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

Khalid Al Rumaihi *, Ahmad A. Majzoub, Nagy Younes, Ahmed Shokeir

Department of Urology, Hamad Medical Corporation, Doha, Qatar

Received 27 March 2012, Received in revised form 28 April 2012, Accepted 29 April 2012
Available online 7 June 2012

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 B, respectively.
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®, Riyadh Pharma, Saudi Arabia) anaesthetic ointment. A 7.5 MHz transducer (Accuvix v10, Madison Ultrasound System, Sammyung 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 ≥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 conditions.
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 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 haematuria, haematospermia and significant rectal bleeding (Table 1).

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 $\beta$-lactamase-producing (ESBL) *E. coli*, sensitive to meropenem 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 would
resulted in a reduction in the infection rate after TRUS-
BP from 8.8% to 3.6%.

Since its first description by Weaver et al. in 1991 [6], TRUSBP has become the standard technique for diag-
nosing prostate cancer. It is a simple procedure that
can be performed on an outpatient basis, providing suf-
ficient tissue for accurate diagnosis and staging.

Although it is considered a safe procedure it is still asso-
ciated 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 re-
quire hospitalisation and treatment with intravenous
antibiotics [9,10]. Infectious complications were attrib-
uted 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 caus-
avative organism of TRUSBP-related infections.

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 caus-
avative organism of TRUSBP-related infections.

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 caus-

| 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:

| Organism          | Group A | Group B |
|-------------------|---------|---------|
| E. coli           | 4       | 2       |
| ESBL E. coli      | 7       | 3       |
| Pseudomonas       | 1       | 0       |
| E. cloacae        | 1       | 0       |
| No growth         | 5       | 4       |

Organisms isolated in blood culture

| Organism          | Group A | Group B |
|-------------------|---------|---------|
| E. coli           | 1       | 0       |
| ESBL E. coli      | 6       | 3       |
| No growth         | 11      | 6       |

Antibiotic sensitivity of

| Urine culture | Group A | Group B |
|---------------|---------|---------|
| Tazocin, Meropenam | Tazocin, Meropenam |

| Blood culture | Group A | Group B |
|--------------|---------|---------|
| Tazocin, Meropenam | Tazocin, Meropenam |
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.

### 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 + tinidazole | 6/79 (7.5)             |
|           | vs (3-day course) ciprofloxacin + tinidazole | 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)             |

### Conflict of interest
Authors have no conflict of interest to declare.

### Source of funding
None.

### References

[1] Ho HS, Ng LG, Tan YH, Yeo M, Cheng CW. Intramuscular gentamicin improves the efficacy of ciprofloxacin as an antibiotic prophylaxis for transrectal prostate biopsy. *Ann Acad Med Singapore* 2009;38:212–6.

[2] Shigemura K, Tanaka K, Yasuda M, Ishihara S, Muratani T, Deguchi T, et al. Efficacy of 1-day prophylaxis medication with fluoroquinolone for prostate biopsy. *World J Urol* 2005;23:356–60.

[3] Matsumoto T, Kiyota H, Matsukawa M, Yasuda M, Arakawa S, Monden K. Japanese guidelines for prevention of perioperative infections in urological field. *Int J Urol* 2007;14:890–909.

[4] Batura D, Rao GG, Bo Nielsen P, Charlett A. Adding amikacin to fluoroquinolone-based antimicrobial prophylaxis reduces prostate biopsy infection rates. *BJU Int* 2011;107:760–4.

[5] Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. *BJU Int* 2000;85:682–5.

[6] Weaver RP, Noble MJ, Weigle JW. Correlation of ultrasound guided and digitally directed transrectal biopsies of palpable prostatic abnormalities. *J Urol* 1991;145:516–8.

[7] Puig J, Darnell A, Bermúdez P, Malet A, Serrate G, Baré M, et al. Transrectal ultrasound guided prostate biopsy: is antibiotic prophylaxis necessary? *Eur Radiol* 2006;16:939–43.

[8] Rodriguez LV, Terris MK. Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. *J Urol* 1998;160:2115–20.

[9] Lindert KA, Kabalin NJ, Terris MK. Bacteremia and bacteruria after transrectal ultrasound-guided prostate biopsy. *J Urol* 2000;164:76–80.

[10] Kapoor DA, Klimberg IW, Malek GH, et al. Single-dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. *Urology* 1998;52:552–8.
Does intravenous cefuroxime improve the efficacy of ciprofloxacin for preventing infectious complications

[11] Shandera KC, Thibault GP, Deshon Jr GE. Variability in patient preparation for prostate biopsy among American urologists. *Urology* 1998;52:644–6.

[12] Taylor HM, Bingham JB. The use of prophylactic antibiotics in ultrasound-guided transrectal prostate biopsy. *Clin Radiol* 1997;52:787–90.

[13] Feliciano J, Teper E, Ferrandino M, Macchia RJ, Blank W, Grunberger I, et al. The incidence of fluoroquinolone resistant infections after prostate biopsy - are fluoroquinolones still effective prophylaxis? *J Urol* 2008;179:952–5.

[14] Young JL, Liss MA, Szabo RJ. Sepsis due to fluoroquinolone-resistant Escherichia coli after transrectal ultrasound-guided prostate needle biopsy. *Urology* 2009;74:332–8.

[15] Araj GF, Kanj SS. Current status and changing trends of antimicrobial resistance in Lebanon. *J Med Liban* 2000;48:221–6.

[16] Goetsch W, van Pelt W, Nagelkerke N, Hendrix MG, Buiting PL, Petit PL, et al. Increasing resistance to fluoroquinolones in Escherichia coli from urinary tract infections in the Netherlands. *J Antimicrob Chemother* 2000;46:223–8.

[17] Arslan H, Azap OK, Ergünül O. Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among Escherichia coli strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother* 2005;56:914–8.

[18] Wang R, Chinnaiyan AM, Dunn RL, Wojno KJ, Wei JT. Rational approach to implementation of prostate cancer antigen 3 into clinical care. *Cancer* 2009;115:3879–86.

[19] Roobol MJ, Schröder FH, van Leeuwen P, Wolters T, van den Bergh RC, van Leenders GJ, et al. Performance of the Prostate Cancer Antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: Exploring the value of PCA3 for a first-line diagnostic test. *Eur Urol* 2010;58:475–81.

[20] Madden T, Doble A, Aliyu SH, Neal DE. Infective complications after transrectal ultrasound-guided prostate biopsy following a new protocol for antibiotic prophylaxis aimed at reducing hospital-acquired infections. *BJU Int* 2011;108:1597–602.

[21] Larsson P, Norming U, Tornblom M, Gustafsson O. Antibiotic prophylaxis for prostate biopsy. benefits and costs. *Prostate Cancer Prostatic Dis* 1999;2:88–90.

[22] Horcajada JP, Busto M, Grau S, Sorlí L, Terradas R, Salvadó M, et al. High prevalence of extended spectrum beta lactamase-producing enterobacteriaceae in bacteremia after transrectal ultrasound-guided prostate biopsy: a need for changing preventive protocol. *Urology* 2009;74:1195–9.

[23] Hori S, Sengupta A, Joannides A, Balogun-Ojuri B, Tilley R, McLoughlin J. Changing antibiotic prophylaxis for transrectal ultrasound guided biopsies of the prostate: are we putting our patients at risk? *BJU Int* 2010;106:1298–302.

[24] Amicosante G, Marchetti F. Cefuroxime stability to beta-lactamases: clinical implications. *Infect Med* 2000;8:66–74.