

ANTIBIOTIC PROPHYLAXIS IN PROSTATE BIOPSY: A COMPARATIVE STUDY BETWEEN SINGLE DOSE & MULTIPLE DOSES OF CIPROFLOXACIN

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Abstract:

Objective: To compare the effect of single dose and multiple doses of ciprofloxacin as prophylaxis for prostate biopsy.

Method and material: This was a prospective quasi-experimental study carried in the department of Urology, Dhaka Medical College Hospital over seventy patients undergoing prostate biopsy. Half of the patients received single dose of ciprofloxacin and the rest half received three doses of the same drug as antibiotic prophylaxis.

Result: Two patients from single dose group and one patient from multiple dose group developed urinary tract infection without any statistical significance

Conclusion: Single dose of ciprofloxacin has equal clinical and bacteriological efficacy as that of multiple doses of the same drug for prophylaxis in prostate biopsy.

Key word: TNBP(Trans-rectal needle biopsy of prostate).

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Introduction:

Biopsy from the prostate is taken for the suspicion of malignancy stipulated by abnormal findings on digital rectal examination (DRE) or by raised prostate specific antigen (PSA) or by both. The trans rectal route is preferred to transperineal and transurethral routes because of its convenience of its being out patient procedure. But this advantage is associated with some infectious and traumatic complications.

Gut micro-organisms including E.coli, Enterobacter, Proteus and Klebsiella get access to the prostate tissue as the biopsy needle pierces the rectal mucosa during the procedure. Some Gram positive aerobes including Enterococci and Staphylococcus saprophyticus have also been identified¹. So prevention of infection during this procedure is an important issue of serious consideration for the urologist and this goal can be achieved with judiciously selected antimicrobial prophylaxis that has been observed to have reduced

the incidence of infection². Antibiotic prophylaxis should have the property to eliminate or at least to decrease the incidence of infection to an acceptable level³.

Keeping in mind the microbiological population responsible for infection in prostate biopsy, fluoroquinolones having a broad spectrum antibacterial activity and good absorption from gut can be a good choice for this purpose. Both multiple doses and single dose of this agent have been used throughout the world as prophylaxis for prostate biopsy. But the efficacy in preventing the infection has not differed significantly between multiple and single dose⁴. Many investigators found single dose antibiotic prophylaxis encouraging as it reduces the chance of developing antimicrobial resistance and for patient compliance and cost saving effect.

This quasi experimental study was designed to compare the efficacy and safety of single dose and multiple doses of ciprofloxacin as prophylaxis for prostate biopsy.

Materials and method:

The study was a quasi experimental one, conducted in the department of urology, Dhaka Medical College

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Hospital from January, 2006 to December, 2007. Patients having serum PSA >4 ng/ml, abnormal digital rectal examination or both, were included in this study. All these patients

were numbered chronologically and randomly allocated into group-A and group -B. Group- A included patients with odd number and was intended for three doses of ciprofloxacin. Group B included patients with even numbers and was intended for single dose of the same drug. Exclusion criteria were diabetes mellitus, hypersensitivity to quinolone antibiotic, uraemia, steroid therapy, indwelling urethral catheter, bleeding disorder and painful rectal pathology & rectal stenosis. Patients were evaluated by history, physical examination and pre-operative investigations. Investigations done preoperatively included urinalysis, urine culture and sensitivity, total count of WBC, random blood sugar, serum creatinine, bleeding-, coagulation- and prothrombin time, USG of KUB and prostate and ECG. Group A patients received three doses of ciprofloxacin 500 mg orally_ first dose one hour before the biopsy, 2nd dose twelve hours after the procedure and 3rd dose 24 hours after biopsy. Group B patients received single dose of 500 mg ciprofloxacin orally one hour before biopsy. Patients of both groups received single dose of laxative the night before biopsy. Patients on aspirin and antiplatelet therapy were asked to stop the medication one week before biopsy. Patients with urinary tract infection were treated with antibiotic according to culture sensitivity and biopsy was deferred for one week after treatment.

All the potential complications including fever greater than 101⁰F, gross haematuria, urinary retention, rectal bleeding, urinary symptoms e.g. frequency, urgency, dysuria, suprapubic pain and flank pain were also explained to the patients. Patients developing urinary retention, fever greater than 101⁰F and flank pain were asked to attend urology department immediately for evaluation and management.

Both ultrasound and digital guided eight to twelve core biopsies were performed using the Bard biopsy gun and 18 gauge needle. Patients were asked to come for follow up on third and seventh POD. During follow up patients were questioned about fever, chill, urinary frequency, urgency, dysuria, haematuria, suprapubic pain, flank pain and rectal bleeding and were requested to submit urine for urinalysis and culture sensitivity and blood for total and differential count of WBC.

Pyuria was defined as the presence of ≥ 5 WBC / HPF in urine.

Positive urine culture was defined as the bacterial growth $\geq 10^5$ CFU /ml of urine.

Urinary tract infection was defined as positive urine culture on 3rd POD or 7th POD or both.

Clinical success was defined as the absence of clinical manifestation of genito-urinary infection evidenced by the rise of temperature >101⁰F with or without frequency, urgency and dysuria.

Bacteriological success was defined as the negative culture (<10⁵ CFU/ml) of urine either on 3rd or 7th POD or on both.

Data were collected in a predesigned and pre-tested sheet and processed and analyzed using software SPSS (statistical package for social science). The test of statistical significance employed to analyze the data were Chi-square (χ^2) or Fisher's exact probability test and student's 't'-test. For all analytical tests, the level of significance was set at 0.05 and p <0.05 was considered significant.

Results:

A total of 64 patients out of 70 were available for final data analysis. Six patients, 2 from group- A and 4 from group-B were not included in final data analysis for violation of study protocol. Of these 64 subjects, a total of 3, 1 from group- A and 2 from group- B, developed clinical as well as bacteriological evidence of urinary tract infection and were treated with antibiotic according to culture and sensitivity report. Three patients, 1 from group- A and 2 from group- B, who developed urinary retention, were managed by temporary catheterization. Four patients, 2 from each group, developed gross haematuria and were advised to take plenty of fluid by mouth. Three patients, 1 from group A and 2 from group- B developed per-rectal bleeding and resolved spontaneously. None having bleeding needed blood transfusion.

Mean age of the groups were 64 ± 6.3 and 64 ± 5.4 years respectively. No significant difference of mean age between groups was found by doing student's 't' test. Prostate volume of the patients was also recorded and was found almost similar between groups (Fig-1).

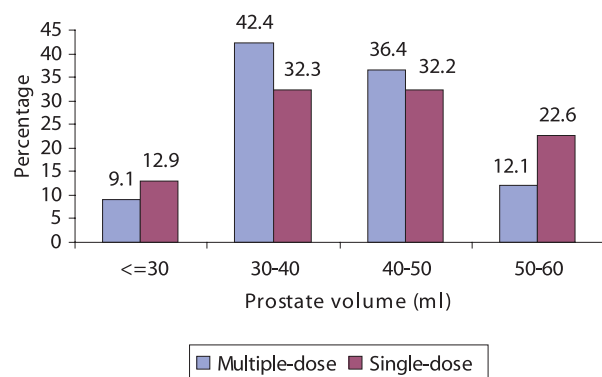


Fig. 1: Comparison of prostate volume between groups (n = 64)

Clinical findings of the patients including frequency, urgency, suprapubic pain, dysuria, chills, flank pain and fever (Temperature $\geq 101^{\circ}\text{F}$) were recorded on 3rd POD (Table- I) and were compared between groups. In group-A, observed findings were—frequency in 9 (27.3%), urgency in 5 (15.2%), suprapubic pain in none, dysuria in 3 (9.1%), chills in 2 (6.1%), flank pain in 1(3.0%) and fever in 1 (3.0%) patients. While in group-B, the observed findings were—frequency in 5 (16.1%), urgency in 2 (6.5%), suprapubic pain in 1 (3.2%), dysuria in 5 (16.1%) fever in 2 (6.5%) and chills and flank pain were nil. These findings were compared between groups using Fisher's exact test and chi-square test and no significant difference was found

Table-I

Comparison of postoperative clinical findings between groups on 3rd POD

Postoperative variables	Regimen		p-value
	Multiple-dose (n = 33)	Single-dose (n = 31)	
Urinary frequency [¶]	9(27.3)	5(16.1)	0.281
Urgency [#]	5(15.2)	2(6.5)	0.240
Suprapubic pain [#]	00	1 (3.2)	0.484
Dysuria [¶]	3(9.1)	5(16.1)	0.319
Chills [#]	2(6.1)	00	0.262
Flank pain [#]	1(3.0)	00	0.516
Fever [#] (Temperature $\geq 101^{\circ}\text{F}$)	1(3.0)	2(6.5)	0.484

Figures in the parenthesis denote corresponding percentage. # Data were analyzed using Fisher's Test; ¶Data were analyzed using Chi-square (χ^2) Test.

The same clinical characteristics were also observed on the 7th POD (Table-II) as were done on the 3rd POD. In both groups urinary frequency, urgency and dysuria decreased substantially while suprapubic pain, chills, flank pain and fever disappeared completely. The findings were also compared between groups using Fisher's exact test and no significant difference was observed between groups.

Table II

Comparison of postoperative findings between groups on 7th POD

Postoperative variables	Regimen		p-value
	Multiple-dose (n = 33)	Single-dose (n = 31)	
Urinary frequency [¶]	3(9.1)	2(6.5)	0.481
Urgency [#]	1(3.2)	1 (3.2)	0.955
Dysuria [#]	1(3.2)	2(6.5)	0.549

Figures in the parenthesis denote corresponding percentage.

Data were analyzed using Fisher's Test.

Table III

Comparison of laboratory findings on 3rd postoperative day

Variables	Regimen	
	Multiple-dose (n = 33)	Single-dose (n = 31)
Positive urine culture (Bacterial count $\geq 10^5$ colony forming unit/ml)	1(3.0)	1(3.5)
Pyuria (pus cell e ⁿ 5/HPF)	2(6.1)	3(9.7)
Leucocytosis (WBC $\geq 11000/\text{mm}^3$)	1(3.0)	2(6.5)

Figures in the parenthesis denote corresponding percentage.

Investigations including urine-R/E &C/S and total count of WBC were done on 3rd and 7th POD.

On 3rd POD, in group- A, only 1 (3.0%) patient developed positive urine culture, 2 (6.1%) patients had pyuria and 1 (3%) developed leucocytosis while in group-B, out of 31 patients, 1(3.0%) developed positive urine culture, 3 (9.7%) had pyuria and 2 (6.5%) developed leucocytosis. The findings were compared between

groups using Fisher's test and no significant difference was observed (Table- III)

Table- IV
Comparison of laboratory findings on 7th postoperative day

Variables	Regimen	
	Multiple-dose (n = 33)	Single-dose (n = 31)
Positive urine culture (Bacterial count $\geq 10^5$ colony forming unit/ml)	0(0.0)	1(3.2)
Pyuria (pus cell ≥ 5 /HPF)	1(3.0)	2(6.5)
Leucocytosis (WBC $\geq 11000/\text{mm}^3$)	1(3.0)	1(3.2)

Figures in the parenthesis denote corresponding percentage.

On 7th POD, in group-A, none developed positive urine culture, 1 (3%) had pyuria and 1(3%) developed leucocytosis while in group-B, 1(3.2%) developed positive urine culture, 2 (6.5%) had pyuria and 1(3.2%) developed leucocytosis (Table-IV) and no significant difference was observed between groups in respect of these findings.

Table V
Comparison of clinical outcome between groups.

Clinical response [#]	Regimen		p-value
	Multiple-dose (n = 33)	Single-dose (n = 31)	
Success	32(97.0)	29(93.5)	0.476
Failure	1(3.0)	2(6.5)	

Figure in the parentheses denoted corresponding percentage

Data were analyzed using Chi-square (χ^2)Test.

In this study, remaining afebrile or temperature less than 101°F was considered clinical success of the prophylaxis. In group- A, only 1 (3%) patient developed temperature 101°F while in group-B, 2(6.5%) patients developed the same feature. Clinical success was compared between groups using Chi-square (χ^2) test and the difference between groups was insignificant ($p=0.476$) (Table- V)

In this study only 1(3%) patient in group-A and 2(6.5%) patients in group-B developed positive urine culture ($\geq 10^5$ cfu/ml) (Table-VI). On comparison using chi-square (χ^2) the observed difference between groups was insignificant ($P=0.476$).

Table VI
Comparison of bacteriological response between groups (n = 64)

Bacteriological response	Regimen		p-value
	Multiple-dose (n = 33)	Single-dose (n = 31)	
Growth of bacteria	1(3.0)	2(6.5)	0.476
No growth of bacteria	32(97.0)	29(93.5)	

Figure in the parentheses denoted corresponding percentage

Data were analyzed using Chi-square (χ^2) Test.

Regarding complication, in group-A, only 1(3.0%) patient developed acute urinary retention, 2 (6.1%) patients noticed gross haematuria and 1(3%) patient developed per rectal bleeding while in group- B, 2 (6.5%) patients developed urinary retention, 2 (6.5%) patients noticed gross haematuria and 2 (6.5%) patients developed per rectal bleeding. On comparison using Fisher's exact test the difference between groups was insignificant ($P=0.05$) (Table-VII).

Table VII
Postoperative complications between groups

Complications	Regimen	
	Multiple-dose (n = 33)	Single-dose (n = 31)
Urinary retention	1(3.0)	2(6.5)
Gross haematuria	2(6.1)	2(6.5)
Per-rectal bleeding	1(3.0)	2(6.5)

Discussion:

Since the beginning of past the century, biopsy of the prostate has been used to diagnose prostate cancer. Astraldi⁵ did the first prostate biopsy through trans-rectal route in 1937. In his original description he did not find any complication without any antibiotic. In 1971 Wendell and Evan et al⁴ first described the danger of infection particularly the risk of infection with coli form organisms. In 1980, Johnson et al⁶ showed incidence of

bacteraemia in 73% cases and that of UTI in 51% cases after trans-rectal needle biopsy of prostate (TNBP) with no antimicrobial prophylaxis. So clinicians attempted to reduce rate of infection with prophylactic antibiotic and reported considerable success. Different prophylactic regimen of antibiotic has been studied both in oral and intravenous form giving rise to a variable opinion as to the choice of agent and dose schedule to be used. In 1987 ciprofloxacin became available and was found to have higher concentration in the prostatic tissue than the serum level, a key factor in preventing infection. In 1998, Shandera KC et al⁷ demonstrated effectiveness of simple and inexpensive pre-biopsy preparation using single dose of ofloxacin. In 1998, Kapoor DA et al² demonstrated the efficacy of single dose of ciprofloxacin in preventing infection in prostate biopsy.

On the 7th POD, suprapubic pain, chills, flank pain and fever disappeared totally while urinary frequency, urgency and dysuria declined substantially in both groups (Table-II). Most of the complications occurred in the early post operative day. This impression was supported by the study of Shandera KC et al⁷ in which complications were detected within 5th POD, the febrile one earlier than the others. In the study of Machado MT et al⁸, the febrile episodes were detected within first 48 hours and positive urine culture was found on the 3rd POD.

No significant difference was observed between groups ($P=0.470$) in respect of UTI on 3rd POD (Table- III). UTI as evidenced by bacterial colony count $\geq 10^5$ CFU/ml. UTI was found in 3.0% and 3.5% patients of multiple doses and single dose group respectively. In the study of Schaeffer et al⁹, positive urine culture (colony count $\geq 10^5$ CFU/ml) was found in 2% of the multiple doses and 5.2% of the single dose patient. In the study of Lindstedt et al¹⁰ the incidence positive urine culture ($\geq 10^5$ CFU/ml) was 4.3% in the single dose treated patients. The incidence of positive urine culture ($\geq 10^5$ CFU/ml) in the above mentioned studies are almost closer to the present study. In the study of Kapoor DA et al² (1998) 3% of single dose ciprofloxacin treated patients undergoing prostate biopsy had significant bacteriuria ($>10^4$ CFU/ml) developed clinical feature of infection.

The number of cases with positive urine culture, pyuria and leucocytosis reduced on 7th POD (Table-IV) than those noted on 3rd POD (Table- III). This was also consistent with the clinical findings observed on the corresponding day (Table- I & II).

No statistically significant difference was observed between group ($P=0.476$) when clinical evidence of infection (defined as temperature $\geq 101^{\circ}\text{F}$) was compared between groups (Table- I & II). Three percent of multiple doses group and 6.5% of the single dose group of patients developed clinical evidence of infection.

In the study of Machado MT et al⁸ 3.1% of the patients developed fever (101°F) in single dose but 2.1% of the patient developed fever in multiple doses. In the study of Kapoor DA et al², the incidence of fever (temp $> 101^{\circ}\text{F}$) was noted in 2% of single dose ciprofloxacin treated patients. The study of Shandera KC et al⁷. Showed only 0.67% clinical evidence of infection using single dose of fluoroquinolone. Febrile complication (temperature $\geq 101^{\circ}\text{F}$) was observed in 2.9% patients in the study of Enlund AL et al¹¹

During follow up only 1 (3%) patient of group-A and 2 (6.5%) patients of group-B developed urinary retention and no significant difference was observed between groups by doing statistical test (Table- VII). These patients were managed with catheterization. In the study of Enlund et al¹¹, 0.2% subject developed urinary retention and in the study of Isen K et al³ retention was noted in 2.7% of the subjects. Acute urinary retention was found in 0.25% of the patient in the study of Griffith BC et al (2002). Gross haematuria was noted in 2 (6.1%) patients of group-A and in 2 (6.5%) patients of group-B (Table- VII). Haematuria was noted in about 14.3% of the patients in the study of Isen K et al³. Per-rectal bleeding was observed in 1 (3%) patients of group-A and in 2 (6.5%) of group-B (Table- VII). The problem was noted in 6.36% of the patients in the study of Isen K et al³ which is consistent with the present study. Only 0.25% patient developed per-rectal bleeding in the study of Griffith BC et al¹¹ which is much lower than that of the present study. In the study conducted by Enlund et al¹³ the incidence of per-rectal bleeding was observed in 21.7% of the patients which is higher than that of the present study

Conclusion:

Trans-rectal needle biopsy of prostate is now a common urological procedure. To prevent infection, antibiotic prophylaxis with proper agent in adequate dose is something of immense value. Antibiotic prophylaxis with single dose of ciprofloxacin has equal clinical and bacteriological efficacy as multiple doses of the same drug in preventing infection and has cost saving effect and increased patient compliance.

Conflict of Interest : None Declared

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Abbreviations:

- DRE : Digital Rectal Examination
 PSA : Prostate Specific Antigen
 UTI : Urinary Tract Infections