Ciprofloxacin-Ceftriaxone Combination Prophylaxis for Prostate Biopsy; Infective Complications

Prostat Biyopsisinde Siprofloksasin-Seftriakson Kombinasyon Profilaksisi; Enfektif Komplikasyonlar

Prostat Biyopsisi Profilaksisi / Prostate Biopsy Prophylaxis

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Özet

Amaç: Siprofloksasin ve seftriakson (üçüncü kuşak sefalosporin) kombinasyon profilaksisi altında, ultrasonografi kılavuzluğunda transrektal prostat biyopsisi uyguladığımız hastalarda gelişen enfektif komplikasyonları sunduk. Gereç ve Yöntem: Çalışmaya biyopsiden 1 saat önce intramuskuler 1 g seftriakson ve biyopsi sonrası 5 gün, günde iki doz, oral 500 mg siprofloksasin uygulanan 1193 hasta dahil edildi. Biyopsi öncesi rutin idrar analizi ve idrar kültürü alınmadı. Akut prostatit ve ürosepsis gibi ciddi enfektif komplikasyonlar ve neden olan mikroorganizmalar değerlendirildi. Bulgular: Hastaların 16 (%1,3)'sında ciddi enfektif komplikasyonlar gelişti. Onbeş hastaya akut prostatit teşhisi konuldu ve 15 hastanın 10'unda idrar kültüründe Escherichia coli pozitif bulundu. Suşlar siprofloksasine dirençliydi. Sadece 1 hastada ürosepsis gelişti. Bu hastanın kan ve idrar kültüründe siprofloksasine dirençli genişletilmiş spektrumlu β-laktamaz üreten (ESBL) Escherichia coli tespit edildi. Hiçbir hastada antibiyotiklere bağlı yan etki gözlenmedi. Tartışma: Belirli bir profilaksi prosedürü olmamasına rağmen transrektal prostat biyopsi profilaksisinde siprofloksasin en yaygın kullanılan antibiyotiktir. Bununla birlikte siprofloksasin dirençli Escherichia coli suş insidansı artmaktadır. Bu nedenle yeni profilaksi stratejileri tartışılmalıdır. Seftriakson ile siprofloksasin kombinasyon profilaksisi prostat biyopsisinde güvenli ve kullanılabilir bir seçenektir.

Anahtar Kelimeler

İnfeksiyon; Profilaksi; Prostat Biyopsisi; Seftriakson; Siprofloksasin

Abstract

Aim: To present our clinical experience about infective complications due to ultrasound guided transrectal prostate biopsy under ciprofloxacin plus third-generation cephalosporin (Ceftriaxone) combination prophylaxis. Material and Method: The 1193 patients that used combination of ceftriaxone 1 g intramuscular 1 hour before biopsy and ciprofloxacin 500 mg twice a day for 5 days after biopsy were included to study. Before biopsy, urine analysis and urinary cultures were not performed routinely. Serious infective complications such as acute prostatitis and urosepsis, causing microorganisms were evaluated. Results: Serious infective complications occurred in (1.3%) 16 patients. Fifteen of them had acute prostatitis and urine culture results were positive in 10/15 patients for Escherichia coli. The strains were uniformly resistant to ciprofloxacin. Only 1 patient had urosepsis and his blood and urine cultures demonstrated extended- spectrum β-lactamase-producing (ESBL) Escherichia coli also resistant to ciprofloxacin. Antibiotic treatment-related side effects were not observed in any patient. Discussion: Although there is not a certain procedure, ciprofloxacin is the most common used antibiotic for transrectal prostate biopsy prophylaxis. On the other hand, the incidence of ciprofloxacin resistant Escherichia coli strain is increasing. Thus, new prophylaxis strategies have to be discussed. Ceftriaxone plus ciprofloxacin prophylaxis is safe and can be useable option for prophylaxis of prostate biopsy.

Keywords

Ceftriaxone; Ciprofloxacin; Infection; Prophylaxis; Prostate Biopsy

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Introduction

Transrectal ultrasound-guided prostate biopsy (TRUSBx) is worldwide used and standard procedure for diagnosis of prostate cancer. Clinics dealing with prostate biopsy, generally, prefer their own procedures. Biopsy cores, numbers, techniques, antibiotic use, anticoagulant use and enema use include differences among clinics. Although TRUSBx is an invasive procedure, it is generally safe with acceptable complication rates in experienced hands. Pain, dysuria, rectal bleeding, haematuria, haematospermia and urinary retention are the possible risks and complications of TRUSBx. On the other hand one of the most serious and frequently occurring complications associated with TRUSBx is infection. Mainly microbial agent, responsible for the symptomatic infection developed after biopsy was Escherichia coli (E. coli) that colonized normally in rectal flora. In addition to E.Coli, anaerobic agents such as enterococcus, Klebsiella species, Bacteroides fragilis, and Clostridium species also reported to cause infection after biopsy [1]. Therefore, it seems that any prophylactic antibiotic regimen prior TRUSBx should protect patients against E. coli as well as anaerobes.

Type and duration of prophylactic antibiotics for transrectal prostate biopsy is not clear. Fluoroquinolones such as ciprofloxacin are one of the most commonly used prophylactic antibiotics for TRUSBx [2]. European Association of Urology (EAU) guidelines recommend single-dose prophylaxis with fluoroquinolones for low-risk patients and prolonged courses of prophylaxis only in high-risk patients [3]. However, recent reports suggest that infectious complications due to fluoroquinolone-resistant organisms are increasing [4]. On the other hand American Urological Association (AUA) Best Practice Policy recommended the use of fluoroquinolone or second/third degree cephalosporin, or alternatively an aminoglycoside with metronidazole or clindamycin, as prophylaxis before TRUSBx [5]. In this study, we present our clinical complication rates about infection with intramuscular third-generation cephalosporin (cephtriaxone) plus oral ciprofloxacin combination which we use routinely at our clinic for TRUSBx prophylaxis.

Material and Method

This study was performed in the Department of Urology, Suleyman Demirel University Hospital. Total 1360 prostate biopsy cases between August 2005 and March 2013 were investigated in this study. The indication for TRUSBx were elevated PSA levels (PSA>4 ng/ml or with family history >2.5 ng/ml) and abnormal digital rectal examination findings. The 167 patients were excluded because of infective endocarditis prophylaxis use before biopsy, being a urinary catheter carrier, administration of antibiotic treatment in the week before the biopsy, manipulation of the urinary tract prior to biopsy, allergy to quinolones and cephalosporines, patients with history of diabetes mellitus and use of immunosuppressive medication. The remaining 1193 patients that used combination of Cephtriaxone 1g intramuscular 1 hour before biopsy and oral ciprofloxacin 500 mg twice a day for 5 days after biopsy were included to study. No routine urine analysis or urinary cultures were performed before biopsy. Rectal preparation with enema or scrub was not performed in any patients. Written informed consent was obtained for each patient.

Biopsy was performed in an outpatient setting with a 7.5-mHz biplanar probe. The TRUSBx was carried out with disposable 18 G needles in all patients. Anesthesia was administered by ultrasound-guided injection of 5 mL lidocaine 1% per side into the angle between the bladder and prostate. Twelve biopsy samples were taken from each patient.

Patients were asked about the complications like dysuria, hematuria, rectal bleeding and fewer after fifteenth days of biopsy by telephone interviews. Patients admitted to our emergency or urology clinic due to serious infective biopsy complications, such as acute prostatitis or urosepsis after biopsy were recorded. Clinical diagnosis of acute bacterial prostatitis was made with pain and sense of fullness in perineum, body temperature >38°C, leukocytes in the urine sediment, and clinical findings on digital rectal examination of prostate. Urine and blood cultures were obtained from prostatitis and septic patients.

All strains were cultured and identified by the Clinical Microbiology Laboratory and were recovered from blood culture and urine. Blood culture was performed by BactAlert and selective media (bioMe´rieux, Marcy l'Etoile, France). Urine culture was performed applied routine internal protocols and using selective media (bioMe´rieux, Marcy l'Etoile, France).

Statistical analysis was performed using Mann-Whitney U. $P<0.05$ was considered significant.

Results

Between August 2005 and March 2013, 1193 patients that used combination of cephtriaxone and oral ciprofloxacin were evaluated about infective complications of prostate biopsy.

Patients' median age was 64 (range 42-93). Median pre-biopsy PSA was 11.2 ng/ml (range 2.4–100) and median prostate volume was 51 cc (range 13-139). All patients underwent the same biopsy protocol regardless of the prostate gland size. The 12-core biopsy technique (sextant biopsy + lateral base, lateral mid-zone, lateral apex, bilaterally) performed to all patients.

Of the 1193 patients, 15 (1,2%) were admitted to our urology clinic with acute prostatitis diagnose and hospitalized. All these patients had fewer up to 39 OC and perineal discomfort. Only 2 patients had urinary retention and indwelling catheter inserted. Acute prostatitis patients have mean age of 63 years, mean prostate volume of 49 cc, and mean PSA 12,8 ng/dl. There were no statistical differences between age, PSA value or prostate volume respectively ($p>0.05$) (Table 1).

Urine culture results were positive in 10 of 15 prostatitis patients for E.Coli. Other micro-organisms cultivated were Klebsi-

Table 1. Patients' characteristics

	Total	Acute Prostatitis (-)	Acute Prostatitis (+)	p
No	1193	1178	15	
Age(Years) (Median) (min-max)	64 (42-93)	64 (42-93)	63 (48-73)	p>0,05
Prostate volume (Median) (min-max)	51 (13-139)	51 (13-139)	49 (21-82)	p>0,05
PSA(ng/dl) (Median) (min-max)	11,2 (2.4-100)	11,2 (2.8-100)	12,8 (3.1-34)	p>0,05

ella species in 2 patients, Bacteroides fragilis in 2 patients and pseudomonas in 1 patient. Of the 10 patients with positive culture for E.Coli, 7 patients had extended- spectrum β-lactamase-producing (ESBL) E.Coli and 3 of them ESBL negative E.Coli. All strains were uniformly resistant to ciprofloxacin. There were no microorganisms isolated from blood cultures of prostatitis patients. These patients with acute prostatiris diagnose treated empirically with gentamicin 160 mg once daily at the beginning, after culture results obtained treatment modified to sensitive antibiotics.

Only 1 patient admitted to emergency via urosepsis clinic after 2 days of biopsy, with bradicardia, hypotension, fewer, acute urinary retention and hospitalized to intensive care unit. Uroseptic patient's blood culture demonstrated ESBL positive E.Coli also resistant to ciprofloxacin. This patient was treated with intravenous ertapenem 1 g once daily for 15 days (Table 2).

Table 2. Urine and blood culture results of patients with acute prostatitis and urosepsis diagnose

	Urine Culture					Blood Culture		Total
	E.Coli		Klebsiella species	Bacteriodes fragilis	Pseudomonas	E.Coli		
	ESBL (+)	ESBL (-)				ESBL (+)	ESBL (-)	
Acute Prostatitis (No.of Patients)	7	3	2	2	1	0	0	15
Urosepsis (No.of Patients)	1					1		1

Discussion

TRUSBx is gold standard procedure for diagnosing prostate cancer. It is simple and safe procedure with low morbidity rate in experienced hands but on the other hand it is invasive procedure. Complications related to prostate biopsy can range from mild and self-limited to severe and life threatening. Hematuria, haematochezia and haematospermia are relatively common minor complications after TRUSBx and have varied between clinics and occur in 5.1% to 89%, 12.5% to 80%, and 1.3% to 59% of patients, respectively [6,7]. Infection-related complications following prostate biopsy include asymptomatic bacteriuria, urinary tract infection, febrile urinary tract infection, acute prostatitis and sepsis [8]. Bacteremia and urosepsis are rare but life-threatening major complications. The incidence of infectious complications following prostate biopsy in large multi-institutional studies ranges from 0.1% to 7%, depending upon the antimicrobial prophylactic regimen used [9]. Nam et al [10] reported 4-fold increase about hospital admission rate after prostate biopsy from 1996 (1.0%) to 2005 (4.1%) and they recommended the majority of hospital admissions (72%) were due to infections. Loeb and colleagues [9] reported that 1.1% of 17,472 patients underwent prostate biopsy required hospitalization for infection-related complications and they also reported the increase in infectious complications after prostate biopsy in recent years while the rate of serious noninfectious complications is relatively stable.

A number of studies have identified potential risk factors for infectious complications of post-prostate biopsy The most common of these risk factors appears to be exposure to antimicrobials within 6 months prior to biopsy [11], presence of fluoroquinolone resistant E. coli strains in fecal flora [12] and recent international travel [13]. The fluoroquinolone-resistance rate in E.coli-associated urinary tract infections has been reported to be about 10% [14]. Currently, the Japanese Society of Chemotherapy has reported the first nationwide study on bacterial pathogens isolated from patients with urinary tract infections. According to that report, the current isolate of E. coli showed a high resistance ratio of 29.3% to fluoroquinolones in Japan [15]. Several studies have documented increasing rates of fluoroquinolone resistance among patients hospitalized for infectious complications after prostate biopsy [4]. Minamida et all [16] found that 13% (13/100) of patients had positive stool cultures for fluoroquinolone-resistant E. Coli and 31% of these 13 patients had acute bacterial prostatitis after TRUSBx.

Antibiotic prophylaxis for TRUSBx reduces the rates of bacteriuria, febrile genitourinary infection and post- TRUSBx sepsis to less than 5% [17]. EAU guidelines classify TRUSBx as a contaminated procedure and, if a urinary catheter or bacteriuria is present, as a dirty procedure warranting antibiotic prophylaxis in all patients. Association recommended the fluoroquinolones as the most suitable antibiotic for the prevention of TRUSBx -derived infectious complications with level of evidence Ib [3]. The prevalence of fluoroquinolone-resistant E. coli is clearly increasing, and this increase poses a problem for TRUSBx. The AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis recommended fluoroquinolones or 1st/2nd/3rd generation cephalosporines [4]. However, there are no recognized consensuses for antibiotic prophylaxis regimens regarding type, route of administration or duration of antibiotics. In several studies various type and combination of antibiotics for prevention of infection after prostate biopsy discussed. Shigemura et al. [18] reported the results of a randomized, controlled trial comparing three prophylactic regimens for TRUSBx: piperacillin/tazobactam with/without a fluoroquinolone and fluoroquinolone alone. Rates of post- TRUSBx febrile infections were 3.74%, 0%, and 5%, respectively, showing reduced infection rates with broader spectrum coverage. Recently, Horcajada et al. [19] compared a preventive protocol using amoxicillin-clavulanate 500 mg three times the day before TRUSBx, the day of the TRUSBx, and 1 day after the TRUSBx, with a new protocol incorporating 2 g cefoxitin 1 h before the TRUSBx and ciprofloxacin 750 mg by mouth twice the day before, the day of the TRUSBx, and 3 days after the TRUSBx. They found a reduced incidence of bacteremia and sepsis compared with their previous preventative protocol (4.4% vs. 0.9%). Gopal et al [20] reported 2.1% infective complication rates after biopsy in 1276 patients with combination of ciprofloxacin 500 mg 12 hourly for 5 days, starting 1 day before and a single dose of amikacin 1 g IV immediately before the procedure.

The AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis recommended fluoroquinolones or 1st/2nd/3rd generation cephalosporines [5] and prevalence of fluoroquinolone-resistant E. coli is clearly increasing. Pace et al [21] compared quinolone administration orally with a combina-

tion of cephalosporin administration periprostatically and a fluoroquinolone orally. In combination group none of their patients developed sepsis, but on the other hand in the group receiving only quinolone 4 patients developed sepsis. Our clinical policy about TRUSBx prophylaxis is Cephtriaxone 1 g intramuscular 1 hour before biopsy and oral ciprofloxacin 500 mg twice a day for 5 days after biopsy. Infective complication rate was 1.3%. Fifteen patients had acute prostatitis diagnose and only one (1/1193) patient had urosepsis diagnose due to TRUSBx while using this prophylaxis. Our results were comparable with the result of 1.1% that recommended by Loeb and colleagues, even in our series only one patient had urosepsis.

Of the 15 patients with acute prostatitis, 7 patients had ESBL- producing E.Coli in their urine cultures and all strains were also resistant to quinolones. Both urine and blood cultures were positive for ESBL-producing E. coli in septic patient The ESBL-producing E. coli are emerging worldwide as a significant group of community pathogens. Ağca [22] reported 15% ESBL production rate in E.Coli. The ESBL-producing strains are particularly feared as they are resistant to all penicillins, to cephalosporines, including third and fourth-generation agents, and to aztreonam and are often cross-resistant to trimethoprim/sulfamethoxazole and quinolones [23].

The need for routine urine culture prior to prostate biopsy is unclear. When bacterial growth is evident urine culture could be useful in the decision to refrain from prostate biopsy [24]. The use of urinalysis or urine dipstick prior to prostate biopsy is widespread; however, there are no published studies to document its benefit. We do not routinely perform urine culture.

The use of prebiopsy enemas is controversial. Those who recommend it believe that enema improves ultrasound imaging and reduces the risk of bacterial infection from the biopsy [25]. Some studies have documented no benefit from the use of prebiopsy enemas [3]. In fact, an enema might increase the amount of feces in the lower rectum, which is normally empty except during defecation. We routinely don't use rectal preparation with enemas before biopsy because we believe that preprocedure rectal enema use speeds up bowel movements and impact on the patient's comfort.

In coclusion, antibiotic prophylaxis protocol for TRUSBx is not clear. Quinolones especially ciprofloxacin are the most preferred antibiotics for prophylaxis of the TRUSBx. But on the other hand recent reports suggest that fluoroquinolone resistance is increasing all over the world. Thus adding ceftriaxone to ciprofloxacin is safe and applicable prophylaxis protocol to protect and reduce post-prostate biopsy septicemia.

Competing interests

The authors declare that they have no competing interests.

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