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Pilot Study to Compare the Efficacy of the Usual Recommended Prophylactic Antibiotic to the Addition of Oral Ciprofloxacin for Patients Undergoing Radical Prostatectomy

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Abstract:

Background: This is a randomized, prospective, double-blind pilot study to compare the efficacy of preoperative cephalosporin to the addition of ciprofloxacin to avoid positive urinary culture in patients undergoing radical prostatectomy. **Material and Methods**: Sixty-four patients with similar clinical features and who underwent radical prostatectomy were split into three antibiotic groups: group A using prophylactic preoperative cephalosporin; group B using the prophylactic cephalosporin plus one day ciprofloxacin and group C using the prophylactic cephalosporin plus ciprofloxacin for 5 days. Urine samples, taken before surgery and after removal of the indwelling catheter, were evaluated. For statistical analysis, we used Chi-square test to establish the association of the antibiotic regimen and positive urinary culture in the univariate analysis and logistic regression in the multivariate analysis. **Results**: Less urinary infection rate was observed in both groups receiving the addition of ciprofloxacin for one and five days (20 and 9.5%, respectively) compared to the use of single preoperative cephalosporin (52.1%; p=0.0047). **Conclusions**: This study suggests that the usual recommendation of preoperative cephalosporin alone may not be adequate to avoid high rates of urinary positive culture in patients undergoing radical prostatectomy.

Keywords: prostate neoplasms; treatment; complications

Introduction

Prostate cancer (PCa) is the most common malignant neoplasm among men and the second cause of death due to cancer. [1,2] The Brazilian National Cancer Institute (INCA) registered 47,280 new cases of PCa in Brazil in 2006. [3] In the USA there is an estimate of 220,000 new PCa cases in 2007 [1] and 27,000 deaths. One of the most popular treatments for localized prostate cancer (T1-T2c) is radical prostatectomy (RP). [4,5] It is a potentially contaminated surgery [6,7] that requires the use of bladder catheterization for 7 to 21 days, depending on the surgeon's routine. It is known that 13 to 25% of the patients with PCa present with acute urinary retention, raising the risk of urinary infection. Despite no scientific data recommending therapeutic antibiotic regimens following potential contaminated surgery, several urology departments, Brazil and worldwide, use long-term antibiotics after radical prostatectomy. Usually, antibiotics are started before the surgery and are kept until the removal of the indwelling catheter. Unfortunately, there is a paucity of data published regarding diagnosis and morbidity of urinary tract infection (UTI) following radical prostatectomy, as well as the role and duration of different antibiotic regimens in this situation. [8] Jackaman

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et al. found 31% of UTI following prostatectomy for benign hyperplasia. [9] Krzeski et al. noted 20% of infected urine among patients who would undergo prostatectomy and almost 80% of UTI after the surgery and use of indwelling catheter. [10] Hooton et al. published a paper suggesting that urine culture is mandatory to diagnosis of UTI. [11] The same diagnosis in postoperative scenery including long-term use of indwelling catheter is more challenging and no consensus is so far accepted. They also stated that ten percent of patients were discharged with infected urine, although 3% remained with the infection after 6 weeks.

The goal of the present study is to evaluate the need and efficacy of different antibiotic regimens to avoid positive urinary cultures in patients undergoing R.P. We evaluated the prophylactic use of first generation cephalosporin versus the addition of one or five days of ciprofloxacin 500mg.

Materials and Methods

All consecutive patients from the urology department of Araujo Jorge Cancer Hospital (HAJ) seen between 03/13/2007 and 02/08/2008 with early stage PCa were accessed. The study was approved by the institution´s ethics committee. Patients with radical prostatectomy indication, who agreed to participate and signed the written informed consent, were included in the study. Bladder catheterization was done immediately before surgery, after antisepsis. Then, the first urine sample was collected (20ml) and sent to laboratory analysis within a maximum of 10 minutes. Patients who were already using an indwelling catheter before the surgery were excluded from the study. We also excluded patients whose first urine sample's culture was positive, those who required therapeutic antibiotic in the postoperative setting for any reason, those who needed to change the bladder catheter during the postoperative period and those hypersensitive to ciprofloxacin or cephazolin. In the operating room, patients underwent randomization by "coin flip" and were initially divided into two groups: group A were patients who would get cephazolin alone before skin incision, and; group B were patients with the same antibiotic regimen as group A plus two ciprofloxacin 500mg oral doses, within the skin closure and 12 hours after. The dose of cephazolin was 1g for patients less than 50Kg or 2g for heavier patients. If the surgery lasted more then 3 hours, another dose of cephazolin was given. A third group (group C), composed of 21 patients (*en bloc* randomization) that had surgery after randomizing groups A and B, got prophylactic cephazolin like group A plus 1g of ciprofloxacin per day, during 5 days, beginning in the eleventh postoperative day (one day before taking out the indwelling catheter). The indwelling catheter was removed 12 days after surgery, for all patients. After removal of the catheter, a second urine sample was collected. The second urine sample was collected from the patients of group C 24 hours after finishing the fifth day of ciprofloxacin to avoid antibiotic misinterpretation of the urinary culture. All other patients had the second urine sample collected on the day of removal of the indwelling catheter (twelfth postoperative day). All urine samples were analyzed by the same laboratory. Diagnose of urinary infection was considered if more than 100,000 colony forming units/ml of one single bacteria were seen in the sample. Patients diagnosed with urinary infection were treated according to the antibiogram results.

Statistical Analisys

The analyzed criteria were patient age, diabetes mellitus, time to complete the surgery and patient's group. Mean age and time to complete surgery between groups were calculated and comparison was done using Student´s t-test. Evaluation of the association among risk variables and urinary infection was done by univariate analysis, using Fisher or Chi-square tests with Yates correction when needed. Multivariate analysis with all variables was also performed by logistic regression in order to establish the association between urinary tract infection (UTI). For all tests, a confidence interval of 95% was used and significance was established with a $p < 0.05$.

Results

One hundred and nineteen patients underwent radical prostatectomy (R.P) in the Uro-oncology Department of Araujo Jorge Cancer Hospital between March 2007 and February 2008. Fifty-five patients were excluded: 18 for not collecting the second urine sample, 3 for receiving antibiotics because of superficial wound infection, 5 patients were excluded because they already had bladder catheterization before surgery, 6 showed infection in the first urine sample and 23 refused to enter the study. No patient was sent to the intensive care unit (ICU) after the surgery. No patient had any major infection or complication related to infection. Sixty-four patients were enrolled. After randomization

23 patients composed group A (cephazolin alone), 20 patients composed group B (cephazolin plus one day of ciprofloxacin), and the last 21 patients were consecutively randomized to group C (cephazolin + ciprofloxacin for 5 days). Patient's features are shown in Table 1.

Table 1 - Patients characteristics and univariate analysis X2 – Chi-square test; SD=Standard deviation

	Group A	Group B	Group C	X2/ Yates
Nuber of patients	23	20	21	–
Mean age	63.30 (SD=7.47)	62.85 (SD=6.78)	62.28 (SD=6.40)	p=0.13
Patients with Diabetes	1	1	0	p=0.13
Mean time to complete surgery (minutes)	117,60	122,85	106,42	p=0.36

There was no statistical difference among the analyzed characteristics in the three groups. Patient age varied between 44 and 76 years, with a median age of 62.79 years. Mean time to complete surgery was 115.8 minutes, ranging from 60 to 240 minutes. Only 2 patients had diabetes, one in group A and another in group B. The last showed UTI in the second sample. From the 64 patients, 18 (28.12%) had urinary infection in the second urine sample: 12 in group A, 4 in group B, and 2 in group C. The isolated agents were: *E. coli*, 9 cases; *Klebsiella sp.*, 6 cases; *S. aureus,* 2 cases and *Enterobacter*, 1 case. Among the 18 patients with infection, only two had fever and none developed complicated UTI or sepsis. All of them complained of dysuria. The UTI rates for group A, group B and group C were 52.1%, 20% and 9.5%, respectively. The univariate analysis to evaluate association between the risk factors and ITU is shown in Table 2.

Multivariate analysis was applied using logistic regression and is shown in Table 3.

The addition of ciprofloxacin to the standard single cephalosporin regimen reduced the risk of ITU in 85% showing significance in uni- and multivariate analysis.

Table 2 - Univariate analysis between patient's characteristics and UTI development.

Variable	UTI		p (CI=95%)
	Yes	No	
Diabets			
Yes	2	0	
No	16	46	0.13 (2.54 – 5.9)*
Time of surgery			
<2 hours	9	22	
>2 hours	9	24	0.87 (0.48 – 2.32)***
AGE			
<63 years-old	6	25	
>63 years-old	12	21	0.13 (0.22 – 1.24)***
GROUP			
A	12	11	
B	4	16	0.0045**
C	2	19	
Ciprofloxacin usage			
Yes	6	35	
No	10	11	

* Chi-Square test with Yates correction; ** Qui-square test; *** Fisher test

Table 3- Multivariate analysis (logistic regression) evaluating association between studied variables and UTI (RR- Relative Risk; IC- Confidence Interval)

Variable	RR	p (CI 0.95%)
Age <63 years-old	2.45	(0.69 – 8.78) 0.16
Mean age	0.77	(0.35 – 1.69) 0.51
Diabetes	–	0.59 ——
Less than 2 hours to complete surgery	0.12	(0.01-1.4) 0.09
Use of ciprofloxacin	0.15	(0.04 – 0.56) 0.0047

Discussion

Until now, there is no consensus in which antibiotic regimen, prophylactic or therapeutic, should be employed for patients who undergo RP, reflecting a paucity of data regarding this issue. According to the Hospital Infection

Control Committee's (HICC) recommendations, the single use of prophylactic cephalosporin regimen (cephazolin or cephamycins) should be sufficient to prevent urinary infection in patients undergoing RP. 6-8,12,13 This would also avoid the use of therapeutic regimens, decreasing the risk of bacterial induced resistance.13-16 Until this moment, there is no prospective and randomized article that evaluates the efficacy of prophylactic antibiotics in radical prostatectomy. UTI is the most common nosocomial infection, mainly in patients with indwelling catheters.14,15 The diagnosis is controversial and complex, although the criteria of over 105 uropathogens in culture of voided urine still seems to be adequate.11-15 The idea of adding ciprofloxacin to the current recommendation of prophylactic cephazolin is based in some published papers regarding this issue 7,15-17 and in the current observed urological practice. In the present study, we observed lower rates of positive urinary cultures among patients receiving cephazolin plus 1g of oral ciprofloxacin in the immediate postoperative setting (20%) comparing to cephazolin alone (52.09%). The difference was statistically significant in multivariate and univariate analysis. An even greater difference was observed in group C (5-day ciprofloxacin regimen) in which only 9.5% of UTI was diagnosed. The resulting 28% of UTI detected is quite unacceptable, although pushed by the infection rate of group A patients. This high infection rate was expected based on data of a minor previous series of patients who had undergone RP in our institution; the reason why we designed the present study. There are few papers regarding this issue in the current literature. In multivariate analysis, patient group was not significant ($p=0.51$) because no statistical difference between groups B and C was shown. However, using logistic regression to compare group A with groups B and C together (cephazolin alone versus addition of ciprofloxacin for 1 or 5 days), the difference becomes extremely significant ($p=0.0047$). Although the number of patients is short (pilot study), the relevance of the statistical difference generates an ethical discomfort in not adding ciprofloxacin to all the patients who undergo RP. Those findings shall aware the infection control committees that the recommended prophylactic antibiotics may not be adequate for this surgery. In potentially contaminated surgeries, infection rates of approximately 10% are expected when prophylactic antibiotics are not used and around a 3% rate when used. 6-8 Even by adding ciprofloxacin for five days, a 9% infection rate was found. Despite all of the patients complaining of dysuria, only two had fever associated to the UTI, favoring the hypothesis of sub-clinic infections, with poor systemic symptoms. One must assume that micturition by itself could eliminate the biofilm of the indwelling catheter. On the other hand, it would be unreasonable not to treat patients with bacteriuria >100,000 CFU/ml associated to dysuria in a recent postoperative setting of a major surgery. This was previously studied by other authors, who found reduction in morbidity and complications when treating bacteriuria >100,000 CFU/ml. Considering the lack of data regarding prevalence of bacteriuria in the postoperative of RP, the findings of the present study are relevant and it is necessary to exploit the real meaning of this information. Bartsch et al. found up to 40% of bacteriuria among 148 patients who underwent to RP in 2002, depending on the day after the surgery. 18 They also found a slightly higher rate of anastomotic stricture among patients with bacteriuria. Jackaman et al. published a 31% of UTI after prostatectomy even when using short prophylactic antibiotic regimens. 9 It is known that the prolonged use of fluorochinoloni is responsible for the development of resistant bacteria, an issue to be considered when indicating prophylactic antibiotics. 14,18,19 The efficacy of prolonged use of ciprofloxacin in RP and the shortest relevant antibiotic regimen remain unknown. Terai et al. 16 and Yamamoto et al., 17 found preoperative infection rates between 1.8 and 6% in patients undergoing urologic surgeries with the use of 3 days of venous cephalosporins or cephamycins, starting at anesthesia induction. We accept that 12 hours after stopping the ciprofloxacin should not be long enough to favor bacterial growth. On the other hand, a sample collected 7 or 14 days after the catheter removal could be residual or a new infection. This would be hard to state and we could generate a new bias. The exclusion rate was expressive (46%), though 11% of them were due to exclusion-planned criteria and 19% due to a refusal to enter the study. The remaining 16% was randomly distributed among patients who, for any reason, did not send the second urine sample for culture. In our point of view, this could not seriously affect the results. Our data should be confirmed in other larger prospective series, considering better discussion regarding the definition of urinary infection.

Conclusion

This study suggests that adding oral ciprofloxacin to the usual venous cephalosporin for RP could result in lower urinary infection rates. The ideal prophylactic antibiotic regimen (type, dose and duration) for RP still needs to be established in a multi-institutional

background, as well the definition of urinary infection in a postoperative setting.

Competing Interests

Nothing to declare

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