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ORIGINAL ARTICLE

Does intravenous cefuroxime improve the efficacy of ciprofloxacin for preventing infectious complications after transrectal prostate biopsy? A prospective comparative study

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KEYWORDS

Complications;
Sepsis;
Transrectal ultrasonography;
Prostate;
Biopsy;
Ciprofloxacin;
Cefuroxime

ABBREVIATIONS

TRUSBP, TRUS-guided biopsy of the

Abstract ***Objectives:*** To compare the frequency of infection after transrectal ultrasonography (TRUS)-guided biopsy of the prostate (TRUSBP) using prophylactic ciprofloxacin with or without adding cefuroxime.

Patients and methods: Between June 2008 and October 2009, 205 consecutive patients had TRUSBP with the use of oral 500 mg ciprofloxacin twice per day, 2 days before and 3 days after the biopsy (defined as group A). Starting from November 2009 and onwards, 250 consecutive patients had TRUSBP using the same previous protocol of antibiotic prophylaxis but with the addition of intravenous 1.5 g cefuroxime given 30 min before the procedure (defined as group B). The incidence of sepsis after TRUSBP, together with the results of urine and blood cultures and antibiotic sensitivity, were compared between the groups.

Results: Fever after TRUSBP was recorded in 18 of 205 patients in group A (8.8%) and in nine of 250 in group B (3.6%); the difference was significant ($P = 0.018$). Urine culture was positive in 14 and five of patients in groups A and

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prostate; ESBL, extended-spectrum β-lactamase-producing; PCA-3, prostate cancer antigen-3

B, respectively, with extended-spectrum β-lactamase-producing (ESBL) *Escherichia coli* as the most common organism. The blood culture was positive in seven and three patients in groups A and B, respectively, with ESBL *E. coli* as the most common organism. All patients who had sepsis after TRUSBP sepsis were treated successfully.

Conclusion: Adding a single intravenous injection with 1.5 g of cefuroxime to oral ciprofloxacin significantly reduced the frequency of infectious complications after TRUSBP.

Introduction

TRUS-guided needle biopsy of the prostate (TRUSBP) is the reference standard procedure for diagnosing prostate cancer. Infection is one of the complications that can follow TRUSBP, and therefore antibiotic prophylaxis is indicated to reduce its incidence. The regimens used for prophylactic antibiotics vary widely among urologists, with no consensus on the most appropriate type of antibiotic and its duration [1–3]. One of the most commonly used agents for this purpose is ciprofloxacin [1,4] and our centre has used this agent for the past 5 years. Nevertheless, despite antibiotic prophylaxis, there are cases of infection after TRUSBP.

Several authors used different antibiotics in combination with ciprofloxacin to augment its efficacy in preventing infection. Some of these agents are gentamicin [1], amikacin [4] and tinidazole [5].

We investigated whether adding a single dose of cefuroxime (a second-generation cephalosporin) would improve the results. We compared the incidence of sepsis after TRUSBP with or without adding cefuroxime in a prospective comparative study. To the best of our knowledge, the present study is the first (in English) to report the effect of adding cefuroxime to ciprofloxacin on the incidence of infectious complications after TRUSBP.

Patients and methods

This was a prospective comparative study including two groups of patients with two different protocols of antibiotic prophylaxis before TRUSBP. Group A included 205 consecutive patients studied between June 2008 and October 2009, who were given oral ciprofloxacin 500 mg twice daily 2 days before and 3 days after TRUSBP. Group B included 250 consecutive patients studied between November 2009 and November 2011, who received the same regimen as group A but with the addition of 1.5 g intravenous cefuroxime 30 min before the procedure.

Inclusion and exclusion criteria

In all patients the indications for a biopsy were an abnormal DRE, an abnormal TRUS in patients with prostatic enlargement and LUTS, and/or an elevated PSA level of >4 ng/mL. We excluded patients who did not receive ciprofloxacin and/or cefuroxime because of allergy. Patients with valvular heart disease who needed a unique combination of antibiotics were also excluded. We also excluded patients with sepsis from other sources of infection, as supported by a history and physical examination and/or investigations. In addition, patients with a UTI were treated appropriately, based on urine culture, and all patients undergoing biopsy were required to have a negative urine culture.

The technique of TRUSBP

The patient was placed in the left lateral decubitus position, and a DRE first performed, using lidocaine hydrochloride 2% sterile gel (Rialocaine®, Ryiadh Pharma, Saudi Arabia) anaesthetic ointment. A 7.5 MHz transducer (Accuvix v10, Madison Ultrasound System, Samsung Town, Seoul, South Korea) was gently advanced into the rectum and 10 mL of lidocaine hydrochloride 2% (Xylocaine®, Pharmaceutical Solutions Industry, Jeddah, Saudi Arabia) was injected locally on both prostate edges. After obtaining the measurements, an 18-G needle loaded in a spring-action biopsy device was used to obtain the specimens. A 12-core biopsy is the standard at our institution.

Follow-up assessment

Patients were observed for $\geqslant 2$ h until they urinated, and were then instructed to return to the hospital if they developed a fever of >38 °C, chills or rigors, gross haematuria or severe LUTS. When the patients were hospitalised non-urological causes of fever were excluded and the diagnosis of sepsis after TRUSBP was established through the history, physical examination and specific investigations. Sepsis was defined as the presence of clinical signs of systemic inflammatory response syndrome associated with infection, confirmed by culture or Gram staining, or strongly suspected clinically. The standard clinical history included the presence of diabetes, LUTS, indications for biopsy, number of cores and the interval between the biopsy and symptoms. The patient was also asked about other symptoms related to other systemic

Table 1 The baseline characteristics of both groups, and complications after TRUSBP.

Variable	Group A	Group B	*P*
No. of patients	205	250	
Characteristic			
Mean (SD):			
Age (years)	63.3 (7.9)	63.2 (8.5)	0.83
Serum PSA level (ng/mL)	10.2 (10.3)	10.8 (9.8)	0.48
Diabetes mellitus, n (%)	33 (16.1)	29 (11.6)	0.1
Mean (SD):			
Prostate volume (mL)	57.5 (33.1)	60.1 (33.2)	0.39
Number of cores	12.1 (0.6)	12.3 (1.2)	0.21
Repeat biopsy, n (%)	17 (8.3)	25 (10)	0.32
Indications for TRUSBP[*]*, n (%)*			
Abnormal DRE	48 (23.4)	80 (32.0)	0.12
High PSA level	175 (85.4)	220 (88.0)	0.24
Complications, n (%)			
Sepsis	18 (8.8)	9 (3.6)	0.018
Haematuria	2 (1)	1 (0.4)	0.43
Haematospermia	1 (0.5)	2 (0.8)	0.21
Significant rectal bleeding	3 (1.5)	4 (1.6)	0.59

[*] Few patients in both groups had an abnormal DRE and a high PSA level.

problems that could be the cause of fever. The physical examination included an abdomino-pelvic examination for the possibility of epididymo-orchitis and other system examinations. Laboratory tests included a complete blood count, urine analysis, urine and blood cultures, together with kidney and liver function tests. All organisms isolated were examined for antibiotic sensitivity. Abdominal ultrasonography and a chest X-ray were also carried out.

Patients who developed an infection were treated with empirical intravenous antibiotics (ceftriaxone 2 g once daily) which were tailored to and guided by the results of cultures. When the fever subsided the antibiotic was switched to an oral form. The patient was instructed to continue the oral antibiotic for 2 weeks after discharge from the hospital.

Patients of both groups were compared for their characteristics before TRUSBP, including age, diabetes mellitus, prostate volume, indications for biopsy, number of cores and any repeat biopsy. The incidence of infection after TRUSBP was compared between the groups. The results of urine and blood cultures, types of organisms and antibiotic sensitivity were also compared between both groups. Continuous variables are expressed as the mean (SD) while categorical variables are presented as the frequency and percentage. A two-tailed Student's *t*-test and the chi-square test were used for statistical analysis as appropriate, with $P < 0.05$ taken to indicate statistical significance.

Ethical considerations

This clinical study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the International Conference on Harmonization guidelines for Good Clinical Practice. All participants provided consent and were informed to the fullest extent possible about the study, in language and terms they were able to understand.

Results

Both groups were comparable for patient characteristics, prostate characteristics and indications for TRUSBP (Table 1). The complications after TRUSBP for both groups are also shown in Table 1. Clinically and bacteriologically confirmed infections after TRUSBP were recorded in 18 of 205 patients in group A (8.8%) and nine of 250 in group B (3.6%), the difference being statistically significant in favour of group B ($P = 0.018$). Both groups were comparable in the frequency of other complications after TRUSBP, including haematospermia, haematuria and significant rectal bleeding (Table 1).

The characteristics of the patients and the results of urine and blood cultures for those who developed sepsis in both groups are shown in Table 2. The most common isolated organism from both groups was extended-spectrum β-lactamase-producing (ESBL) *E. coli*, sensitive to meropenam and tazocin (pipracillin-tazobactam). All patients with sepsis after TRUSBP in both groups were treated successfully and none of the complications had a significant effect on their subsequent management. The mean (SD) hospital stay for patients who developed sepsis was 3.3 (2.1) and 3.4 (1.7) days for patients in group A and B, respectively, and the difference was not statistically significant.

Discussion

Our study showed that adding one dose of intravenous cefuroxime to the standard dose of oral ciprofloxacin

Table 2 The characteristics of the patients who developed sepsis after TRUSBP in groups A and B.

Variable	Group A (18)	Group B (9)
Mean (SD) age (years)	61 (8.20)	58 (9.17)
Diabetes mellitus, n/N (%)	4/18 (22)	2/9
Mean (SD) prostate volume (mL)	52.4 (19.7)	53.8 (32.2)
Repeat biopsy, n (%)	16/18 (89)	7/9
Patients with + ve urine cultures, n (%)	13/18 (72)	5/9
Organisms isolated in urine culture, n:		
E. coli	4	2
ESBL *E. coli*	7	3
Pseudomonas	1	0
E. cloacae	1	0
No growth	5	4
Patients with + ve blood cultures (n)	7	3
Organisms isolated in blood culture		
E. coli	1	0
ESBL *E. coli*	6	3
No growth	11	6
Antibiotic sensitivity of		
Urine culture	Tazocin, Meropenam	Tazocin, Meropenam
Blood culture	Tazocin, Meropenam	Tazocin, Meropenam

resulted in a reduction in the infection rate after TRUSBP from 8.8% to 3.6%.

Since its first description by Weaver et al. in 1991 [6], TRUSBP has become the standard technique for diagnosing prostate cancer. It is a simple procedure that can be performed on an outpatient basis, providing sufficient tissue for accurate diagnosis and staging. Although it is considered a safe procedure it is still associated with various minor and major complications. Haematuria and haematospermia are the most common minor complications of TRUSBP, as defined by several studies [7,8]. Major complications are mostly infection-related, and studies have shown that 2% of patients will develop a febrile UTI, bacteraemia or sepsis, and will require hospitalisation and treatment with intravenous antibiotics [9,10]. Infectious complications were attributed to either performing the procedure on a previously infected prostate or to direct inoculation of bacteria from the rectum [7].

Many studies have been conducted to evaluate the effectiveness of antibiotic prophylaxis for TRUSBP, and there was a statistically significant reduction in the rate of infective complications [7,10]. Nevertheless, to date the optimum antibiotic prophylactic regimen has yet to be determined, and there is considerable debate in the search for an answer. Studies from USA and UK found a wide variability in antibiotic prophylactic regimens amongst urologists [11,12].

For decades fluoroquinolones have been the most commonly used antibiotics, as they can be administered orally and have a potent urinary bactericidal activity, with the ability to penetrate prostatic tissue. They are effective against *E. coli*, which is the most common causative organism of TRUSBP-related infections.

Studies from the USA, Europe and the Middle East have described the emergence of fluoroquinolone-resistant strains of *E. coli* [13,14] and noted an increase in resistance patterns [15,16]. This resistance is almost always attributed to the previous use of fluoroquinolones [17].

There are several ways that could be used to decrease the incidence of TRUSBP-related infections by resistant organisms. First, and most important, is to reduce the unnecessary use of fluoroquinolones in the treatment of uncomplicated UTIs. Second is to search for other tumour markers that could increase the specificity of PSA, thereby excluding unnecessary TRUSBP. Prostate cancer antigen-3 (PCA-3) is a gene that has a non-coding mRNA that is overexpressed in prostate cancer. A few studies on PCa-3 have shown an improvement in identifying disease compared with the PSA test [18,19]. Our institute is currently in the process of using PCA-3 in addition to PSA as a tool for diagnosing prostate cancer.

Many studies have been reported comparing different antibiotic prophylactic regimens in an attempt to reduce TRUSBP-related infections. Ciprofloxacin was found to be better than a combination of coamoxiclav and gentamicin in one study [20], with an incidence of infection of 2.4% and 12.9%, respectively. Ho et al. [1] compared oral ciprofloxacin with a combination of single-dose intramuscular gentamicin plus oral ciprofloxacin, and found a reduction in the incidence of infectious complications after TRUSBP from 3.3% to 1.3%. Amikacin was also evaluated in a study by Batura et al. [4], who concluded that adding amikacin to a previous regimen of ciprofloxacin and metronidazole reduced the rate of bacteraemia by almost 10%. Different antibiotic prophylaxis regimens reported to date are shown in Table 3 [1,4,5,20–23] and compared with the present study results.

To the best of our knowledge no previous study has evaluated the efficacy of cefuroxime combined with

Table 3 Comparison of different antibiotic prophylaxis regimens.

Reference	Antibiotic regimens	Rate of infection, n/N (%)
[1]	Ciprofloxacin	12/374 (3.2)
	vs Ciprofloxacin + gentamicin	5/367 (1.3)
[5]	Placebo	19/75 (25.3)
	vs. (Single-dose) ciprofloxacin + tinizadole	6/79 (7.5)
	vs. (3-day course) ciprofloxacin + tinizadole	8/77 (10.3)
[4]	Ciprofloxacin + coamoxiclav + metronidazole	11/281 (3.9)
	vs. Ciprofloxacin + metronidazole + amikacin	6/590 (1.01)
[21]	No antibiotic	9/145 (6.2)
	vs. ciprofloxacin + metronidazole	5/289 (1.7)
[20]	Ciprofloxacin	11/454 (2.4)
	vs. Co-amoxiclav + gentamicin	33/255 (12.9)
[22]	Co-amoxiclav	9/204 (4.4)
	vs. Ciprofloxacin + cefoxitin	2/207 (0.9)
[23]	Ciprofloxacin	2/119 (1.6)
	vs. Co-amoxiclav	8/110 (7.2)
Present	Ciprofloxacin	18/205 (8.7)
	vs. Ciprofloxacin + cefuroxime	9/250 (3.6)

ciprofloxacin in reducing the incidence of TRUSBP-related infectious complications. Cefuroxime is a second-generation cephalosporin with a wide range of activity against Gram-positive and -negative organisms, and it is also effective against ESBL *E. coli*. It has a high rate of stability against β-lactamases [24]. However, the newer ESBL organisms are resistant to it. Tazocin and meropenam are the only drugs left that are effective against ESBL organisms. Nevertheless, their use as a prophylactic antibiotic is not advisable, as overuse can also result in resistance.

Our study has the advantages of being a prospective comparative study with a large sample in which all patients were well investigated. However, the absence of randomisation and blinding of observers to the type of antibiotic prophylaxis used can be considered as limitations.

TRUSBP is a standard procedure that is indispensable for the diagnosis and proper management of prostate cancer. However, it is associated with infectious complications that can put patients at serious risk. Although antimicrobial prophylaxis has been shown to decrease the risk of such complications, no standardised regimen has been proposed by international guidelines. The emergence of fluoroquinolone-resistant strains of *E. coli* raises further concern about the need to adjust prophylactic regimens. Until a standardised regimen is devised prophylaxis should be tailored to meet the local bacterial resistance patterns. Awareness by primary-healthcare physicians about the current resistance patterns, with guidance for correction, is recommended.

In conclusion, our study showed that adding a single dose of intravenous cefuroxime to oral ciprofloxacin was associated with a statistically significant reduction in infectious complications after TRUSBP.

Conflict of interest

Authors have no conflict of interest to declare.

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None.

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