RESEARCH ARTICLE / Araştırma Makalesi

Acute Prostatitis Incidence In Patients Receiving Prophylactic Ceftibuten and Gentamicin Before Prostate Biopsy

Prostat Biyopsisi Öncesi Profilaktik Seftibuten ve Gentamisin Uygulanan Hastalarda Akut Prostatit Sıklığı

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Abstract

Aim We aimed to investigate the incidence and characteristics of acute prostatitis after transrectal prostate biopsy in men who were given prophylactic ceftibuten combined with gentamicin. **(Sakarya Med J 2018, 8(3):489-496)**

Methods We analyzed the retrospective data from 245 patients who underwent transrectal ultrasound (TRUS) guided prostate biopsy over a 2 year period. Men in which acute prostatitis occurred after the procedure were investigated. All patients received 400 mg ceftibuten orally once daily for 5 days, beginning 12 and 2 hours before biopsy; combined with single dose 160 mg gentamicin intramuscularly just before the procedure. All biopsies were performed as outpatient procedures.

Results Of the 245 cases, acute prostatitis developed in 2 (0,8%). Escherichia Coli that was positive for extended spectrum -lactamase activity was isolated both from blood and urine in 1 case. The bacteria detected in urine and blood cultures were resistant to ciprofloxacin, levofloxacin, gentamicin, cefepime, ceftriaxone and cefuroxime. However, no bacteria was isolated either from blood or urine in the other case. Both patients had acute prostatitis after the first biopsy.

Conclusion Prophylactic ceftibuten combined with single dose gentamicin seems effective in preventing acute bacterial prostatitis after TRUS-guided prostate biopsy. Due to increasing rate of quinolone resistance among the world, alternative prophylaxis regimens including cephalosporins such as ceftibuten should be considered in men undergoing prostate biopsy. Prospective randomized trials with larger series may give more conclusive data.

Keywords Acute bacterial prostatitis; Antibiotic prophylaxis; Ceftibuten; Core Needle Biopsy

Öz

Amaç Profilaktik seftibuten, gentamisin kombinasyonu verilen erkeklerde transrektal prostat biyopsisi sonrası akut prostatitin insidansını ve özelliklerini araştırmayı amaçladık. **(Sakarya Tıp Dergisi 2018, 8(3):489-496).**

Yöntem Transrektal ultrasonografi (TRUS) eşliğinde prostat biyopsisi yapılan 245 hastanın 2 yıllık bir süre içinde retrospektif verileri incelendi. İşlemden sonra akut prostatit gelişen erkekler araştırıldı. Tüm hastalara biyopsiden 12 ve 2 saat önce başlamak üzere 5 gün boyunca günde bir kez 400 mg ceftibuten verildi; buna ek olarak prosedürden hemen önce, tek doz 160 mg gentamisin intramüsküler olarak yapıldı. Tüm biyopsiler ayakta tedavi prosedürü olarak gerçekleştirildi.

Bulgular 245 olgunun 2'sinde (% 0,8) akut prostatit gelişti. Genişlemiş spektrumlu -laktamaz aktivitesi pozitif olan Escherichia Coli, 1 olguda hem kan hem de idrardan izole edildi. İdrar ve kan kültürlerinde tespit edilen bakteri siprofloksasin, levofloksasin, gentamisin, sefepim, seftriakson ve sefuroksime dirençliydi. Bununla birlikte, diğer olguda kan veya idrardan hiçbir bakteri izole edilmedi. Her iki hastada da ilk biyopsi sonrası akut prostatit geliştiği görüldü.

Sonuç Tek doz gentamisin ile kombine profilaktik seftibuten, TRUS kılavuzluğunda prostat biyopsisi sonrası akut bakteriyel prostatitin önlenmesinde etkili görünmektedir. Dünyada kinolon direncinin artması nedeniyle, prostat biyopsisi yapılan erkeklerde seftibuten gibi sefalosporinleri içeren alternatif profilaksi rejimleri düşünülmelidir. Bu konuda daha büyük serili prospektif randomize çalışmalar daha kesin veriler verebilir.

Anahtar Kelimeler Akut bakteriyel prostatit; Anitibiyotik profilaksisi; Seftibuten; İğne biyopsi

Introduction

Prostate cancer is an important public health problem in the male population. It is the most often seen cancer type in men, and takes second place in cancer-related deaths, after lung cancer.

Transrectal needle biopsy (TRNB) has become the standard diagnostic procedure for prostate cancer, and today is the most widely used and most reliable procedure for diagnosis. However, TRNB is highly traumatic and has potential for infectious complications, which cannot be neglected. Unwanted side effects following this operation may preclude ambulatory treatment and require inpatient treatment.

Antibiotic prophylaxis before a transrectal prostate biopsy can reduce infectious complications.[1] In both the guidelines of the Europe Urology Society (EAU) and the American Urology Association (AUA), routine antibiotic prophylaxis has been recommended. Various prophylactic antibiotic regimes, oral and intravenous, have been examined to date, but there is no agreement on antibiotic use or the selection of agents.

In this study, we examined the effects of ceftibuten in combination with gentamicin given before prostate biopsy on the prevention of acute prostatitis.

Materials and Methods

After approval by the Ethics Committee (Institutional Review Board) of the Faculty of Medicine, Bülent Ecevit University we designed a retrospective cohort study and included 254 patients with high prostate-specific antigen (PSA) and/or who underwent a needle biopsy guided with transrectal ultrasonography (TRUS) because of an abnormal digital rectal exam and treated with ceftibuten for antibiotic prophylaxis in the pre-operation period from December 2011 to April 2013 in our clinic. Patients treated with antibiotics other than ceftibuten were not included.

Prostate biopsy indications were patients with abnormal findings on rectal exam and/or with a PSA value greater than 2.5 ng/mL and findings of high-grade prostatic intraepithelial neoplasia(HGPIN) and atypical small acinar proliferation(ASAP) on previous biopsy pathological examinations. Patients with urinary tract infections related to resistant microorganisms, with urethral catheters, with heart valve prostheses, and rectal stenosis, all of which may increase the risk of infective complications, were excluded

As an antibiotic prophylaxis, 12 and 2 h before the biopsy operation, single-dose oral ceftibuten 400 mg tablets and a daily dose of a single tablet for 5 days after completing the therapy was given. Other than this, immediately before the operation, a single dose of gentamicin 160 mg was injected intramuscularly.

No bowel prep was done for any patient. A rectal topical gel with lidocaine was used for local anesthesia before the biopsy operation.

Before the biopsy, the prostate was examined in transverse and sagittal axial planes, by forwarding the ultrasound probe up to the seminal vesicles. They were assessed according to their size, symmetry, and other characteristics. Then, as the probe was pulled out slowly, the zonal anatomy

and ultrasonographic characteristics of the tissue were examined from the bottom to the top of the prostate. The size and volume of the prostate gland were measured and recorded.

To perform the biopsy, an 18 gauge, 25 cm long biopsy needle, a biopsy attachment, and an appropriate biopsy gun were used. Some biopsies were conducted with 10 cores (traditional six-pack + four focal peripheral) and some with 12 cores (traditional six-pack + six focal peripheral).

Each biopsy sample taken from a different focus was put into a separate bottle containing 10% formalin as fixative and sent for pathological examination as soon as possible. The localization of each biopsy taken was indicated for mapping.

Patients were informed about the complications that may develop post-biopsy. When the patients came back for their pathology results, they were asked about any complications.
Patients with acute prostatitis secondary to the prostate biopsy were identified as follows:
• Fever >38°C together with or without chills and shivering.
• Having prominent lower urinary system symptoms.
• Having no infection focus other than the prostate.

Statistical analyses were carried out using the SPSS software (ver. 13.0). Site measurement variables are reported as averages (mean), medians, standard deviations, and minimum and maximum values, and categorical variables are reported as frequencies and percentages. Conformance of the measured variables to a normal distribution was tested with the Shapiro-Wilk test. For comparing two groups of variables showing a normal distribution, the Mann-Whitney U-test was used. For group comparisons of categorical variables, Pearson's 2 test was used. In all statistical analyses, p values < 0.05 were considered to indicate statistical significance.

Results

In total, 245 patients underwent TRNB. They were aged between 46 and 85 years, with serum levels of PSA between 2.49 and 3048 ng/mL. After digital rectal examination, pathological findings (abnormality, hardness, nodules on the prostate) were determined in 76 (31%) patients.

In the pathology results, 36 (14.7%) patients had adenocarcinomas, 145 (59.2%) had benign prostate hyperplasia and chronic prostatitis, and 64 (26.1%) had ASAP.

In total, 179 patients did not use any antibiotics to lower PSA before the operation. The numbers of patients using quinolone antibiotics were 6 (2.4%) for 1 week, 27 (11%) for 2 weeks, 26 (10.6%) for 3 weeks, and 7 (2.9%) for 4 weeks. No statistically significant differences were found between the groups using antibiotics for lowering PSA and the group not using antibiotics from the point of view of PSA levels. Table 1

The biopsy-positive rate was 9.1% in 66 patients who used antibiotics for PSA and 16.8% in those who did not. Antibiotic use and histopathological examination results are shown in Table 1. In 2 (0.8%) patients who underwent biopsies, acute prostatitis developed.

On histopathological examination of each of the two patients who developed acute prostatitis,

prostatic adenocarcinoma Gleason scores of 3+3 were found. This was the first biopsy of each patient. In one patient's blood and urine culture, no growth occurred, while in the other, Extended-spectrum beta-lactamases (ESBL)-positive Escherichia coli growth occurred. The patient with positive blood and urine cultures had used a quinolone antibiotic (levofloxacin) for 2 weeks, while the other whose cultures showed no growth had not used an antibiotic. On an antibiogram test of the patient with growth in blood and urine cultures, sensitivity to imipenem and ertapenem was seen, as was resistance to ceftriaxone, levofloxacin, and ciprofloxacin. Table 2

Table1. Relationship between antibiotic use for lowering PSA and PSA level, PSA intervals and histopathological examination results. (p = 0.99).

Antibiotic use to reduce PSA	n	PSA Level (ng/ml) (Min-Max)	PSA Intervals (ng/ml)					Results of the histopathological examination		
			<2,5 (n)	2,5-4 (n)	4-10 (n	10-20 (n)	>20 (n)	BPH and Chronic Prostatitis n (%)	ASAP n (%)	Malign n (%)
Yes	66	13.01 (2.49-66.0)	1	0	34	22	9	42 (63.6)	18 (27.3)	6 (9.1)
No	179	41.41 (2.89-3048)	0	9	108	36	26	103 (57.5)	46 (25.7)	30 (16.8)
TOTAL	245	33.7 (2.49-3048)	1	9	142	58	35	145 (59.2)	64 (26.1)	36 (14.7)

(PSA: Prostate Spesific Antigen, BPH: Benign Prostate Hyperplasia, ASAP: Atypical Small Acinar Proliferation)

Table 2.Antibiogram of patient whose urine and blood cultures showed ESBL-positive, E. coli growth

Antibiotic	Urine culture	Blood culture
Amikacin	Susceptible	Susceptible
Amoxicillin - ClavulanicAcid	Susceptible	Susceptible
Ampicillin	Resistant	Resistant
Cefoxitin	Susceptible	Susceptible
Cefepime	Resistant	Resistant
Ceftriaxone	Resistant	Resistant
Cefuroxime	Resistant	Resistant
Cefalotin	Resistant	-
Ciprofloxacin	Resistant	Resistant
Fosfomycin	Susceptible	-
Gentamicin	Resistant	Resistant
Imipenem	Susceptible	Susceptible
Levofloxacin	Resistant	Resistant
Nitrofurantoin	Susceptible	-
Piperacillin	Resistant	Resistant
Tobramycin	Susceptible	Susceptible
Trimetoprim-sulfametoxazol	Resistant	Resistant
Piperacillin-tazobactam	Susceptible	Susceptible
Ertapenem	Susceptible	Susceptible

(ESBL:Extended Spectrum Beta Lactamase, E.Coli: Escherichia Coli)

Following advice from the Department of Infectious Diseases, treatment with 1 ertapenem was given to the patient who did not show culture growth, starting from 48 h post-biopsy for 7 days. Then the patient was discharged from the hospital with the agreement of the Department of Infectious Diseases. The other patient was started on empirical ceftriaxone (2× 1000 mg iv therapy) when ESBL-positive E. coli growth occurred that was resistant to ceftriaxone. Then this was changed to 1 ertapenem iv therapy with advice from the Department of Infectious Diseases. After taking ertapenem for 9 more days, the patient was discharged from the hospital because no more growth occurred in urine cultures. The results of the two patients with acute prostatitis are provided in Table 3.

Table 3. Evaluation of the two patients with post-biopsy acute prostatitis.

	Patient 1	Patient 2
Antibioticusetoreduce PSA	No	Two weeks
The growth in urine culture	No	ESBL(+) E.coli
The growth in blood culture	No	ESBL(+) E.coli
Treatment	Ertapenem/7 days	Ceftriaxone/3 days plusErtapenem/9 days

(PSA: Prostate Spesific Antigen, ESBL:Extended Spectrum Beta Lactamase, E.Coli: Escherichia Coli)

Discussion

Today, a final diagnosis of prostate cancer is typically established by a histopathological examination for patients with suspected prostate cancer. A transrectal prostate needle biopsy, conducted with TRUS, is taking its place as a standard diagnostic method.

One of the most frequent factors causing elevated PSA values other than prostate cancer is chronic prostate inflammation. The high PSA seen in symptomatic patients may regress after appropriate antibiotic therapy. Fluoroquinolones are frequently used because they penetrate well into prostate tissue. Simardi et al.2 determined that PSA values increased as inflammation increased in prostate tissue in a study of 51 patients where biopsies were planned because of high PSA levels, although there was no other reason to suspect prostate cancer or prostatitis. Seretia et al.3 gave 500 mg ciprofloxacin (1 × 2 therapy) for 3 weeks to 99 patients where prostate biopsies were planned because of high PSA levels; at end of the 3 weeks, PSA levels were lower in 59.6% of the patients. Karazanashvili et al.4 studied 61 patients with no findings or complaints suggestive of prostate cancer or chronic prostatitis, except high PSA. Fifteen days of 400 mg ofloxacin (tb 1 × 2 daily) lowered PSA in 80% of the patients.

In our study, the number of patients with chronic prostate issues pre-diagnosis who used antibiotics to lower PSA levels in the pre-biopsy period was 66 versus 179 patients who did not use any antibiotics. The mean PSA value was 13.0 in the group that used antibiotics and 41.4 in the other group. No statistically significant differences were found between the patients that used antibiotics and those that did not from the point of view of PSA levels. The biopsy-positive ratio was 9.1% in the 66 patients who used antibiotics and 16.8% in patients who did not use antibiotics.

Following a prostate biopsy, fluoroquinolone-resistant acute prostatitis may develop[5–7]. In studies carried out in Turkey, ciprofloxacin resistance has been observed at various rates, between 8.3% and 38% [8]. This may make urologists question the need to use antibiotics to lower PSA. Akduman

et al.[5] studied 558 patients who underwent prostate biopsies; 205 patients took 500 mg levofloxacin for 3 weeks to lower PSA and 353 patients did not use any antibiotic. In the post-biopsy period, 5.4% of the antibiotic group developed sepsis, whereas 1.7% of the others did; no statistically significant differences were determined from the point of view of sepsis development (p = 0.0297).

In another study,[6] acute prostatitis developed in 17.1% of 41 patients who used fluoroquinolones for prophylaxis, and in 4.5% of 66 patients who did not use fluoroquinolones, a statistically significant difference (p = 0.042). Among patients who developed acute prostatitis, 85.7% showed fluoroquinolone-resistant Gram-negative bacteria growth.

Minamida et al.[7] studied 100 patients who were to undergo prostate biopsies. The patients were treated prophylactically with a fluoroquinolone (500 mg levofloxacin daily for 3 days). E. coli resistant to fluoroquinolones were found in feces cultures of 13% of the patients taken 1 month before the biopsy; in 31% of patients, acute prostatitis developed.

In a retrospective review of medical records of 1541 males who underwent prostate biopsies over a period of 5 years, the ratio of acute bacterial prostate development post-biopsy was 1.36%.[8] The most frequently isolated microorganism from prostatitis patients was E. coli (71.4%). Fluoroquinolone-resistant strains were isolated from 5 (23.8%) of 21 patients who developed prostatitis. Even so, the authors noted that because fluoroquinolones have high bioavailability in prostate tissue, they were still the most preferred antibiotic in the pre-biopsy period. In our study, we assessed the clinical efficacy of ceftibuten, another cephalosporine-group antibiotic, and obtained a rate of acute prostatitis (0.8%) similar to theirs (1.36%).

Otrack et al.[9] reported that almost half of patients who visited their hospital for urinary tract infections in the post-biopsy period were infected with fluoroquinolone-resistant E. coli. We are also of the opinion that, in recent years, fluoroquinolone-resistant urinary system infections have increased. For this reason, we recommend not relying on quinolones for pre-biopsy prophylaxis. The addition of a single dose of gentamicin to the antibiotic protocol in the pre-biopsy period for antibiotic prophylaxis is still a subject of discussion. However, in recent studies, rates of acute prostatitis have been much lower with protocols to which an aminoglycoside was added.[10] Aminoglycosides are inexpensive and may be used im/iv under inpatient (ambulatory) conditions. Low-volume gentamicin doses, such as 2 cc, may be injected without the need for an infusion. For this reason, pain and hematoma are very rare at the injection site.[11] In our study, no local or systemic side effects related to the gentamicin injection were seen in any patients. The effectiveness of gentamicin, particularly with regard to Gram-negative bacilli such as Pseudomonas, has been combined with third-generation cephalosporins. Given that infectious complications that develop in relation to prostate biopsies are frequently due to Gram-negative bacilli, we recommend the use of single-dose gentamicin together with third-generation cephalosporins.

Some studies have compared the use of aminoglycosides or cephalosporins for prophylaxis before biopsies to quinolone antibiotics.[12-15] Such studies have indicated that cephalosporins or aminoglycosides are not as effective as quinolones, in contrast to the results of studies on cephalosporins. One point to note regarding these studies is that the doses of aminoglycosides and cephalosporins were low. It is our opinion that a sufficient dose of the antibiotic combination of aminoglycoside

+ cephalosporine used post-biopsy may reduce prostatitis development to a significant degree. Indeed, in our study, the combination of a single dose of 160 mg gentamicin i.m. and ceftibuten was associated with a low rate (0.8%) of acute prostatitis.

The only reported study on the clinical use of ceftibuten as prophylaxis in prostate biopsies is Hosokowa et al..[16] In that study, 60 patients who underwent prostate biopsies were divided into two groups. Thirty patients received 200 mg oral ceftibuten (twice per day) starting on the operation day for 3 days; another thirty patients received the same thing but only on the day of operation. Post-biopsy, no one in the first group developed a fever over 38°C whereas 2 (6.7%) patients in the second group did; the difference was not statistically significant. However, due to the small sample sizes, the results should be considered with caution.

One international, multi-center, prospective study considered the prevalence of infective complications after prostate biopsy across 84 centers throughout the world.17 Of the 702 patients who were observed, fluoroquinolones were used for prophylaxis in 92.5% of patients. Of these patients, 3.5% developed symptomatic urinary tract infections with fever and 6 of 10 cases in which microorganisms were isolated showed resistance to fluoroquinolones. The researchers emphasized that such complications occur at a level that is not negligible. Fecal fluoroquinolone-resistant bacteria have been considered the most important risk factor from the point of view of post-biopsy infectious complications.

Because acute prostatitis can rapidly cause urosepsis, early diagnosis and treatment are important. Lange et al.[18] examined 24 patients who developed urosepsis post-biopsy and found that the microorganism that most often caused urosepsis was E. coli (67%). They retrospectively examined 4749 biopsies and reported a urosepsis rate of 0.5%. However, in 91.6% of patients in whom urosepsis developed, ciprofloxacin had been given for prophylaxis before the biopsy. Thus, substantial ciprofloxacin resistance occurred, and it is necessary to approach this antibiotic carefully.

In conclusion, in geographic locations with high rates of resistance to quinolones, this family of drugs should not be the preferred prophylactic agent. Instead, oral third-generation cephalosporins may be used together with single-dose aminoglycosides. Given that urosepsis is a serious disease that may be fatal, it is important to select the most appropriate prophylactic antibiotic.

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