%)	2/30(6.67%)	0.335
Pyuria	9(30%)	2(6.67%)	0.021
Urine C/S (+) UTI	9(30%)	2(6.67%)	0.021
Urine C/s Organism			
E. coli	4 (44.4%)	2 (100%)	-
Klebsiella	2 (22.2%)	0	-
Enterococcus	1 (11.1%)	0	-
Pseudomonas Aeruginosa	1(11.1%)	0	-
Proteus	1(11.1%)	0	-
Hematuria			
D_1	11/30(36.7%)	7/30(23.3%)	0.389
D_2	4/30(13.3%)	1/30(3.3%)	0.500
Pain (Med VAS)			
D_0	4	4	0.778
D_1	2	2	0.200
D_2	0	0	0.981
Side effects (Ciprofloxacin)			

Diarrhea	1	3	Clavein-I
Headache	0	1	
Nausea/Vomit	2	2	
Adverse Events (Hospitalized)			
Rectal bleeding	1 (3.3%)	-	Clavein-II
Severe Hematuria	-	1(3.3%)	

Med VAS: Median Visual analogue pain score, D_1-Day 1

The salient observations/results are depicted in Table-1 showing no significant intra-group differences. UC was positive in 11(9 and 2 in groups I and II); *E. coli* was isolated in 4/9(44.4%) cases in group I and 2/2(100%) in group II, *Klebsiella* was isolated in 2/9(22.2%) in group I , *Enterococcus* was isolated in 1/9(11.1%) in group I, *Pseudomonas* was isolated in 1/9(11.1%) in group I and *Proteus* was isolated in 1/9(11.1%) in group I, (p=0.021).

Table 2A: Sensitivity to various antibiotics in urine culture

Antibiotic	Group I (9)	Group II (2)	Both Groups (11)
Ciprofloxacin	4/9(44.44%)	1/2(50%)	5/11(45.45%)
Nitrofurantoin	3(33.33%)	1/2(50%)	4/11(36.36%)
Gentamicin	3(33.33%)	0	3/11(27.27%)
Amikacin	3(33.33%)	0	3/11(27.27%)
Ampicillin	1(11.11%)	0	1/11(9.09%)
Norfloxacin	5(55.56%)	0	5/11(45.45%)

Table 2B: Rectal swab culture and sensitivity

Parameter	Group I (7)	Group II (2)	Both Groups
Rectal Swab +	7	2	9/60
Organisms Isolated			
E. Coli	5 /7 (71.4%)	2/2 (100%)	-
Staphylococcus Aureus	2/7 (28.5%)	-	-
Ciprofloxacin Sensitivity	4/7(57.14%)	2/2(100%)	6
Urine C/S (+) Among (+) Rectal Swabs	3/7(42.86%)	0(0%)	-

The UC antibiotic sensitivity pattern is depicted in table 2A. RC was positive in 9/60(15%) of which seven and two belonged to group I and II respectively with *E. coli* as the commonest isolate (7/9~77.8%) depicted in Table 2B. RC and UC relationship is depicted in Table 2B. 4/7(57.14%) of group I and 2/2 (100%) in group II RC were sensitive to CF. 3/7 (42.8%) cases in group I and no patient of group II with positive RC had a positive UC. Among the positive RC in group I, 4/5 *E. coli* (80%) isolated was sensitive to CF out of which two (50%) developed UC positive UTI (*E. coli* in one and *Klebsiella* in another). In group II both RC were positive for *E. coli* (2/2- 100%) and sensitive to CF while none reported UTI. Hematuria occurred in 11/30(36.7%~D_1), 4/30(13.3%~D_2) group-I while 7/30 (23.3%~D_1) and 1/30(3.3%~D_2) in group-II had hematuria, this difference was not significant (p=0.389 and 0.500 on D_1 and D_2 respectively), see Table 1. Pain (VAS score-median) after TRPB was 4, 2, 0 on day 0,1st and 2nd respectively in both groups which was not significant (see Table 1). There were minor self-limiting side effects with CF (Table 1).

There were two major complications. Two patients were hospitalized due to hematuria and rectal bleeding, however there was no reported hospitalization overall due to infectious complications. Gross severe hematuria (Clavien-II) was reported in one (group II), this patient required hospitalization, haemostatics and intermittent bladder irrigation. Abnormal rectal bleeding (Clavien–II) was reported in one (group I) with UC positive UTI (*Klebsiella*) post TRPB, which too required hospitalization, blood transfusion and haemostatics.

Discussion

The study's findings indicate that there were no significant differences observed within the groups, labeled as Group I and Group II, across various parameters. Urine cultures tested positive in a total of 11 cases, with 9 occurrences in Group I and 2 in Group II. Notably, *E. coli* was the predominant isolate in both groups, accounting for 44.4% in Group I and 100% in Group II. Additionally, *Klebsiella, Enterococcus, Pseudomonas*, and *Proteus* were identified in Group I. The antibiotic sensitivity patterns for urine cultures are detailed in the study. Rectal cultures showed a 15% positivity rate, with 7 cases in Group I and 2 in Group II, primarily comprising *E. coli* isolates (77.8%). In Group I, 4 out of 7 rectal cultures were sensitive to CF, with 3 of them also yielding positive urine cultures. In Group II, all 2 rectal cultures were sensitive to CF, with no cases of positive urine

cultures reported. Hematuria occurred in both groups, with no significant differences in incidence. Pain scores (VAS) following TRPB were similar in both groups on days 0, 1, and 2. Minor, self-limiting side effects associated with CF were reported. The study did highlight two major complications necessitating hospitalization: severe hematuria in a patient from Group II, requiring haemostatics and bladder irrigation, and abnormal rectal bleeding along with urinary tract infection in a Group I patient, which necessitated hospitalization, blood transfusion, and haemostatics.

Antibiotic prophylaxis before TRPB helps reduce infection risk. AUA recommends single-dose fluoroquinolones [10]. Studies show mixed results on single vs. multiple doses. Kapoor *et al* [11] found a single dose of CF reduced bacteriuria. Zhonghua *et al* [12] RCT concluded single-dose CF was effective. Lindstedt *et al* [13] showed high-dose CF was equally effective. Bateni *et al* [14] concluded 3-day prophylaxis reduced bacteriuria. Cochrane review [15] favored prophylactic antibiotics, with some studies supporting 3-day regimens. Rectal flora impacts post-TRPB septic complications, with targeted prophylaxis reducing infections. Dai *et al*'s [16] study suggested rectal swab-directed prophylaxis lowers infection risk. Shahait *et al* [17] identified age and hypertension as predictors of urosepsis. Cussans [18] systematic review favored targeted antibiotics to prevent infections. Yang *et al* [19] meta-analysis recommended single-dose antibiotics with additional coverage. Hematuria and pain are common non-infectious complications, with no significant difference between single and three-day prophylaxis. Rectal bleeding is usually minor, and hemospermia may occur but typically resolves spontaneously.

Conclusion

In conclusion, this study conducted a comprehensive analysis of prophylactic antibiotic use in transrectal prostate biopsy (TRPB) procedures, comparing two distinct groups labeled as Group I and Group II. While no significant intra-group differences were found in most parameters, including hematuria, pain scores, and self-limiting side effects, the study did reveal important insights into the antibiotic sensitivity patterns of urine and rectal cultures. Notably, *E. coli* emerged as a prevalent pathogen in both groups, and the sensitivity of cultures to specific antibiotics, particularly CF, was of clinical significance. Moreover, the study identified two major complications, one involving severe hematuria and the other concerning rectal bleeding with associated urinary tract infection, both necessitating hospitalization and medical interventions. These findings underscore the importance of tailored prophylactic antibiotic regimens in TRPB procedures, taking into account the unique microbiological characteristics of individual patients, to minimize infectious complications and optimize patient outcomes.

Limitations: Limitations of this study include its relatively small, single-center sample, potentially limiting generalizability. The study didn't explore risk factors influencing prophylactic antibiotic choice, had a short duration with no long-term follow-up, and didn't investigate antibiotic resistance or economic implications. In summary, this study provides insights into antibiotic prophylaxis in TRPB but has limitations. Future research should address these areas to enhance our understanding of infection prevention in prostate biopsy procedures.

Recommendations: Based on the study's findings, we recommend the use of a three-day course of ciprofloxacin (CF) as a more effective prophylactic regimen compared to a single-dose CF therapy following transrectal prostate needle biopsy (TRPB). This three-day regimen significantly reduces the risk of infective complications, as evidenced by lower pyuria and positive urine cultures. Furthermore, it is important to consider patient-specific microbiological characteristics, as no clear correlation could be established between rectal swab and urine cultures. While the frequency of hematuria and post-prostate biopsy pain was similar in both groups, this recommendation emphasizes the importance of extended antibiotic prophylaxis for optimal patient outcomes and infection prevention during TRPB procedures.

Acknowledgement: We are thankful to the patients; without them the study could not have been done. We are thankful to the supporting staff of our hospital who were involved in patient care of the study group.

List of abbreviations:

1. TRPB - Transrectal Prostate Needle Biopsy
2. CF - Ciprofloxacin
3. AUA - American Urological Association
4. RCT - Randomized Controlled Trial
5. UTI - Urinary Tract Infection
6. UC - Urine Culture
7. RC - Rectal Culture
8. PSA - Prostate-Specific Antigen
9. VAS - Visual Analogue Scale
10. SD - Standard Deviation
11. Clavien-II - Clavien-Dindo Classification Grade II (a measure of surgical complications)
12. FQ - Fluoroquinolone
13. RFT - Renal Function Test
14. CI - Confidence Interval
15. IEC-HR - Institutional Ethics Committee for Human Research

Source of Funding: No funding received.

Conflict of Interest: The authors have no competing interests to declare.

References

1. Lalitha K, Suman G, Pruthvish S, Mathew A, Murthy NS. Estimation of time trends of incidence of prostate cancer- an Indian scenario. Asian Pac J Cancer Prev. 2012; 13(12):6245-5 0.
2. Silletti JP, Gordon GJ, Bueno R, Jaklitsch M, Loughlin KR. Prostate biopsy: past, present, and future. Urology. 2007; 69(3):413-6.
3. Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL and et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013; 190(2):419-26.
4. Schaeffer AJ, Montorsi F, Scattoni V, Perroncel R, Song J, Haverstock DC and 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.
5. Pinkhasov GI, Lin YK, Palmerola R, Smith P, Mahon F, Kaag MG, and et al. Complications following prostate needle biopsy requiring hospital admission or emergency department visits - experience from1000 consecutive cases. BJU Int. 2012; 110(3):369-74.
6. Bulut V, Şahin AF, Balaban Y, Altok M, Divrik RT, Zorlu F. The efficacy of duration of prophylactic antibiotics in transrectal ultrasound guided prostate biopsy. Int Braz J Urol. 2015; 41(5):906-10.
7. Heidari Bateni Z, Shahrokh H, Salimi H, Safari H, Tabatabai M, Saedi D. Single-dose versus multiple-dose ciprofloxacin plus metronidazole prophylaxis in transrectal ultrasound-guided biopsy of the prostate: a randomized controlled trial. Acta Med Iran. 2014; 52(9):664-70.
8. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989; 142(1):71-4; discussion 74-5.
9. Issa MM, Al-Qassab UA, Hall J, Ritenour CW, Petros JA, Sullivan JW. Formalin disinfection of biopsy needle minimizes the risk of sepsis following prostate biopsy. J Urol. 2013; 190 (5):1769-75.
10. Toner L, Bolton DM, Lawrentschuk N. Prevention of sepsis prior to prostate biopsy. Investig Clin Urol. 2016; 57(2): 94–99.
11. Kapoor DA, Klimberg IW, Malek GH, Wegenke JD, Cox CE, Patterson AL and et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology. 1998; 52(4):552-8.
12. Yang L, Hu J, Wei H, Wang L, Zhong H. Clinical significance of antibiotic prophylaxis for transrectal prostate biopsy. Zhonghua Wai Ke Za Zhi. 2001;39(12):940-2.
13. Lindstedt S, Lindström U, Ljunggren E, Wullt B, Grabe M. Single-dose antibiotic prophylaxis in core prostate biopsy: Impact of timing and identification of risk factors. Eur Urol. 2006; 50(4):832-7.
14. Heidari Bateni Z, Shahrokh H, Salimi H, Safari H, Tabatabai M, Saedi D. Single-dose versus multiple-dose ciprofloxacin plus metronidazole prophylaxis in transrectal ultrasound-guided biopsy of the prostate: a randomized controlled trial. Acta Med Iran. 2014; 52(9):664-70.
15. Zani EL, Clark OA, Rodrigues Netto N Jr. Antibiotic prophylaxis for transrectal prostate biopsy. Cochrane Database Syst Rev. 2011 May 11; (5):CD006576.
16. Dai J, Leone A, Mermel L, Hwang K, Pareek G, Schiff S and et al. Rectal swab culture-directed antimicrobial prophylaxis for prostate biopsy and risk of post procedure infection: a cohort study. Urology. 2015; 85(1):8-14.
17. Shahait M, Degheili, El-Merhi F, Tamin H, Nasir R. Incidence of sepsis following TRUS guided prostate biopsy at a tertiary-care medical centre in Lebanon. Int Braz J Urol. 2016 ;42(1):60-8
18. Cussans A, Somani BK, Basarab A, Dudderidge TJ. The role of targeted prophylactic antimicrobial therapy before TRUS guided prostate biopsy in reducing infection rates: a systematic review. BJU Int. 2016; 117(5):725-3.
19. Yang L, Gao L, Chen Y, Tang Z, Liu L, Han P and et al. Prophylactic Antibiotics in Prostate Biopsy: A Meta-Analysis Based on RCTs. Surg Infect (Larchmt). 2015; 16(6) :7 33-47.