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Is there any effect of long term alpha-adrenergic blocker and a single dose antibiotic usage in reducing febrile urinary tract infections after prostate biopsy?

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ABSTRACT

Aim: To investigate whether the using long term alpha-adrenergic blockers before biopsy has an effect on preventing febrile urinary tract infections (FUI) secondary to biopsy in patients undergoing prostate biopsy due to elevated prostate specific antigen (PSA) .

Material and Method: The data of 2558 patients who underwent transrectal ultrasonography-guided prostate biopsy (TRUS+BX) due to elevated PSA in our clinic between January 2008 and July 2021 were analyzed retrospectively. The patients were divided into two groups as those who used alpha-blockers for a minimum of three months or longer before biopsy (Group 1) and those who did not use alpha-blockers before applying to the outpatient clinic (Group 2) . Demographic data of the groups and post-biopsy FUI development rates were compared.

Results: It was observed that 1340 (52.4%) of the patients were using alpha-blockers (Group 1) and 1218 (47.6%) did not (Group 2) . The median age of the patients in the pre-biopsy groups was similar [Group 1=68 (IQR=9) years and Group 2=68 (IQR=9) years, p=0.887]. There was no significant difference between the groups in terms of median prostate volume [Group1=57 (31) ml and Group 2=58 (34) ml, p=0.199]. The median PSA value was found to be significantly higher in Group 1 than in Group 2 [10.50 (5.40) ng/dl vs 10.35 (6.80) ng/dl, p=0.026]. Postvoid residual urine volume (PVR) was found to be significantly higher in Group 2 [Group 1=40 (30) ml and Group2=60 (90) ml, p<0.001]. Similarly, the frequency of FUI development after biopsy was found to be significantly higher in Group 2 [Group 1=17 (1.3%) and Group 2=65 (5.3%) , p<0.001].

Conclusion: The use of alpha-adrenergic blockers for a minimum of three months or longer before prostate biopsy significantly reduces the incidence of FUI that may develop secondary to biopsy.

Keywords: Urinary tract infection, prostate, core needle biopsy

INTRODUCTION

Prostate cancer is the most common type of cancer in elderly men and ranks sixth among the causes of death from cancer (1). Today, although the development of radiological imaging methods helps to diagnose prostate cancer, the definitive diagnosis is made with transrectal ultrasound-guided prostate biopsy (TRUS+BX) (2). Although prostate biopsy is also taken transperineally in some centers, the transrectal route is still routinely used (3). Prostate biopsy is an invasive procedure and causes mini-perforation and injury in the rectal mucosa and surrounding tissues. Therefore, minor complications such as hematuria, dysuria, rectal bleeding and hematospermia are frequently observed after a biopsy (4). However, FUI that can develop after TRUS+BX is a severe complication and may result in sepsis (5). For this reason, antibiotic prophylaxis is routinely applied before biopsy in many centers (6). It has been shown in many studies that antibiotic prophylaxis performed before TRUS+BX significantly reduces FUIs that may develop after biopsy (7). While a significant portion of the patients diagnosed with prostate cancer consist of patients using alpha-blocker medication due to lower urinary tract symptoms (LUTS), some of them are patients who have not started medical treatment yet and who have had a biopsy due to primarily elevated PSA levels. Numerous studies have shown that alpha-blocker drugs relax prostatic smooth muscle fibers, increase voiding rate (Q-max), decrease postvoid residual urine volume (PVR), and

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provide significant improvement in LUTS (8). It is also a known fact that alpha-blocker drugs make a significant contribution to the prevention of chronic prostatitis and lower urinary tract infections (9). There is not enough literature yet on whether alpha-blocker drugs have any effect on FUI developing after prostate biopsy. Therefore, in this study, we aimed to indicate whether the use of alpha-blockers for a minimum of three months or longer before TRUS+BX has an effect on preventing FUIs that may develop secondary to biopsy.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Keçiören Training and Research Hospital Ethics Committee (Date: 14.09.2021, Decision No: 2012-KAEK-15/2370). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Data Collection

The data of 2558 patients who underwent TRUS+BX due to PSA elevation in our clinic between January 2008 and July 2021 were analyzed retrospectively. The patient record information in the biopsy registry of our clinic and the electronic data system of our hospital and the information in the hospitalization file were used to collect the data. The patients were divided into two groups as those who used alpha-blockers for a minimum of three months or longer (long-term) before the biopsy (Group 1) and those who did not use alpha-blockers before applying to the outpatient clinic (Group 2). Patients who could not obtain sufficient data on whether they were using alpha-blockers or who had irregular drug use were excluded from the study. The urinalysis and urine cultures of the patients who applied to the outpatient clinic and were found to have elevated PSA were examined for possible urinary tract infection. Antibiotic treatment+alpha blocker was initiated in accordance with the antibiogram sensitivity test in patients with bacterial growth in urine culture. Alpha-blocker was initiated in patients who did not have symptoms of urinary tract infection and did not have bacterial growth in urine culture. Patients with bacterial growth in their urine culture and who did not show a significant decrease in PSA level after antibiotic treatment were prepared for biopsy. On the other hand, a single dose of prophylactic antibiotic treatment was administered before biopsy in patients with elevated PSA levels and only alpha-blocker therapy. Except for PSA elevation, MRI was requested beforehand, and as a result, patients who underwent biopsy with suspicion of cancer were excluded from the study. To exclude confounding factors in our research, we also excluded patients with prostate volumes greater than 100 ml, which may cause elevated PSA. Additionally, the study did not include patients with upper urinary tract or bladder stones, urethral stenosis, previous transurethral prostate surgery, upper urinary tract or bladder tumors, and a neurogenic bladder history. Age, PSA level, prostate volume, Q-max and PVR value, pathological findings of TRUS-BX, presence of hypertension (HT) and diabetes mellitus (DM), presence of urethral catheterization and previous biopsy history of the patients in both groups were determined and recorded.

Biopsy Procedure

Two days before the biopsy, routine urine analyzes and urine cultures of all patients were performed and active urinary tract infection was ruled out. Anticoagulant drugs of the patients were discontinued one week before the biopsy if they were using. Before the biopsy procedure, the patients were informed in detail about the procedure, and patient consent forms were obtained and retained. Prophylactic single dose oral 500 mg ciprofloxacin or a single dose oral 1 gr 3rd generation cephalosporin prophylaxis was administered to all patients about 12 hours before the biopsy. Rectal swab was achieved by performing a rectal enema (fleet-enema) in all patients just before the biopsy. The patients were placed in the lateral decubitus position and all biopsies were performed using a 22 gauge biopsy needle under the guidance of transrectal ultrasound (Philips, Logiq C-2). The biopsy procedure was performed under periprostatic local anesthesia (lidocaine, prilocaine) in accordance with the recommendations of the European Association of Urology (EAU) guideline, and 12 core biopsies were taken (10).

Follow-up and Complication Management

After the biopsy, the patients were especially informed about AUE and followed closely. The patients were also informed about possible complications such as hematuria, dysuria, rectal bleeding, and hamatospermia, and these complications were followed up and treated as an outpatient without the need for hospitalization. Patients presenting with a high fever after biopsy were hospitalized and followed closely because of possible sepsis. Intravenouz catheterization was established for these patients, appropriate hydration was provided, and empirical intravenous ceftriaxone 2×1 and appropriate analgesic treatment was ordered. CBC, biochemical analyzes, urine analysis and urine cultures of patients hospitalized for FUI were studied and followed-up. The patients with bacterial growth in their urine culture were evaluated according to the antibiogram sensitivity results and their antibiotic treatments were rearranged. The groups were compared in terms of demographic data, minor complications after biopsy and incidence of FUI.

Statistical Analysis

Data were analysed using SPSS 24.0 (IBM Corp., Armonk, NY, USA) software. The Kolmogorov-Smirnov test was used to assess the distribution of parameters. Median and interquartile range were used for describing data. Chi-Square Test was used for nominal data, while the Mann-Whitney U-test was used for nonparametric variables. Statistical significance was set at $p<0.05$.

RESULTS

It was determined that 1340 (52.4%) of the patients included in the study were using alpha-blockers (Group 1), while 1218 (47.6%) were not (Group 2). The median age of the patients was 68 (9) years, and the median prostate volume was 57 (33) ml. It was observed that 82 (3.2%) of the patients were hospitalized and treated for FUI that developed after biopsies (**Table 1**). While the median prostate volume was 57 (31) ml in Group 1, it was 58 (34) ml in Group 2 (p=0.199). While the median PSA value was 10.50 (5.40) ng/dl in Group 1, it was 10.35 (6.80) ng/dl in Group 2 (p=0.026). There was no significant difference between the groups in terms of median Q-max values [Group 1=13 (5)ml/sec and Group 2=13 (5) ml/sec ,p=0.833]. The median pre-biopsy PVR value was found to be significantly lower in Group 1 compared to Group 2 [40 (30) ml and 60 (90) ml, p<0.001] (**Table 2**).

Within the first month after biopsy, FUI was observed in 17 (1.3%) patients in Group 1, while it was developed in 65 (5.3%) patients in Group 2 (p<0.001). The number of bacterial growth in the urine cultures of patients who developed FUI was also found to be significantly higher in Group 2 than in Group 1 [43 (4%) vs 13 (1%), p<0.001]. There was no significant difference between Group 1 and Group 2 in terms of minor complications observed after biopsy [hematuria= 551 (41.1%) vs 498 (40.9%), rectal bleeding= 218 (16.3%) vs 194 (15.9%), hematospermia=260 (19.4% vs 238 (19.5), acute urinary retention (AUR)=196 (14.6) vs 175 (14.4), p=0.905, p=0.775, p=0.930 and p=0.895, respectively] (**Table 3**, **Graphic 1**). Post-biopsy PVR volume was found to be significantly lower in Group 1 than in Group 2 [35 (30) ml vs 65 (80) ml, p<0.001]. According to the pathological findings, prostate adenocarcinoma was detected in 398 (30%) patients in Group 1, while cancer findings were detected in 366 (30%) patients in Group 2 (p=0.863). In addition, chronic prostatitis was detected in 123 (8%)patients in Group 1, while it was found in 123 (10%) patients in Group 2 (p=0.036) (**Table 4**).

Table 1: Characteristics and complications of the patients

Age, Median (IQR), years	68 (9)
PSA, Median (IQR), ng/dl	10.4 (5.8)
Prostate volume, Median (IQR), ml	57 (33)
Q-max, Median (IQR), ml/sec	13 (5)
PVR, Median (IQR), ml	40 (42.5)
Alpha- blocker, n (%)	
User	1340 (52.4)
Non-user	1218 (47.6)
Prophylaxy, n (%)	
FQ	1440 (56.3)
3rd Gen-Cephalosporine	1118 (43.7)
HT, n (%)	
(+)	1112 (43.5)
(-)	1446 (56.5)
DM, n (%)	
(+)	452 (17.7)
(-)	2106 (82.3)
Urethral catheter, n (%)	
(+)	108 (4.2)
(-)	2450 (95.8)
Secondary Biopsy, n (%)	
(+)	120 (4.6)
(-)	2438 (95.4)
FUI, n (%)	
(+)	82 (3.2)
(-)	2476 (96.8)
Urine culture growth, n (%)	
E. coli	19 (0.7)
ESBL (+) *E. coli*	14 (0.5)
Klebsiella	5 (0.2)
Enterobacter	7 (0.3)
Enterococcus	5 (0.2)
Pseudomonas	6 (0.2)
Hematuria, n (%)	
(+)	1049 (41)
(-)	1509 (59)
Rectal bleeding, n (%)	
(+)	413 (16.1)
(-)	2145 (83.9)
Hematospermia, n (%)	
(+)	498 (19.5)
(-)	2060 (80.5)
AUR, n (%)	
(+)	370 (14.5)
(-)	2188 (85.5)

IQR: Interquartile range, PSA:Prostate specific antigen, Q-max: Maximum urine flow, PVR: Post-void residual urine volume, FQ: Fluorokinolone, HT: Hypertension, DM: Diabetes mellitus, FUI: Febrile urinary tract infection, *E. coli*: Escherichia Coli, ESBL (+) *E. coli*: Extended-spectrum beta-lactamase producing Escherichia Coli, AUR: Acute urinary retention

Table 2. Characteristics and pre-biopsy findings of the groups

	Group 1 (n=1340)	Group 2 (n=1218)	p
Age, Median (IQR), years	68 (9)	68 (9)	0.887
PSA, Median (IQR), ng/dl	10.50 (5.40)	10.35 (6.80)	0.026
Prostate volume, Median (IQR), ml	57 (31)	58 (34)	0.199
Q-max, Median (IQR), ml/sec	13 (5)	13 (5)	0.833
PVR, Median (IQR), ml	40 (30)	60 (90)	<0.001
Prophylaxy, n (%)			0.895
FQ	756 (56.4)	685 (56.2)	
3 rd Gen-Cephalosporine	584 (43.6)	533 (43.8)	
HT, n (%)	582 (43.4)	530 (43.5)	0.967
DM, n (%)	239 (17.8)	214 (17.6)	0.899
Urethral catheter, n (%)	56 (4.2)	51 (4.2)	0.988
Secondary Biopsy, n (%)	60 (4.5)	58 (4.8)	0.725

IQR: Interquartile range, PSA:Prostate specific antigen, Q-max: Maximum urine flow, PVR: Post-void residual urine volume, FQ: Fluorokinolone, HT: Hypertension, DM: Diabetes mellitus

Table 3. Post-biopsy findings and complications of the groups

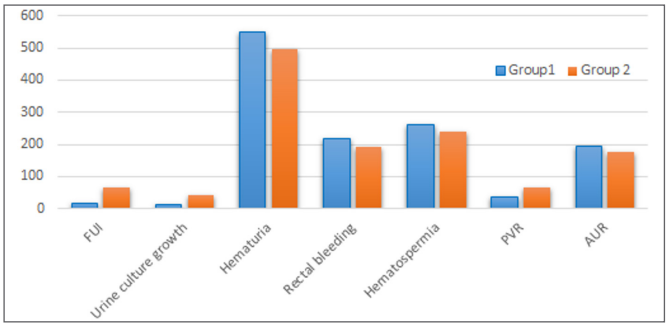
	Group1 (n=1340)	Group 2 (n=1218)	p
FUI, n (%)	17 (1.3)	65 (5.3)	<0.001
Urine culture growth, n (%)	13 (1)	43 (4)	<0,001
E. coli, n	4	15	
E. coli (ESBL+), n	4	10	
Klebsiella, n	1	4	
Enterobacter, n	3	4	
Enterococcus, n	0	5	
Pseudomonas, n	1	5	
Hematuria, n (%)	551 (41.1)	498 (40.9)	0.905
Rectal bleeding, n (%)	218 (16.3)	194 (15.9)	0.775
Hematospermia, n (%)	260 (19.4)	238 (19.5)	0.930
PVR, Median (IQR), ml	35 (30)	65 (80)	<0.001
AUR, n (%)	196 (14.6)	175 (14.4)	0.895

FUI: Febrile urinary tract infection, *E. coli*: Escherichia Coli, ESBL (+) *E. coli*: Extended-spectrum beta-lactamase producing Escherichia Coli, AUR: Acute urinary retention, PVR: Post-void residual urine volume.

Table 4. Pathological findings of the Groups

	Group 1 (n=1340)	Group 2 (n=1218)	p
BPH, n (%)	813 (61)	707 (58)	0.184
Chronic prostatitis, n (%)	103 (8)	123 (10)	0.036
HG-PIN, n (%)	14 (1)	12 (1)	1
ASAP, n (%)	12 (0.9)	10 (0.8)	1
Prostate adenocarcinoma, n (%)	398 (30)	366 (30)	0.863

BPH: Benign prostate hyperplasia, HG-PIN: Hıgh grade prostatic intraepithelial neoplasia, ASAP: Atypical Small Acinar proliferation



Graphic 1. Post-biopsy complications of the groups

FUI: Febrile urinary tract infection, PVR: Post-void residual urine volume, AUR: Acute urinary retention.

DISCUSSION

FUI is one of the most important complications observed after TRUS+BX procedure for the diagnosis of prostate cancer. If the infection is not intervened in a timely and correct manner, it can lead to serious life-threatening consequences that progress to septic shock (5). Mini-perforation in the rectal mucosa during biopsy and direct inoculation from there to the blood or urinary system, or inoculation of an abscess or infection focus in the prostate tissue are the main sources of infection (11). Studies have shown that up to 70% of patients develop bacteremia after biopsy (12,13). Therefore, rectal enema or rectal washing applications and antibiotic prophylaxis procedures have been established to prevent FUIs that may develop after biopsy. Hwang et al. (14) reported that FUI developed after biopsy in 16 (2%) patients in their retrospective study, in which they examined the results of 841 patients in whom they performed TRUS+BX. In this study, it was reported that rectal cleansing with povidone-iodine significantly reduced the rate of severe FUI compared to the group without rectal cleansing (0.3 vs 3.5%, p=0.001). In the study conducted by Kalkanlı et al. (15) in 400 patients, patients given a single dose of 750 mg oral ciprofloxacin before TRUS+BX and the patient groups given 500 mg oral ciprofloxacin for a total of 7 days after biopsy were compared . According to this study, it was reported that there was no significant difference between the groups in terms of infection that developed after biopsy in a total of 4 weeks of follow-up (single dose: 3% vs prolonged 3%, p>0.05). In another study conducted by Choi et al. (16) in a total of 1,995 patients, it was emphasized that FUI was seen in 39 (3.1%) patients after TRUS+BX and that quinolone resistance was the most important factor in developing infections (p=0.014), therefore the necessity of finding alternative prophylactic agents . In a retrospective study by Wu et al. (17) reported the results of 1,523 biopsy patients, fluoroquinolone (FQ) monotherapy, third-generation cephalosporin combined with FQ, and antibiotic groups started according to rectal swab culture results were compared in terms of the development of infection after biopsy. In this study, it was reported that the combined treatment provided a significant advantage in preventing post-biopsy infection from the FQ monotherapy group (1.0% vs 4.0%, p<0.001). In the same study, it was reported that there was no significant difference in the development of FUI between the antibiotic group started according to rectal swab culture and the FQ monotherapy group (p=0.349). According to the univariate analysis of this study, obesity was shown to be an important risk factor in terms of post-biopsy infection (OR=12.827, 95% CI:0.983-8.925, p=0.001). In our study, however, prophylactic combined antibiotic therapy was not used in any patient , and there was no difference in the frequency of prophylactic single

dose FQ or single dose 3rd generation cephalosporin use between the groups. It has been reported that the maximum effect of alpha-blockers occurs 4-6 weeks after the start of treatment (18). Under the guidance of this information, we included patients who used drugs for a minimum of 3 months or longer, assuming that the maximum effect of alpha-blocker drugs began in our study (Group 1). Our study observed that the use of alpha-adrenergic blockers for a minimum of three months or longer before the biopsy in addition to single-dose prophylaxis significantly decreased the frequency of FUI developing after biopsy.

Alpha-blockers constitute the most widely used first-line medical treatment option to reduce LUTS secondary to benign prostatic hypertrophy (BPH) (19). In addition to eliminating LUTS symptoms, alpha-blockers eliminate the need for surgical intervention in many patients with the significant increase in Q-max and a decrease in PVR (20). Alpha-1 adrenergic receptor blockers eliminate storage and obstructive symptoms by acting on both alpha-1a receptors in prostate tissue and alpha-1b receptors in the bladder (21). Masumori et al. (22) started tamsulosin 0.2 mg/day in a total of 112 patients with LUTS symptoms and reported 5-year follow-up results. According to their study, the mean international prostate symptom score (IPSS) of the patients decreased from 17.7±6.1 to 12.6±6.0 ($p<0.001$) after five years of follow-up, and the mean quality of life index (QOL) from 4.2±1.1 to 2.7±1.3, and It was reported that significant improvement was achieved ($p<0.0001$). Alpha-blockers have an important place in the literature in the treatment of non-bacterial or bacterial prostatitis as well as LUTS symptoms. Nickel et al. (23) conducted a study on 58 patients with chronic prostatitis/chronic pelvic pain syndrome and showed that the improvement in the group who received 0.4mg tamsulosin daily for 6 weeks was significantly higher than that of placebo ($p=0.04$). In another study, Barbalias et al. (24) showed the effectiveness of alpha-adrenergics in preventing recurrence in a 22-month follow-up of a patient with Category-2 chronic bacterial prostatitis, including 64 patients. According to this study, the recurrence rate was 41% in the antibiotic+alpha-blocker group, while it was 88% in the antibiotic-only group .

As stated in the studies highlighted above, many treatment and prophylaxis modalities have been described to prevent FUI after TRUS+BX. However, there is not yet sufficient literature data on alpha-blockers in this area. One of the most important factors of AUE developing after TRUS+BX is prostatic abscess and possible bacterial growth in this abscess (11). The fact that the frequency of FUI developing after biopsy was significantly lower in the group using long-term alpha-blockers in our study supports the idea that these drugs reduce the possibility of infection by facilitating the drainage of bacterial abscess focus present in the prostate tissue. In addition, the fact that the presence of chronic prostatitis in Group 1 was significantly lower than Group 2 in the pathology findings of our study can be considered as another factor supporting this idea.

According to the EAU guideline information, a PVR value of more than 50 ml can be evaluated in favor of the presence of obstruction (25). Numerous studies have shown that alpha-blockers reduce PVR volume in patients with LUTS symptoms (26,27). Consistent with the literature data, pre-biopsy and post-biopsy PVR volumes were found to be significantly lower in the group using long-term alpha-adrenergic blockers in our study. High PVR volume is another important factor that predisposes the patient to lower urinary tract infection (28). The decrease in PVR volume by using long-term alpha-adrenergic blockers can be considered as another factor contributing to the prevention of FUI that may develop after biopsy. On the other hand, post-biopsy AUR rates were found to be similar between the groups in our study. In our study, although the post-biopsy PVR value was significantly higher in Group 2, we think that the antibiotic and alpha-blocker treatment that we started before the biopsy may be a preventive factor for AUR, and therefore, there was no significant difference between the groups in terms of the development of AUR in the post-biopsy period.

Limitations: The most important limitation of the study is its retrospective nature. Another limitation can be considered as the fact that the contribution to the post-biopsy FUI could not be evaluated due to the unknown duration of catheterization of patients with bladder catheters before the biopsy. The need for catheterization after biopsy and the effect of catheterization on the development of post-biopsy FUI could not be determined, can be considered as another limitation. However, we believe that the fact that the number of patients included in the study is quite high compared to the literature data will increase the contribution of our study to the scientific literature.

CONCLUSION

In our study, the frequency of FUI developing after TRUS+BX in patients using alpha-adrenergic blockers for a minimum of three months or longer before the biopsy was found to be significantly lower than the non-user group. Alpha adrenergic blockers recommended as first-line medical therapy to reduce LUTS symptoms. Long-term usage of these drugs could make a significant contribution to the reduction of possible FUI that may develop after TURS+BX for prostate cancer diagnosis.

The fact that the alpha-adrenergic blockers relax the prostate smooth muscle and bladder neck and facilitate prostatic abscess drainage may explain their contribution in preventing infection. In addition, the usage of long-term alpha adrenergic blockers prevent possible urinary infection focus by reducing the PVR volume can be considered as another additional factor causing this result.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Keçiören Training and Research Hospital Ethics Committee (Date: 14.09.2021, Decision No: 2012-KAEK-15/2370).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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