Original Article

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The Evaluation of Goal-Directed Antibiotics Prophylaxis Applied Via Rectal Swab Before Transrectal Ultrasound-Guided Prostate Biopsy

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Abstract

Objective: This study examined bacterial resistance to antibiotics administered for prophylaxis in rectal swaps taken before biopsy in patients who underwent transrectal ultrasound-guided prostate biopsy (TRUS).

Materials and Methods: This prospective study evaluated 251 patients who underwent TRUS in the clinic between January 2015 and December 2016. The patients were administered ciprofloxacin one day before the biopsy, the day of the biopsy, and five days after the biopsy. Urinalysis of patients was performed before biopsy and those with active infection were excluded from the study. Swap samples of patients were taken from the rectal mucosa before the biopsy. These samples were cultivated in blood agar and EMB growth medium. *E. coli* and *Klebsiella* reproductions were assessed. Antibiogram tests were studied in terms of resistance/sensitivity after identifying these bacterial subgroups.

Results: In the comparison of resistance and sensitivity of microorganism-independent antibiotics, the highest resistance was detected in amoxicillin (70%). The resistance to ciprofloxacin was 41.8%. The highest sensitivity was detected for fosfomycin (97.6%) and ceftazidime (91.6%). Extended spectrum beta-lactamase (ESBL) positivity was detected based on the bacterial species (p=0.001). The study found that ESBL positivity did not affect prostatitis development (p=0.447). The study also found that prostatitis development was not based on ciprofloxacin sensitivity/resistance in the rectal swap (p=0.803). A total of 105 patients showed resistance to ciprofloxacin. Prostatitis development was observed in 5 (4.8%) of these patients. Prostatitis development was observed in 11 (4.3%) of 251 patients.

Conclusion: According to the results of this study, antibiotic prophylaxis for rectal swab culture taken before TRUS does not affect prostatitis development after the biopsy. Although rectal swap guided goal-oriented prophylaxis does not reduce infective complications, it may be beneficial so as not to administer additional antibiotics to patients.

Keywords: Antibiotherapy, benign prostatic obstruction, prostate needle biopsy, prostatitis

Introduction

Prostate cancer is one of the most common types of cancer among men and is ranked the second among deaths due to cancer after lung cancer (1). The main diagnostic methods for prostate cancer are digital rectal examination (DRE) and the measurement of prostate-specific antigen (PSA) in blood. However, the definitive diagnosis of prostate cancer is made by histopathological examination. Transrectal ultrasound guided prostate biopsy (TRUS) is the standard technique used in the histopathological examination for the diagnosis of prostate cancer (2). Despite generally being a safe and well-tolerated process, different complications are reported in 50% of patients after the biopsy. These complications are pain, hematuria, urinary retention and infection (3). The incidence of urinary tract infection reported after TRUS changes between 2% and 6%. The incidence of severe sepsis settings accompanied by bacteremia is between 0.1-2.2% (4). It is recommended to use antimicrobials before the biopsy to prevent infectious complications after the surgery (5). Thus, fluoroquinolones are usually preferred as the first option in prophylaxis choice (6). However, increasing

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resistance to fluoroquinolone use has been associated with increased infection rates after biopsy in many countries (7,8). The new recommendation is screening of patients for resistant pathogens before biopsy instead of the classical approach (9). Some approaches recommend rectal swap culture-oriented antibiotic treatment in patients with risk factors to minimize serious infections induced by resistant rectal flora (10).

This study was conducted to examine bacterial resistance to antibiotics administered before biopsy in patients who underwent TRUS, and to investigate the effectiveness of taking rectal swap as prophylactic agent choice and which antibiotics group should be selected in the patients who underwent TRUS with the data obtained.

Materials and Methods

This prospective study was approved by the Local Ethical Committee (KAEK 2015/61). The sample size was calculated as 181 patients with the power analysis. This prospective study evaluated 351 male patients who underwent TRUS-guided TRUS in the Urology Clinic of our hospital between January 2015 and December 2016. Written informed consent was obtained from all patients who agreed to participate in this study. Each patient was administered antibiotic prophylaxis with ciprofloxacin for seven days, including one day before the biopsy, the day of the biopsy, and five days after the biopsy. Complete urinalysis was conducted on all patients, and the patients with active infection were excluded from the study. The patients underwent TRUS guided 12 core prostate biopsy. Abnormal DRE findings, serum total PSA value of more than 4 ng/mL, and/or the presence of abnormal PSA derivatives were determined as criteria for biopsy decision. Treatments of patients who received antiaggregant therapy were discontinued seven days before the biopsy after consultations with relevant clinics. Biopsy procedure was performed in the lateral decubitus position, using a standard gray-scale ultrasonography and 7.5 MHz rectal probe (Mindray M5, Shenzhen, P.R. China) guided 18 Gauge biopsy needle and an automatic biopsy gun (GEOTEK Estacore, Daventry, UK). Twelve aliquots were resected from each patient, and all aliquots were sent for pathological examination in individually numbered tubes. Patients with colorectal pathology, urinary infection due to resistant microorganisms that may increase the risk of developing infective complications after TRUS, with urethral catheter, heart valve prosthesis, and non-pathogenic bacterial reproduction in their rectal swabs were excluded from the study. After considering all exclusion criteria, 251 patients were evaluated. Swap samples of each patient were taken from the rectal mucosa before the biopsy and these samples were cultivated in blood agar and EMB growth medium. *E. coli* and *Klebsiella* species reproductions was examined in these growth mediums and the subgroups of these bacteria with reproduction were identified. Antibiogram tests in terms of resistance/sensitivity. The antibiotics to be studied in the antibiogram were determined as amoxicillin, ciprofloxacin, gentamicin, ceftriaxone, fosfomycin, trimethoprim sulfamethoxazole (TMP-SMX), ceftazidime, cefoxitin and cefazolin. Patients with a fever above 38.5, polyuria, urgency, dysuria, and reproduction in the urine culture were acute prostatitis in this study.

Statistical Analysis

The results of the study were analyzed using IBM SPSS V23. Chi-square test was used to compare the qualitative variables. Sensitivity rates were compared with the Marascuillo technique using the R Project package program. The results are presented as frequency (percentage). The significance level was $p<0.05$.

Power analysis was performed to determine the minimum number of patients to be included in the study considering previous studies. The number of patients to be included in the study was determined using the "simple random sampling" method based on the criteria of the number of patients who applied to the hospital in the last six months, and it was concluded that at least 181 patients should be studied at a 95% confidence level and 5% margin of error to obtain clinically significant results.

Results

Mean age was 66 (44-93), mean total PSA was 7 (0.6-704) ng/dL, mean free PSA was 1.8 (0.2-90) ng/dL and the mean prostate volume was 45 (18-220) cc (Table 1).

In the comparison of resistance and sensitivities of microorganism independent antibiotics, the lowest sensitivity was detected in amoxicillin. Ciprofloxacin was determined to be the antimicrobial agent with the second lowest sensitivity rate. The highest sensitivity rates were obtained for fosfomycin and ceftazidime (Table 2).

Considering the examination of ESBL positivity according to bacterial species, the positivity rate was 3.8% in *E. coli* while it was 25% in *Klebsiella* (p=0.001) (Table 3).

Table 1. Patient's demografic data

	Mean	Minimum	Maximum
Age (Year)	66.0	44.0	93.0
Total PSA (ng/dL)	7.0	0.6	704.0
Free PSA (ng/dL)	1.8	0.2	90.0
Prostate volume (cc)	45.0	18.0	220.0

PSA: Prostate-specific antigen

Table 2. Comparison of the sensitivity rates of antibiotics

	Sensitive	Resistant
Amoxicillin	75 (29.9%)	176 (70.1%)
Ciprofloxacin	146 (58.2%)	105 (41.8%)
Ceftriaxone	192 (76.5%)	59 (23.5%)
TMP-SMX	149 (59.4%)	102 (40.6%)
Ceftazidime	230 (91.6%)	21 (8.4%)
Phosphomycine	245 (97.6%)	6 (2.4%)
Cefoxitin	218 (86.9%)	33 (13.1%)
Cefazolin	202 (80.5%)	49 (19.5%)
Gentamicin	208 (82.9%)	43 (17.1%)

TMP-SMX: Trimethoprim sulfamethoxazole

A total of 105 patients showed resistance to ciprofloxacin. Prostatitis development was observed in 5 (4.8%) of 105 patients with ciprofloxacin resistance. Prostatitis development was observed in 6 (4.1%) of 146 patients without ciprofloxacin resistance. While the rate of sensitivity to ciprofloxacin was 54.5% in patients who developed prostatitis, it was 58.3% in patients who did not develop prostatitis. There was no difference between the results. The study determined that prostatitis development is not based on sensitivity/resistance to ciprofloxacin in rectal swab (p=0.803) (Table 4).

Considering the relationship between ESBL positivity and the development of prostatitis development, the ESBL positivity rate was 5% in those who did not develop prostatitis while ESBL was found to be negative in those who developed prostatitis. The study found that ESBL positivity was not effective in prostatitis development (p=0.447) (Table 5).

This study found the ciprofloxacin resistance was 72.7% in urine culture antibiograms of patients who developed prostatitis (Table 6).

Discussion

Histopathological examination and TRUS-guided TRUS are needed for the definitive diagnosis of prostate cancer in today's world (11). Although different complications may occur after TRUS, most serious complications are due to infectious causes (12). The lack of standard definitions of infectious complications, and differences in the biopsy technique and patient preparation before biopsy make it difficult to objectively determine the incidence of these complications (12,13). Therefore, antibiotic prophylaxis is often administered peroperatively to protect the patient from infectious complications and is also recommended as guidelines. Ciprofloxacin, recommended in many clinical practices and guidelines, is routinely used without goal-oriented examination. Studies conducted because of an increase in the frequency of urinary tract infections that develop due to ciprofloxacin-resistant bacteria after TRUS reveal the *E. coli* colonization resistant to fluoroquinolone in the rectum (14). Despite the different prophylaxis regimens performed, the rates of development of acute prostatitis after biopsy in the literature changes from 0% to 37% (15,16,17). This rate was detected as 4.3% in this group of patients considering the evaluation of *Klebsiella* and *E. coli*. The most common factor in the patients who developed an infection after the prostate biopsy was *E. coli* (*E. coli* in 10 patients, *Klebsiella* in 1 patient). Considering all the patients with infection, ciprofloxacin resistance was detected as 72.7% in urine culture antibiograms. Considering that 10-20% fluoroquinolone resistance rates were reported in patients with *E. coli* in urine culture after TRUS in various studies, it can be said that the ciprofloxacin resistance rate in our patient group with prostatitis is quite high (18,19).

The literature reported the discontinuation of the use of ciprofloxacin in prophylaxis or new prophylaxis administrations with different combinations in which Ciprofloxacin is included (20,21,22,23). Although positive results and recommendations regarding individual-specific and goal-oriented prophylaxis administrations by taking rectal swabs and studying antibiotics in addition to a general prophylaxis application are reported, some studies show otherwise. Singh et al. (24) focused on the concept of targeted prophylaxis and applied prophylaxis by performing rectal swabs and antibiogram evaluations in all 247 patients whom they prospectively applied biopsy. It has been reported that only two patients (0.9%) developed a fever and no patients developed sepsis. This rate is quite low compared to the rate found in this study as 4.3%. The same study determined a fluoroquinolone resistance of 41.7% in rectal swabs. A new study by Dai et al. (25) conducted with 487 patients showed that prostate biopsy prophylaxis based on rectal swab results taken before biopsy reduced infective complications from 2.9% to 1.9% compared with empirical prophylactic antibiotic therapy. A recent study conducted in North America reported a significant decrease in hospitalization from 1.19% to 0.47% compared to the historical practice of empirical antibiotic prophylaxis after the addition of antibiotic prophylaxis according to culture results (26). Taylor et al. (27) found ciprofloxacin resistance in 20% of patients in their study conducted to detect fluoroquinolone resistance in rectal swabs. In their study conducted with 457 men, they found that goal-oriented antimicrobial prophylaxis reduces infective complications, while 38 rectal swabs taken before biopsy can prevent one infective complication. Considering this rate, although it suggests that rectal swab sampling before biopsy may cause a serious cost, Qi et al. (28) demonstrated that targeted antibiotic prophylaxis with rectal swab culture can be a cost-effective way to reduce increased fluoroquinolone resistance.

Table 3. Comparison of EBSL positivity based on the type of bacteria

		ESBL			
		Negative	Positive	Test statistic	p
Bacteria	*E. coli*	230 (96.2%)	9 (3.8%)	$\chi2$ =11.317	0.001
	Klebsiella	9 (75%)	3 (25%)		

Frequency (percentage), χ^2: Chi-square test statistic, ESBL: Extended spectrum beta-lactamase

Table 4. Comparison of prostatitis development and ciprofloxacin resistance/sensitivity

		Ciprofloxacin			
		Sensitive	Resistant	Test statistic	p
Prostatitis	Negative	140 (58.3%)	100 (41.7%)	$\chi2$ =0.062	0.803
	Positive	6 (54.5%)	5 (45.5%)		

Frequency (percentage), χ^2: Chi-square test statistic

Table 5. Examination of the relation between prostatitis development and ESBL

	ESBL			
Prostatitis	Negative	Positive	Test statistic	p
No prostatitis development	228 (95%)	12 (5%)	$\chi2$ =0.578	0.447
Prostatitis development	11 (100%)	0 (0%)		

Frequency (percentage), χ^2: Chi-square test statistic, ESBL: Extended spectrum beta-lactamase

But some authors expressed the opinion that targeted prophylaxis with rectal swab culture before TRUS does not affect the development of prostatitis after TRUS (29,30,31). Farrell et al. (30) conducted a study with 268 in 2017 and administered antibiotic prophylaxis for rectal swab culture to 152 patients and empirical antibiotic prophylaxis to 116 patients. Considering the analysis results of the study, they found the incidence of prostatitis development after TRUS as 4.3% and 0.66%, respectively, and found no statistical difference between the groups (p=0.08). A multicenter study by Liss et al. (29) in 2015 retrospectively examined the data of 5.355 patients and grouped them into 1803 patients in the prophylactic antibiotic group and 3.553 patients in the empirical prophylactic antibiotic group according to the rectal swab result. The development of prostatitis was detected in eight patients (0.4%) in the prophylaxis group according to the results of the rectal swab. In the group administered empirical antibiotic prophylaxis, the development of prostatitis was observed in 20 patients (0.6%). It was found that prophylaxis administered based on the rectal swab results did not statistically affect the development of sepsis compared with normal prophylaxis (p=0.568). It was observed that ciprofloxacin was sensitive in patients who developed prostatitis in the group administered prophylactic antibiotic prophylaxis based on the rectal swab results, while no prostatitis development was observed in five patients (60%) although ciprofloxacin prophylaxis was given. Ciprofloxacin resistance was observed in 105 patients in this study. Prostatitis development was observed in five (4.8%) of 105 patients with ciprofloxacin resistance while prostatitis development was observed in six (4.1%) of 146 patients without ciprofloxacin resistance. Ciprofloxacin sensitivity was detected in the rectal swabs of six (54.5%) of 11 patients who developed prostatitis while ciprofloxacin resistance was detected in the rectal swabs of five other patients (45.5%). There was no statistical difference in prostatitis development between two groups of patients with and without ciprofloxacin resistance in rectal swabs (p=0.803). Although there are different findings and opinions on this issue in the literature, the data of this study suggest that the development of prostatitis after TRUS is independent of possible ciprofloxacin resistance that will be detected because of the rectal swab, and that rectal swab culture is insufficient to predict the development of prostatitis.

An important issue examined in this study was whether ESBL positivity was effective in predicting the development of prostatitis. A study conducted in Korea reported the incidence of ESBL-secreting *E. coli* and *Klebsiella* as 3.8% and 1%, respectively (32). This study determined the rates of ESBL-secreting *E. coli* and *Klebsiella* as 3% and 25%. The rate of ESBL-positive *E. coli* in rectal swabs was found as 19% in another prospective study conducted with 400 patients in 2014 (33). However, no statistically significant difference was found between the development of prostatitis after biopsy and ESBL positivity in rectal swabs. This study detected ESBL-positive bacteria in rectal swabs of 12 (4.7%) of 251 patients (9 *E. coli*, 3 *Klebsiella*). ESBL positivity rate was 5% in the group of patients who did not develop prostatitis after biopsy, while all patients who developed prostatitis were found to be ESBL negative (p=0.447). The results of the study that ESBL positivity detected in rectal swab did not affect the development of prostatitis were consistent with the literature.

Although the findings discussed so far in this study show that the antibiogram study with rectal swabs and goal-oriented antibiotic prophylaxis is not effective, it is a fact that we are

Table 6. Comparison of prostatitis development and antibiotics resistance/sensitivity in rectal swab and urine cultures

		Urine	Rectal	Test statistic	p
Amoxicillin	Sensitive	3 (27.3%)	4 (36.4%)	Z=-0.46	0.646
	Resistant	8 (72.7%)	7 (63.6%)		
Ciprofloxacin	Sensitive	3 (27.3%)	6 (54.5%)	Z=-1.35	0.176
	Resistant	**8 (72.7%)**	5 (45.5%)		
Ceftriaxone	Sensitive	7 (63.6%)	9 (81.8%)	Z=-0.98	0.328
	Resistant	4 (36.4%)	2 (18.2%)		
TMP-SMX	Sensitive	5 (45.5%)	10 (90.9%)	Z=-2.62	0.009
	Resistant	6 (54.5%)	1 (9.1%)		
Ceftazidime	Sensitive	7 (63.6%)	10 (90.9%)	Z=-1.61	0.107
	Resistant	4 (36.4%)	1 (9.1%)		
Phosphomycine	Sensitive	10 (90.9%)	11 (100%)	Z=-1.05	0.294
	Resistant	**1 (9.1%)**	0 (0%)		
Cefoxitin	Sensitive	7 (63.6%)	11 (100%)	Z=-2.51	0.012
	Resistant	4 (36.4%)	0 (0%)		
Cefazolin	Sensitive	4 (36.4%)	10 (90.9%)	Z=-3.23	0.001
	Resistant	7 (63.6%)	1 (9.1%)		
Gentamicin	Sensitive	9 (81.8%)	11 (100%)	Z=-1.56	0.118
	Resistant	2 (18.2%)	0 (0%)		

Frequency (percentage), χ^2: Chi-square test statistic, TMP-SMX: Trimethoprim sulfamethoxazole

faced with a serious resistance to ciprofloxacin. It was found that the resistance rates to fosfomycin (9.1%), ceftazidime (36.4%) and ciprofloxacin (72.7%) in urine cultures in the group of patients who develop prostatitis are similar to the resistance rates found in rectal swabs taken in general. Considering the rectal swab culture resistance rates of the patients evaluated in this study, it was found that resistance rates to fosfomycin, ceftriaxone, ceftazidime and gentamicin were significantly lower than quinolone resistance in accordance with the literature. Thus, the use of non-quinolone antibiotics is necessary to pre-TRUS prophylaxis. However, studies evaluating this subject in a prospective randomized controlled manner are needed to determine the correct prophylaxis.

Study Limitations

The limitation of our study is all the patients with serum PSA below 4 ng/mL were not subjected to TRUS-Bx. Hence the sensitivity, specificity, positive and negative predictive values for PSA cut off of 4 ng/mL is not accurate in this study. The other limitation of our study, the antibiotic taken 1 day before the rectal swab culture may affect the results.

Conclusion

In the selection of prophylactic antibiotics for prostate biopsy result, which is the gold standard in the diagnosis of prostate cancer, antibiotic resistance via rectal swab culture taken before the procedure and/or goal-oriented antibiotic prophylaxis applied with ESBL do not affect the development of prostatitis after biopsy in patients. Although the contribution of goal-oriented prophylaxis administration has not been determined, the detection of high ciprofloxacin resistance found in the swab culture results in this study and the similarly high ciprofloxacin-resistant microorganism in patients with prostatitis revealed that the use of ciprofloxacin in prophylaxis should be seriously questioned. Although resistance to fosfomycin, ceftriaxone, ceftazidime, and gentamicin is been significantly lower than quinolone resistance, prospective randomized controlled trials on this issue are needed to determine the correct pre-TRIB prophylaxis.

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Ethics

Ethics Committee Approval: Approval for the study was obtained from Ondokuz Mayıs University Clinical Research Ethical Committee (approval no: 2015/16, date: 12.02.2015).

Informed Consent: Written informed consent was obtained from all patients who agreed to participate in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A., Design: E.A., M.K., Supervision: M.A., Ö.G., M.K.A., L.I., Data Collection or Processing: A.B., Analysis-Interpretation: S.G., Writing: E.A.

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