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ANTIBIOTIC PROPHYLAXIS IN PROSTATE BIOPSY. A COMPARATIVE RANDOMIZED CLINICAL ASSAY BETWEEN CIPROFLOXACIN, NORFLOXACIN AND CHLORAMPHENICOL

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ABSTRACT

Objective: To compare, prospectively, 4 different schemes of antibiotic prophylaxis previously to transrectal prostate biopsy.

Materials and Methods: 257 patients were randomized in 4 groups: Group I: single dose of ciprofloxacin 2 hours before the procedure; Group II: ciprofloxacin 3 days; Group III: chloramphenicol 3 days; and Group IV: norfloxacin 3 days. The complication rate was assessed in a blind way on the third and on the thirtieth days through a questionnaire. Groups were compared by the qui-square method and, in small samples, by the Fisher method, with statistical significance of 95%.

Results: Complications index throughout the sample differed between the 4 groups of patients under study, being 3.1% for group I, 2.1% for group II, 18.3% for group III and 10.5% for group IV. Schemes employing ciprofloxacin were statistically superior to those that used norfloxacin or chloramphenicol ($p < 0.05$). There was no difference between a single dose and 3 days of ciprofloxacin ($p > 0.05$).

Conclusion: Schemes using ciprofloxacin presented better results in prophylaxis previously to prostate biopsy. We recommend using a single dose of ciprofloxacin due to its posologic ease and low cost, associated with a therapeutic response equivalent to 3-day regimens.

Key words: prostate; biopsy; needle; ultrasonography; antibiotic prophylaxis
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INTRODUCTION

Transrectal prostate biopsy (TPB) is simple and fundamental in the diagnosis of prostate adenocarcinoma (1). However, it is reported that TPB can be accompanied by infectious events in 3% to 37% of the cases (2-6). Urinary tract infections, transitory bacteremia and fever episodes are complications that can occur following transrectal prostate biopsy (3,4).

The majority of works points to the need of antibiotic prophylaxis previously to TPB (6-19). However, there is a lot of controversy and diversity of therapeutic schemes in the literature concerning the ideal drug to be used and the time employed for infectious prophylaxis (20).

The objective of this study was to assess 4 different schemes of antimicrobial prophylaxis, previously to TPB, aiming to identify potential infectious complications following prostate biopsy. Our results will be discussed and compared to the literature, in order to enable one to conclude which is the best prophylactic schemes tested in our patient population.

MATERIALS AND METHODS

From April 2001 to April 2002, 285 patients underwent TPB, with 257 patients being randomly selected and sequentially included in this study. Were excluded from the protocol those patients with ind-

welling urethral catheter, positive urine culture, presence of cardiac valve prosthesis, diabetes mellitus, rectal stenosis and patients using antimicrobials in the 7 days prior to biopsy.

After explanation and obtaining the informed consent, patients were divided into 4 groups: 1) Group I: 64 individuals (24.9%) receive a single oral dose of ciprofloxacin, 500 mg, 2 hours before the procedure; 2) Group II: 46 individuals (17.9%) received ciprofloxacin 500 mg, orally, during 3 days, being instructed to take a dose of the medication 12 hours before the examination, other dose 1 hour before biopsy, maintaining treatment for 2 additional days, each 12 hours; 3) Group III: 71 patients (27.62%) received chloramphenicol 500 mg, orally, with posologic instructions similar to group II; 4) Group IV, with 76 patients (29.57%), received norfloxacin 400 mg, orally, with a similar posology to groups II and III.

Blood cultures for aerobes and anaerobes were collected in patients from group I 1 hour and 3 hours after the procedure. All patients had urine cultures before and 3 days after TPB, with a growth equal or superior to 10^5 UFC/ml being considered as presence of urinary infection. Rectal preparation with enema was not used before the biopsy. Twelve fragments were taken from the prostate in each patient.

Patients had their axillary temperature measured each 8 hours during the first 2 days and were assessed, by a questionnaire applied by another clinician that did not participate in the study, on the third and on the thirtieth days.

We considered as minor infectious complication the presence of fever alone or the presence of mild urinary symptoms, that resolved with the use of antipyretic and/or antibiotic therapy, with no need of hospitalization. We classified as major infectious complication the presence of fever associated with intense urinary symptoms, sepsis, bacteremia or need of hospitalization and intravenous antibiotic therapy.

The comparative statistical analysis was assessed by the qui-square method and, in small samples, by the Fisher method, with a level of statistical significance of 95%, calculated by the EPI INFO 6.0 software.

RESULTS

All patients used the medication and performed the biopsy according to the protocol. Patients' mean age was 68.77 (± 8.37) years, mean PSA was 15.19 (± 14) ng/mL and prostate volume as assessed by transrectal ultrasound was 35.67 (± 18.2) grams, without statistical difference in this parameters between the 4 groups studied ($p > 0.05$). (Table-1).

Table-2 shows the frequency of minor and major complications in patients for each group of antibiotic prophylaxis.

In patients from group I (ciprofloxacin single dose), 2 minor complications occurred (3.1%), corresponding to an episode of temperature equal to 38°C in the first day post-biopsy, with sodic dipyrone being administered in both cases with clinical improvement. There were no major complications in this group of patients, and there was no evidence of bacterial growth in the respective urine cultures as well. In relation to the blood cultures, only 1 of the patients included in group I presented a positive result for *Staphylococcus epidermidis*. We also observed

Table 1 – *Comparison of mean and standard deviation for age, serum PSA level and prostate volume between the 4 groups of patients who underwent transrectal prostate biopsy, evidencing the homogeneity between the 4 groups under study.*

Patients	Group I	Group II	Group III	Group IV
Age (years)*	66.5 ± 8.5	68.0 ± 9.0	69.1 ± 8.2	68.7 ± 9.5
PSA (ng/ml)*	13.5 ± 12.2	14.2 ± 11.5	16.0 ± 13.2	15.2 ± 12.1
Prostate volume (g)*	37.2 ± 23.2	35.8 ± 15.8	38.5 ± 18.3	36.5 ± 17.2

** $p > 0.05$ for all studied parameters.*

Table 2 – *Relation and frequency of infectious complications obtained in the 257 patients who underwent transrectal prostate biopsy according to the groups of patients under study.*

Variables	Group I	Group II	Group III	Group IV	Total
Number of patients	64	46	71	76	250
Minor Complication					
Self-limited fever	2	0	3	4	9 (3.5%)
Prostatitis not requiring hospitalization	0	0	4	2	6 (2.3%)
Urinary tract infection	0	0	2	2	4 (1.5%)
Orchiepididymitis	0	0	3	0	3 (1.5%)
Fever and acute urinary retention	0	1	0	0	1 (0.4%)
Major Complications					
Prostatitis with bacteremia and hospitalization	0	0	1	0	1 (0.4%)
Total	2 (3.1%)	1 (2.1%)	13 (18.3%)	8 (10.5%)	24 (9.6%)

that this patient did not present fever or any voiding symptom following transrectal prostate biopsy.

The only complication (2.7%) that occurred among patients from group II (ciprofloxacin during 3 days) corresponded to an episode of fever and acute urinary retention, requiring antibiotic therapy for 7 days. Upon treatment, the patient presented no complaints, no fever and had his voiding reestablished. There was no need for hospital admission or major complications.

Among patients in group III (chloramphenicol), 13 (18.3%) presented complications following transrectal prostate biopsy (Table-2). Among them, there was a major infectious complication corresponding to acute prostatitis with bacteremia due to *Escherichia coli*, with need of hospitalization for treatment and intravenous antibiotic therapy.

As for the 76 patients from group IV (norfloxacin), 8 (10.5%) presented minor complications following TPB (Table-2). There were no major complications in this group of patients.

In the late follow-up visit after 30 days, none of the patients reported fever or other symptom due to infectious process. In relation to global comparative results, there was a statistically significant difference between groups (Tables-3, 4 e 5).

When we compared groups I and II (ciprofloxacin) we did not observe significant difference (Fisher monocaudal p = 0.6) (Table-3). Aiming to compare the schemes using ciprofloxacin (groups I and II) with the other groups, we performed the sample gathering between groups I and II.

A statistical difference was observed concerning the infection index between patients who received ciprofloxacin both when compared to chloramphenicol (x^2 = 13.0 and p = 0.0003) (Table-4) and when compared to norfloxacin (Fisher monocaudal p = 0.03) (Table-5).

We did not observe statistically significant differences when we compared the complication general indexes between chloramphenicol and norfloxacin (p > 0.05).

DISCUSSION

Programs for early detection of prostate cancer have surprisingly increased the number of pros-

Table 3 – *Occurrence of infectious complications, comparing the groups of patients who received ciprofloxacin single dose (Group I) and ciprofloxacin for 3 days (Group II).*

Prophylactic Scheme	Infectious Complications		p value
	Yes	No	
Group I	2	62	0.6
Group II	1	45	

Table 4 – *Occurrence of infectious complications, comparing the group of patients who received ciprofloxacin (Groups I and II) with the group who received chloramphenicol (Group III).*

Prophylactic Scheme	Infectious Complications		p value
	Yes	No	
Groups I e II	3	107	0.0003
Group III	13	58	

Table 5 - *Occurrence of infectious complications, comparing the group of patients who received ciprofloxacin (Groups I and II) with the group who received norfloxacin (Group VI).*

Prophylactic Scheme	Infectious Complications		p value
	Yes	No	
Groups I e II	3	107	0.03
Group IV	8	68	

tate biopsies (7,8). More recent series show that infectious complications can occur between 0.8% and 17% of the cases, with spontaneously resolving fever, probably due to transitory bacteremia, being the most frequent symptom. Urinary tract infection, prostate abscess with urinary retention, sepsis and death have also been described (9-19).

The main microbial agents responsible for symptoms are Gram-negative germs, which normally colonize the rectum, in particular *Escherichia coli.* Patients with some degree of immunologic depression can develop infection due to anaerobes.

A comparative analysis with randomized studies in the literature tends to show a superiority of schemes using antibiotics in relation to placebo, with the use of quinolones being preferred, presenting the lowest infection indexes (6,10,12,14-17,20). However, there are few randomized prospective studies aimed to assess which antibiotic is more effective, its ideal dose, as well as the administration route, duration and cost of treatment for prophylaxis in transrectal prostate biopsy (11,20). In Table-6 we present the results obtained by several authors according to the antibiotic regimen employed.

In our patient population we could observe that the prophylactic effectiveness of schemes using ciprofloxacin was similar between them and significantly superior to the others. We also had a concern to document the possibility of bacteremia when the ciprofloxacin was administered in a single dose, since we did not find this information available in the literature.

Aron et al. observed that the use of ciprofloxacin in a single dose was similar to the 3-day scheme (16), an impression that was confirmed by our results.

Our results, compared to the experience of other authors (12,13,20), testify that norfloxacin is a feasible option with a low index of infectious complications.

Results with the use of chloramphenicol were discouraging. We observed a high index of minor complications, including orchiepididymitis, which is rarely reported with other schemes, in addition to significant complication requiring hospitalization. Its wide range of action, low cost and lack of previous report in literature concerning antibiotic prophylaxis previously to TPB motivated its utilization in this study. Thus, we believe that its use is not recommended for such purpose.

We could also observe that initiating the antibiotic therapy before the biopsy has an important impact when compared to schemes initiated after the biopsy (12,13). Such data suggest that higher probability of infection occurs during the procedure. If this hypothesis is correct, therapeutic schemes with single dose and longer half-life should present infection indexes similar to more prolonged schemes.

Coverage for anaerobes, little studied up to now, however, seems to have little impact on the infection index (9,16,18). In our selected sample of 257 patients, we did not isolate in culture any case of anaerobes, reinforcing this hypothesis.

Table 6 – *Incidence of infectious events in randomized comparative studies using several schemes of antibiotic prophylaxis following TPB.*

Ref.	N	Regime de Antibiótico	Infecção	P
(3)	117	Netilmicina, 1,5 mg/kg, IV + metronidazol, 500 mg, VO, 60 min antes da biópsia	17%	0,01
		Trimetoprim, 320 mg + sulfametoxazol, 1600 mg, VO, 60 min antes da biópsia	2%	
(6)	55	Ciprofloxacina, 500 mg, VO, 12 h antes da biopsia e 12 h após a primeira dose	7%	0,0032
		Gentamicina, 1,5mg/kg, IV, 2 h antes da biópsia + 80 mg , IV, 8 h após biópsia	37%	
(8)	537	Ciprofloxacina, 500 mg, VO, dose única, 30-120 min antes da biópsia	3%	0,009
		Placebo	8%	
(12)	347	Norfloxacina, 400 mg, imediatamente após a biópsia, com uma dose adicional no mesmo dia	6,5%	< 0,05
		Norfloxacina, 400 mg, 60 min antes do exame e continuada por 2 dias	1,4%	
(13)	491	Norfloxacina, 400 mg, VO, 12-12 h, por um dia, início após a biópsia	11%	< 0,05
		Norfloxacina, 400 mg, VO, 12-12 h, por uma semana, início após a biópsia	4,9%	
		Controle	26%	
(15)	111	Trimetoprim, 160 mg + sulfametoxazol, 800 mg, VO, dose única, 60 min antes da biópsia	6,6%	< 0,05
		Ofloxacina, 40 mg, VO, dose única, 60 min antes da biópsia	4,7%	
(16)	231	Placebo, duas vêzes ao dia, por três dias	8%	0,003
		Ciprofloxacina, 500 mg + tinidazol 600 mg , dose única	2%	
		Ciprofloxacina, 500 mg + tinidazol 600 mg, duas vezes ao dia, por três dias	3%	
(17)	29	Lomefloxacina, 400 mg, VO, 2 h antes da biópsia	0%	0,05
		Cefazolina, 1 g, IV, 2 h antes da biópsia	7,6%	
(18)	20	Lomefloxacina, 40 mg, VO, 3 h antes da biópsia, repetindo por dois dias após o procedimento	0%	Não realizado
		Lomefloxacina, 40 mg, VO + metronidazol, 500 mg, VO, 8-8 h, ambos iniciando 3 h antes da biópsia, até dois dias após o procedimento	0%	
(19)	110	Cefuroxima, 1,5 g, IV, 20 min antes da biópsia	5,3%	0,45
		Piperacilina/tazobactan, 4,5 g, IV, 20 min antes da biópsia	7,2%	

Ref. – referência, N – número de pacientes, P – valor de p
Ref. – reference, N – number of patients, P – p value

Finally, we found that in our patient population the prophylactic effectiveness of schemes using ciprofloxacin was significantly superior to the other groups of antibiotics under study. Our studied showed as well that the use of ciprofloxacin in a single dose 2 hours before the biopsy was equivalent to using it for 3 days. Norfloxacin is a feasible option with a low morbidity and chloramphenicol, in our opinion, should not be used for this purpose.

CONCLUSION

Based on the results of this study we currently recommend in our service the use of ciprofloxacin, in a single dose, 2 hours before TPB.

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