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Epidemiology of the Postoperative Bacteriuria and Urinary Tract Infections Following Transurethral Resection of the Prostate

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Authors' contributions

This work was carried out in collaboration between all authors. Author BLDSM had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis, study concept and design; author CLDS for all ultrasound measures and acquisition of data; author FPM for acquisition of data; author HCM for statistical analysis and interpretation of data and author ADF for critical revision of the manuscript for important intellectual content. All authors read and author approved the final manuscript.

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ABSTRACT

Aims: Despite guidelines and recommendations, a pragmatic approach, i.e., that treatment will improve patient-centered outcomes when performed by typical clinicians in typical patients, is necessary to evaluate the effectiveness of antibiotic prophylaxis in urological surgery.
Study Design: Prospective, randomized, double-blinded, pragmatic trial.
Place and Duration: The study was performed in a tertiary hospital at Federal University of Uberlandia, Brazil, from January 2012 to December 2013.

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Methods: One hundred and thirty patients were randomly assigned to receive a single dose of 2 g intravenous (IV) ceftriaxone (66 subjects) or 2 g IV cefazolin (64 subjects) thirty minutes before transurethral resection of the prostate (TURP). We evaluated their physical status, preoperative urinary catheter use, urological risk factors, prostate size, and the duration of surgery.
Results: Ceftriaxone showed a non-significant trend towards superiority to cefazolin (OR = 0.567, 95% CI [0.234-1.414], p = 0.228) for the prevention of infections among TURP patients.
Conclusion: No significant difference in the effectiveness of a single dose of ceftriaxone compared with cefazolin for the prevention of postoperative infections was found in patients undergoing TURP following the early postoperative removal of an indwelling catheter. Due to the pragmatic assumptions of this trial, this result might not represent a negative finding; instead, it may indicate the importance of risk factors influencing the patients' susceptibility to infection.

Keywords: Transurethral resection of prostate; surgical site infection; urinary tract infections; bacteriuria; antibiotic prophylaxis; cefazolin; ceftriaxone.

1. INTRODUCTION

Surgical site infections (SSIs) are an important cause of postoperative morbidity. In endoscopic urologic procedures, complicated urinary tract infections (UTIs), pyelonephritis, and septicemia are the most feared complications [1]. Great efforts have been made to diagnose these health care-associated infections (HAIs) and to decrease their incidence using standardized preventive, epidemiological, and educational measures [2].

Transurethral resection of the prostate (TURP) is still the most commonly performed surgical procedure for benign prostate hypertrophy (BPH), despite the development of new medications and less invasive surgical techniques [3]. Infection following TURP is a concern because it may present as asymptomatic bacteriuria, UTI, epididymitis, prostatitis or even septicemia [4]. Antibiotic prophylaxis is one of several methods for preventing SSIs [5], and while the Best Practice Policy Statement of the American Society of Urology (AUA) recommends prophylaxis with first- or second-generation cephalosporins [6] for all patients undergoing TURP, the European Association of Urology (EAU) guidelines suggest that patients receive trimethoprim-sulfamethoxazole or cephalosporins (second or third generation) as prophylaxis, except for individuals at low risk or with a small prostate [7]. First-generation cephalosporins, such as cefazolin, show excellent activity against Gram-positive organisms and mild activity against Gram-negative species. Nevertheless, cefazolin shows good activity against *Escherichia coli*, *Klebsiella* species, *Haemophilus influenzae*, and *Proteus mirabilis* as well as some *Enterobacter* species. Ceftriaxone exhibits good activity against Gram-negative microorganisms but is associated with a high risk of developing bacterial resistance [8].

There is a low rate of compliance with recommendations regarding prophylaxis, and the prescribing patterns for different antibiotics vary significantly [9]. A pragmatic approach is necessary to implement guidelines while considering patient comorbidities and urological risk factors related to endoscopic urologic surgeries [10,11].

The presence of preoperative bacteriuria, indwelling catheters, urinary tract stones, urinary tract abnormalities, and recurrent UTIs can complicate patient management, and these conditions are common exclusion criteria in studies of the efficacy of antimicrobial prophylaxis in urologic procedures [12,13]. The standard antimicrobial susceptibilities of pathogens should also be considered because the widespread use of antibiotics, especially fluoroquinolones, has led to the emergence of bacterial resistance, which is currently a major concern [14].

The aim of this study was to determine whether a single dose of ceftriaxone is superior to a single dose of cefazolin for the prevention of postoperative infectious complications in patients undergoing TURP following the short-term removal of urinary catheters. We also sought to identify predictors of infectious complications in these patients.

2. METHODS

2.1 Study Area

We performed this prospective, randomized, double-blinded, pragmatic study at a tertiary hospital at Federal University of Uberlandia, Brazil, from January 2012 to December 2013.

2.2 Selection of Subjects

All patients who had been scheduled to undergo TURP who were 45 years of age or older and clinically stable were considered for inclusion in the study. The exclusion criteria included a known history of allergy to the study antibiotics, a history of recurrent UTIs, treatment with antibiotics within 10 days prior to surgery, the administration of antibiotic therapy for any other reason, severe renal or hepatic failure, the presence of a distant focus of concurrent infection, and immunosuppression.

The study protocol was approved by the Committee on Human Research of the Federal University of Uberlandia, Brazil, with the record number CEP/UFU 169/1. Data were prospectively collected by the principal investigator during hospitalization and in an ambulatory setting after discharge. Each patient received information on the study protocol and provided written informed consent before participating.

A total of 135 patients were randomized into two different groups. Block randomization (2:2) was performed in a blinded fashion by the anesthesiologist one day prior to surgery for all study participants. On the day of surgery, the patients received either 2 g cefazolin (Group 0) or 2 g ceftriaxone (Group 1) intravenously 30 minutes before surgery. The patients and surgeons were blinded to the drug administered.

2.3 Parameters Assay

A complete blood count (CBC), chemistry panel, electrocardiogram, urinalysis (to detect pyuria), and ultrasonography of the pelvic and abdominal portions of the urogenital tract were performed preoperatively. In the operating room, the researcher recorded the age, body mass index (BMI), comorbidities and medication intake of the patients to grade their physical status according to the American Society of Anesthesiologists (ASA) criteria. Data regarding the preoperative presence of an indwelling urinary catheter, ultrasonographic abnormalities, prostate volume and operative duration were also recorded.

Urinary symptoms such as urgency, frequency, dysuria, and suprapubic tenderness were recorded as well. A physical examination was performed preoperatively and included measurements of blood pressure, pulse and axillary temperature (> 38°C). Urinalysis and urine cultures were collected at baseline. Following resection, prostate fragments were cultured.

Thirty minutes before the beginning of surgery, the patients received the previously allocated study drug. No additional doses were administered to any of the patients except for those with known colonization at baseline, who were treated during their hospital stay or for a longer period based on an antibiogram or empirical findings when these data were not available. During surgery, standard antiseptic measures were followed. Surgery was performed by a urologist, with a 3-way Foley catheter with a closed drainage system that was continuously irrigated with saline solution being placed at the end of surgery. The catheter remained in place until discharge, when it was removed, except in patients who exhibited complicating urological factors (such as urethral stricture) that required prolonged catheter placement. An assessment of clinical symptoms, CBC, urinalysis and urine cultures were performed after catheter removal at the time of discharge and in an ambulatory setting at one week and at one month after surgery.

The primary outcome was postoperative infection, which was diagnosed according to the European Association of Urology guidelines and CDC definitions and included the following signs and symptoms: asymptomatic bacteriuria (positive urine culture of $\geq 10^5$ CFU/ml with no more than 2 species), UTI (at least one sign or symptom, including fever above 38°C, urgent or frequent urination, dysuria, suprapubic tenderness or a positive urine culture of $\geq 10^4$ CFU/ml with no more than 2 species), clinical epididymitis, prostatitis, and septicemia [7,15].

The general risk factors of the patients were assessed according to the ASA physical status classification. Specific urological risk factors included anatomic anomalies of the urinary tract, urinary obstructions, urinary stones, and an indwelling or externalized catheter [16].

2.4 Statistical Analysis

To calculate the sample size, we considered previous systematic reviews, which have shown that antibiotic prophylaxis decreases the frequency of postoperative bacteriuria in men receiving antibiotic prophylaxis versus placebo or no treatment (from 26% to 9%). Therefore, the difference in risk was -0.17, with a 95% confidence interval ranging from -0.20 to -0.15 [11,12]. Based on these findings, the following parameters were employed for our calculations with the G*power program [17] using the two-tailed z-test: an alpha error probability of 0.05, a power (1- beta error probability) of 0.80, and an allocation ratio of 1. A large proportion of the differences between the two evaluated antibiotic groups (as observed in the above-cited systematic reviews of placebo versus antibiotic prophylaxis showing significant differences in risk, both statistically and clinically) were expected to provide evidence supporting the use of one antibiotic over the other. The proportion of infections (0.09 for group A and 0.29 for group B) was considered post-intervention. Hence, a risk difference of 0.20 was expected. These parameters necessitated a minimum sample size of 132 patients (66 in the cefazolin group and 66 in the ceftriaxone group) to identify a difference in risk of 0.20.

Logistic regression was used to evaluate the effectiveness of the antibiotic treatment (ceftriaxone versus cefazolin) in decreasing infection rates at 30 days after surgery, applying an intention-to-treat analysis. Due to the pragmatic assumptions of this trial (i.e., that treatment will improve patient-centered outcomes when performed by typical clinicians in typical patients) [17], the patients were permitted to exhibit bacteriuria or prostate colonization at the baseline assessment.

To evaluate other variables associated with infection in patients following the intervention, a sequence of bivariate analyses was performed that included age, BMI, ASA status, the duration of surgery, preoperative catheter use, prostate size, and infection. Variables with p-values < 0.20 at this stage of the analysis were then selected for inclusion in an initial multiple logistic regression model [18]. The covariates were also inspected based on multicollinearity, considering (a) whether two or more independent covariates were correlated (correlation matrix); (b) whether significant changes in the coefficient estimates occurred when variables were added or excluded; and (c) whether the sign or coefficient order of a magnitude estimate was different from what was expected [19]. The final model retained variables that were clinically important and were not candidates for causation of multicollinearity.

Finally, two subgroup analyses of treatment effectiveness were carried out for patients whose urine was sterile to evaluate the prophylactic effectiveness of the drugs as well as for those who did not exhibit any urologic risk factors. Mplus software (Los Angeles, CA, EUA) was used for the analysis [20].

3. RESULTS

Eligible participants attended ambulatory visits. Among the 142 patients with indications for elective TURP, 7 were excluded, and 135 were randomized on the day before surgery. All patients in Group 0 (except for one patient in whom the surgical technique had to be changed due to a complication during surgery) were randomized to the originally allocated group (intention-to-treat analysis). No patients were lost to follow-up. Of the 134 patients, 67 were allocated to each group, and four were not included in the analysis (three in Group 0 and one in Group 1) because they did not meet the criteria for complete cases.

This prospective study was carried out from January 2012 to March 2014. There was no reason to stop the study early. Table 1 shows the patient characteristics for each group. Of the 33 patients showing preoperative bacteriuria and/or colonization of the prostate (25.38%), most had a preoperative indwelling catheter (63.64%), and all 21 exhibited asymptomatic bacteriuria. For the 109 patients without a preoperative catheter, the incidence of bacteriuria and/or colonization of the prostate was 11.01%. Moreover, 4 patients out of the 12 without a catheter presented a negative urine culture, and the colonization status at baseline was due to positive prostate fragment cultures (33.33%). Sepsis was not observed in any patient.

Twenty patients in Group 0 and 16 in Group 1 developed a postoperative infection. Table 2 shows the results of univariate regression for each covariate individually. Although the randomized allocation variable ceftriaxone was not significant, it was maintained in subsequent analyses because it demonstrated the effectiveness of the randomized clinical trial.

Table 3 shows that the covariates presenting p-values of less than 0.20, as determined through univariate regression analysis, were used to build a multivariate regression model. We failed to reject the null hypothesis regarding differences in the effectiveness of the two drugs. An ASA status of PS3 was strongly correlated with the incidence of postoperative infection, increasing the chance of infection by 5.3 times compared with an ASA status of PS2.

A strong correlation between preoperative catheter usage and the baseline bacteriuria/colonization status of 0.965 (p=0.026) was found. The reduction in the odds ratio of preoperative catheter usage between the univariate and the multivariate regression analyses may suggest multicollinearity. The final model (Table 4) included the baseline drug allocation data and urological risk factors. The adjusted multivariate analysis again demonstrated a statistically non-significant effect of ceftriaxone.

Table 1. Patient characteristics for each arm

Groups	Patient characteristics	Group 0 - Cefazolin (n = 64)	Group 1 - Ceftriaxone (n = 66)
Categorical measurements: absolute values	With bacteriuria and/or prostatic colonization at baseline	n = 16	n = 17
	PS1 ASA – normal/healthy	n = 20	n = 18
	PS2 ASA - mild systemic disease	n = 32	n = 34
	PS3 ASA - severe systemic disease	n = 12	n = 14
	Urological risk factors	n = 12	n = 12
	Catheter use before surgery	n = 10	n = 11
Continuous measurements: mean (SD)	Age (years)	66.01 (8.94)	66.40 (9.13)
	BMI (m2/kg)	25.59 (4.19)	25.14 (3.87)
	Surgery duration	39.74 (14.71)	38.67 (14.15)
	Prostate size	56.55 (14.28)	51.91 (15.14)

PS ASA = Physical Status, American Society of Anesthesiology; and BMI = Body Mass Index

Table 2. Univariate regression of all case covariates

Outcome: Infection status post-surgery	Beta	SE	Odds ratio	P-value	95% CI for exp (beta)	
					Lower	Upper
With bacteriuria and/or prostatic colonization at baseline	1.297	0.436	3.657	0.003	1.555	8.603
Ceftriaxone	-0.404	0.405	0.667	0.318	0.302	1.475
Age	0.020	0.022	1.020	0.383	0.976	1.065
BMI	0.043	0.049	1.044	0.378	0.949	1.149
PS2 ASA*	-0.650	0.494	0.522	0.188	0.198	1.373
PS3 ASA*	0.875	0.539	2.4	0.104	0.835	6.902
Duration of surgery	0.001	0.014	1.001	0.929	0.974	1.029
Catheter use before surgery	1.023	0.497	2.781	0.040	1.049	7.372
Prostate size	0.006	0.013	1.006	0.661	0.98	1.033
Urological risk factors	1.903	0.485	6.705	< 0.001	2.593	17.342

** PS1 ASA (Physical Status, American Society of Anesthesiology) was used as a reference.*
Abbreviations: CI = Confidence Interval; and SE = Standard Error

Table 3. Multivariate regression of covariates showing p < 0.20, except for ceftriaxone

Outcome: Infection status post-surgery	Beta	SE	Adjusted odds ratio	P-value	95% CI for exp (beta)	
					Lower	Upper
With bacteriuria and/or prostatic colonization at baseline	1.368	0.708	3.926	0.053	0.980	15.733
Ceftriaxone	-0.637	0.470	0.529	0.175	0.211	1.329
PS2 ASA*	-0.342	0.582	0.710	0.557	0.227	2.222
PS3 ASA*	1.327	0.705	3.771	0.060	0.947	15.012
Catheter use before surgery	-0.071	0.818	0.932	0.931	0.187	4.632
Urological risk factors	2.388	0.581	10.890	< 0.001	3.488	34

** PS1 ASA (Physical Status, American Society of Anesthesiology) was used as a reference; Abbreviations: CI= Confidence Interval; and SE = Standard Error*

Table 4. Multivariate regression: final model

Outcome: Infection status post-surgery	Beta	SE	Adjusted odds ratio	P-value	95% CI for exp (beta)	
					Lower	Upper
With bacteriuria and/or prostatic colonization at baseline	1.564	0.492	4.777	0.001	1.820	12.540
Ceftriaxone	-0.552	0.459	0.576	0.228	0.234	1.414
Urologic risk factors	2.102	0.534	8.182	< 0.001	2.875	12.282

PS ASA = Physical Status, American Society of Anesthesiology

Two sub-analyses were conducted. The first considered only patients without preoperative bacteriuria and/or colonization of the prostate (n = 97) and indicated likely prophylactic efficacy of ceftriaxone over cefazolin, but no statistically significant difference was found. For the second subgroup analysis, which considered patients with no urological risk factors (n = 110), we again failed to reject the null hypothesis regarding the effectiveness of ceftriaxone over cefazolin. Regarding the covariates included in the model, ASA III, the pre-surgery infection status and catheter use pre-surgery are noted as predictors of a higher probability of post-surgery infection.

4. DISCUSSION

In the present era, humans are faced with an increased life expectancy. Elderly surgical patients therefore require special consideration due to the high prevalence rates of comorbidities among individuals in this age group who require surgery [21]. Benign prostatic hypertrophy is prevalent in the elderly. Each patient's ability to tolerate the intravascular volume changes associated with the apparently non-invasive surgical technique of TURP should be evaluated. Moreover, TURP is occasionally associated with significant morbidity and even mortality [22].

A great deal of evidence supports the use of antibiotic prophylaxis in TURP patients, but three large meta-analyses suggesting that prophylactic antimicrobials may be effective in all patients undergoing TURP included only low-risk patients and those with preoperatively sterile urine [12,13,23]. However, the presence of preoperative bacteriuria/prostate colonization and an indwelling urinary catheter are not independent factors, and the presence of infection must be properly assessed, for example, by performing urine cultures before and after surgery [24].

A reduction in the proportion of infections after surgery was observed among the patients treated with ceftriaxone; however, this difference was statistically non-significant. Such a result might not represent a negative finding. Instead, it may indicate an absence of evidence regarding the differences in the treatments. Thus, the use of tertiary cephalosporins for antimicrobial prophylaxis in TURP patients may be unnecessary. Ceftriaxone was expected to be more protective than cefazolin due to its broader spectrum, but statistical analysis showed no significant difference in this regard. Consistent with this finding, a report by the American Society of Health-System Pharmacists (ASHP) recommends that broad-spectrum antimicrobials, such as third-generation cephalosporins and carbapenems, should be reserved for patients with active infections or for those who require additional coverage for intestinal organisms. Routine use of third-generation cephalosporins is not recommended due to their high cost and the potential to promote resistance to HAI Gram-negative bacilli. Cefazolin may therefore be an appropriate drug for UTI prophylaxis in TURP patients due to its good coverage of most microorganisms that cause infections in TURP patients and its low probability of causing resistance [25].

Many urological conditions are associated with an increased risk of UTIs and urosepsis, primarily obstruction of the urinary tract, the presence of contaminated stones, and postoperative placement of indwelling catheters. In the present study, urological factors were found to be directly related to risk of postoperative infection, and it was challenging to determine how each of these factors influenced the patients' susceptibility to infection. Further studies are necessary to answer these questions.

5. CONCLUSION

No significant difference in the effectiveness of a single dose of ceftriaxone compared with cefazolin for the prevention of postoperative infections was found in patients undergoing TURP following the early postoperative removal of an indwelling catheter. Due to the pragmatic assumptions of this trial, this result might not represent a negative finding; instead, it may indicate the importance of risk factors influencing the patients' susceptibility to infection and an evaluation over 30 days is very important to detect postoperative infections in TURP patients.

ETHICAL APPROVAL

The study protocol was approved by the Committee on Human Research of the Federal University of Uberlandia, Brazil; with a record number CEP/UFU 169/1. Each patient received information on the study protocol and provided written informed consent beforehand.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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