Original Article

Intramuscular Gentamicin Improves the Efficacy of Ciprofloxacin as an Antibiotic Prophylaxis for Transrectal Prostate Biopsy

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Abstract

Introduction: Infection-related complications after transrectal ultrasound guided prostatic biopsy (TRPB) could be life threatening. Our centre observed sepsis after TRPB despite prophylactic oral ciprofloxacin. We reviewed all cases of post-TRPB sepsis with their bacteriology and evaluated if the addition of intramuscular (I/M) gentamicin to standard prophylaxis before TRPB could reduce its incidence. Materials and Methods: In a single urological centre, we performed an interventional study that compared a prospective group with retrospective control. The latter is known as the "cipro-only" group included consecutive patients who underwent TRPB between 1 September 2003 and 31 August 2004. The addition of I/M gentamicin 80mg half an hour before TRPB started on 1 September 2004. All subsequent patients who underwent TRPB until 31 August 2005 were included in the "cipro+genta" group. Patients who did not receive the studied antibiotics were excluded. Results: There were 374 patients in the "cipro+genta" group and 367 patients in the "cipro-only" group with comparable profiles. There were 12 cases of post-TRPB sepsis in the "cipro-only" group and 5 cases in the "cipro+genta" group. Ciprofloxacin-resistant *Escherichia coli (E. coli)* was the only pathogen isolated in both groups. In the "cipro-only" group, 9 patients had positive blood cultures and 8 were sensitive to gentamicin. In the "cipro+genta" group, the only positive *E. coli* was gentamicin-resistant. One patient in the "cipro+genta" group was admitted to the intensive care unit with septicaemia. Conclusion: The addition of I/M gentamicin to oral ciprofloxacin is a safe and effective prophylactic antibiotic regime in reducing the incidence of post-TRPB sepsis.

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Key words: Antibiotics, Infection, Prophylaxis, Prostate Biopsy

Introduction

Transrectal ultrasound guided prostate biopsy (TRPB) is one of the modalities in the diagnosis of prostate cancer. Its use has increased with the widespread use of serum prostate-specific antigen (PSA). It is generally a safe procedure with acceptable complication rates.[1] However, when infective complications occur, it is potentially fatal.[2] The risk of such infection is reduced with prophylactic antibiotics.[3] There is wide variation in the prophylactic antibiotic regimens used by the urologist with no consensus on the most appropriate type of antibiotic or its duration.[4-6] Fluoroquinolones such as ciprofloxacin is one of the most commonly used prophylactic antibiotics for TRPB[7] and our centre has been doing so for the past 10 years. Despite antibiotics prophylaxis, we observed cases of post-TRPB sepsis. In this study, we reviewed these cases and their bacteriology. Based on the findings, we introduced intramuscular (I/M) gentamicin to our standard prophylaxis of oral ciprofloxacin alone. We also compared the incidence of sepsis before and after its introduction.

Materials and Methods

We performed the study in the Department of Urology at the Singapore General Hospital from 1 September 2003 to 31 August 2005. This was an interventional study with retrospective analysis of the pre-intervention period and prospective follow-up of the post-interventional period. The former included patients who underwent TRPB between 1 September 2003 and 31 August 2004. After reviewing the bacteriology of those post-TRPB sepses that occurred within that period, the addition of I/M gentamicin 80mg to

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our standard protocol was introduced from 1 September 2004. It was injected in the gluteal region half an hour prior to prostate biopsy. During the study period, our indications for prostate biopsy were raised PSA (>4 mg/mL), abnormal digital rectal examination and findings in the first prostate biopsy that necessitated a repeat biopsy such as the presence of atypical glands. The latter was performed at least 3 months apart.

The primary endpoint of the study was hospitalisation secondary to sepsis within 1 week after TRPB. This was evidenced by the presence of fever (>38.0°C) with chills and rigors. The patients may have lower urinary tract symptoms (LUTS) with the presence of pyuria on urine microscopy. While positive blood or urine cultures were not necessary for inclusion, other non-urological causes for fever must be excluded. The secondary end-point was the isolated bacteria and its antibiotic susceptibility. We also studied the onset of symptoms and duration of hospitalisation.

The transrectal ultrasound (TRUS) guided prostate biopsy was performed in an outpatient clinic setting with the following prophylactic antibiotics protocol: oral ciprofloxacin 500mg twice daily for 3 days, which was started 24 hours before the procedure. Patients' bowel movement ensured with dulcolax suppositories. Before its commencement, their urine was tested with urine dipstick for leucocytes and nitrites. If it was positive, TRPB would be postponed till the urine culture and sensitivity was known. All patients had a cleansing enema before the procedure. With the patient in the left decubitus position, TRUS was performed by the urologist with a multi-planar multi-frequency probe (75 MHz) attached to the ultrasound scanner (Aloka SSD-7000, Dynaview II). Prostate biopsies (10 to 16 cores) were taken with an 18 Gauge x 20 cm Biopsy cut (Core biopsy) with the automated spring loaded gun mechanism (Bard Biopty Gun). They were obtained at the apex, middle and base of the left and right prostate lobes in the parasaggittal plane. The prostate volume as measured on the TRUS determined the number of cores of prostate biopsies. Prostate volume was calculated using the prostate ellipsoid formula: volume (V) = 0.52 (L x W x H) where L is the cephlocaudal diameter, W is the width and H is the antero-posterior diameter.

Patients were instructed to return to our hospital if they developed fever of >38.0°C, chills or rigors, severe irritative voiding symptoms and macroscopic hematuria with clots. In addition, the clinical nurse would contact them by telephone within 24 hours of the procedure to assess for fever or any complications.

When the patients were hospitalised, the diagnosis of sepsis was established and non-urological causes of the symptoms were excluded. The standard clinical history was obtained with emphasis on the presence of diabetes mellitus and LUTS, indications for prostate biopsy, the number of cores of biopsy, interval between biopsy and the onset of fever. We also sought for other symptoms that might indicate another possible source of infection. Physical examination included body temperature measurement, signs of epididymo-orchitis and abdominal examination. Other systems examined included respiratory and cardiac systems. Laboratory tests included complete blood count, renal panel, and urine and blood cultures (aerobic and anaerobic). The cultures were repeated if patients remained febrile or unwell with elevated total white counts. All organisms isolated were tested for antibiotic susceptibility. Chest X-rays were also performed. The patients were started on empirical intravenous (IV) ceftriaxone, which was adjusted according to the culture results. When the fever settled, the antibiotic was switched to an oral form and patients were discharged with 2 weeks of oral antibiotics.

We excluded patients who did not receive the standard antibiotic prophylactic or I/M gentamicin from the study. They included those with ciprofloxacin or gentamicin allergy and renal impairment. Patients who needed a unique combination of antibiotics such as those with valvular heart disease were also excluded. Patients with sepsis from other sources of fever as supported by history, physical examination or investigations were also excluded.

Results

Patients' characteristics for the historical control group and I/M gentamicin group are shown in Table 1. They are similar in terms of mean ages, mean PSA levels, indications for biopsy, prostate volume and the number of biopsy cores taken. The number of diabetic patients is also similar in both groups.

The mean age of the 17 patients hospitalised for post-TRPB febrile UTI was 50.4 years (range, 44 to 72). A

Table 1. Patient Population from Both Groups

	Cipro-only	Cipro + Genta
Patient excluded	32	43
No. of evaluable patients	367	374
Age (y)	60.1 ± 5.4	58.8 ± 7.6
Serum PSA (ng/mL)	10.74 ± 4.7	9.08 ± 6.5
Prostate volume (mL)	28.3 ± 10.1	26.7 ± 11.4
Number of biopsy	10.6 ± 2.5	11.2 ± 2.4
Diabetes mellitus	42	31
Repeat biopsy	89	73
Prostate nodule	52	39

PSA: prostate-specific antigen
Data presented as mean ± standard deviation
All *P* values are non-significant

Table 2. End-points Results

	Cipro-only	Cipro+Genta	*P*
Admission for infection	12	5	0.0458*
Positive blood culture (*E. coli*)	9	1	
Ciprofloxacin resistant *E. coli*	9	1	
Gentamicin sensitive *E. coli*	8	0	
Mean onset of symptoms (day)	1	1	
Intravenous antibiotics	Ceftriaxone	Ceftriaxone	
Average length of stay (days)	3.7 (2-7)	3.2 (3-10)	
Others	ICU stay		

ICU: intensive care unit
* Pearson's chi-square test

single patient had diabetes mellitus and another 9 had hypertension. Their mean prostate volume (TRUS) was 32.3mL and the mean number of cores of prostate biopsies was 10. There was a single case of histological prostatitis while the remainder was benign prostate hyperplasia. There was no prostate cancer.

Table 2 summarised the end-point findings of our study. After the introduction of I/M gentamicin, the number of hospitalisation secondary to febrile UTI was reduced from 3.3% to 1.3%. This represented a 50% reduction but the difference was not statistically significant (Pearson's chi-square test). While three-quarters of the blood cultures was positive in the control group, only one-fifth was positive in the gentamicin group. All the cultures grew *Escherichia coli (E. coli).* Two of them in the control group also had positive urine cultures, which also grew *E. coli*. All of them were resistant to ciprofloxacin. In the control group, 8 of the 9 cases demonstrated sensitivity to gentamicin. The only case of *E. coli* in the gentamicin group was resistant to ciprofloxacin and gentamicin. This patient stayed in the intensive care unit for 2 days. He was admitted the next day after TRPB with fever and chills. On admission, he was found to be hypotensive and despite fluid resuscitation, needed inotropic support. *E. coli* was isolated from his blood and urine cultures. He improved with IV cefepime and was discharged after 9 days of hospital stay.

The fever and urinary symptoms started the next day after TRPB for all patients except for 1. The latter's symptoms started 4 days later and medical help was sought only after 1 week. His blood and urine cultures were negative for pathogens. Upon hospitalisation, all patients were started with empirical IV ceftriaxone and adjusted to the appropriate antibiotics when the culture results and sensitivities were known. Ten patients continued on IV ceftriaxone, 4 patients were adjusted to IV cefepime and only a single patient was started on IV gentamicin. All patients were discharged with oral antibiotics for 2 weeks. The mean length of hospitalisation for both groups is similar (3 days). There was no morbidity such as bleeding or infection directly related to I/M gluteal injections. There was also no renal impairment in any patient that was due to gentamicin.

Discussion

Infective complications after TRPB are serious and potentially life-threatening.[8] In the pursuit of the ideal antibiotic prophylaxis, various regimens have been utilised with no clear consensus among urologists. In addition to a regimen's efficacy in preventing infection, its cost-effectiveness and clinical applicability should be considered. Our centre observed post-TRPB sepsis after 10 years of usage of oral ciprofloxacin for surgical prophylaxis and treatment. While it remains as a cheap and effective antibiotic, we aimed to improve its efficacy without concomitant increase to the patient's cost or inconvenience.

When our centre employed "cipro-only" prophylaxis, the incidence of sepsis was 3.3 %. In a review of 5802 TRPB by Raaijmakers et al, 200 patients (3.5%) developed fever after biopsy.[1] Their prophylactic antibiotic was trimethoprim-sulfamethoxazole and ciprofloxacin was only used if the patient was immunocompromised with diabetes mellitus or steroids. In another contemporary series that utilised ciprofloxacin as the prophylactic antibiotic with similar patient recall at 24 hours, their incidence was only 1.7%.[9] Our cases were due to ciprofloxacin-resistant *E. coli*. We attributed its emergence to our rampant use of ciprofloxacin for prophylaxis or treatment.[10] With the addition of I/M gentamicin to oral ciprofloxacin, our incidence had reduced to 1.3%. This data represented the first local data on an important complication of TRPB.

E. coli was the only causative organism identified in all our positive cultures. Over the 2-year study period, we had 10 positive blood cultures and 2 positive urine cultures in 15 cases of post-TRPB sepsis. Our finding was consistent with other centres and it directed our antibiotic prophylaxis at *E. coli*. Tal et al had also identified *E. coli* as the most common pathogen in their series of 23 UTI after TRPB with a variety of antibiotic regimens. However, only 6 of their cases (26.1%) were identified on blood culture.[11] Linbert et al found that the bacterial growth in the blood cultures was strongly correlated with bacterial growth in the prostate tissue. They also found that bacterial growth in the prostate tissue is more common in men with a larger prostate and a higher American Urological Association score.[12] The absence of other bacteria cultures suggested the susceptibility of the urinary tract to *E. coli* virulence and possible sub-optimal dosing of prophylactic antibiotics.

There was also a change in the gentamicin susceptibility of *E. coli* between the 2 groups. In the "cipro-only" group, 8 of the 9 cases of *E. coli* were sensitive to gentamicin while in the "cipro+genta" group; the only case of *E. coli* was

resistant to gentamicin. Our finding in the "cipro-only" group was the basis for adjuvant I/M gentamicin. The reduced incidence of sepsis demonstrated that the addition of I/M gentamicin was effective in improving the efficacy of ciprofloxacin. However, the presence of sepsis with gentamicin-resistant *E.coli* also reminded us that achieving complete protection by any antibiotic regimen may be difficult. Notwithstanding, reviewing the bacteriology of post-TRPB sepsis had refined our prophylactic antibiotic regimen.

To our knowledge, we are one of the few groups that combine oral ciprofloxacin and I/M gentamicin injection for antibiotic prophylaxis in routine TRPB. In a survey of 900 practising American urologists, only 3.3% of them used a combination of oral and I/M prophylactic antibiotics.[7] Rodriguez et al used I/M gentamicin if the patient had valvular heart disease.[13] Probable explanations for low utilisation are cost, disruption to outpatient workflow and patient's inconvenience. Our study had shown that the additional protection from sepsis with I/M gentamicin was effective and could be obtained at a low cost with patient's compliance and without major disruption to outpatient workflow.

The single dose of 80 mg gentamicin is cheap and appropriate for outpatient clinical application. Each vial contains 2 mL of gentamicin. Its small volume makes it easy for I/M injection, which negates the need for an infusion set and its associated cost. Its pharmacokinetics also matches the prophylactic role. The 30 minutes lag time between I/M injection and TRPB allows for maximal serum bioavailability at the time of procedure, which concurs with the principle of surgical antibiotic prophylaxis.[14] While this dose allows easy application, it may be suboptimal dosing in some patients. Playing this unique prophylactic role, we are mindful of possible dose-dependent renal toxicity. As such, we kept it at the lowest end of the treatment range (1.0 to 1.5 mg/kg). This is of particular importance as we only have the patients' serum creatinine results and not creatinine clearance before its use for TRPB.

The cost of gentamicin is favourable; each vial costs US$0.15. We have considered other antibiotics such as ceftriaxone. However, its cost is higher (US$1.50) and the larger reconstitution volume needed may not be well tolerated by patients. A recent randomised trial demonstrated that TRPB with piperacillin/tazobactum (P/T) prophylaxis had a lower incidence of bacteriuria and febrile UTI, when compared with oral ciprofloxacin. While they recommended I/M P/T 2250g for 2 days, the issue of high cost and impaired clinical applicability, in terms of patients' compliance with I/M injections, was raised.[15]

We did not find predisposing factors to sepsis after TRPB in our patients. Linbert et al did not observe any correlation between the incidence of bacteremia and bacteriuria with increasing numbers of prostate biopsies. They also observed that pre-biopsy bacteriuria and a history of UTI did not predict post-biopsy infective complications.[12] On contrary, Hodge et al found that patients with a history of UTI or LUTS were at an increased risk of infective complications.[16] In a study that involved a single 500mg dose of levofloxacin prophylaxis, they found only 1 of the 377 (0.27%) low-risk patients with symptomatic UTI. They emphasised the patient's compliance as the key factor for such a low infection rate.[17]

Although this study was not randomised, there were valid reasons for comparison. Our centre's protocol for performing prostate biopsies and management of post-TRPB sepsis had not changed during the short study period (2 years). Moreover, the patients' characteristics in both groups were comparable.

This study is fraught with several drawbacks. Using sepsis (clinical diagnosis) as a primary end-point, its precise definition can be difficult. While in the most ideal scenario, positive blood cultures for bacterial growth may be more robust. However, in our study, the patients are already on antibiotics before TRPB. As such, those patients with clinical symptoms despite negative cultures are still included. We also recognise the possibility that the observed incidence of post-TRPB sepsis of 1.3% in the "cipro+genta" group may be due to I/M gentamicin alone. Together with sub-optimal gentamicin dosing, we are in the process of performing a 3-armed prospective randomised trial that compares "cipro-only", "genta-only" with "cipro+genta" to address these issues.

Conclusion

The incidence of infective complication after TRPB in our centre with ciprofloxacin prophylaxis is 3.3 % and *E. coli* is the only pathogen isolated. The addition of I/M gentamicin 80mg has reduced the incidence to 1.3 %. Gentamicin is less costly and can easily be delivered to the patients without disruption to the routine outpatient workflow while ensuring patients' compliance. In addition, our practice of reviewing the bacteriology of septic cases has also proven to be useful in identifying the optimum antibiotic regimen. As ciprofloxacin and gentamicin are commonly used antibiotics in many centres, our findings should find widespread clinical applications.

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REFERENCES

1. Raaijmaker R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rate and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002;60:826-30.
2. Gilad J, Borer A, Maimon N, Riesenberg K, Klein M, Schlaeffer F. Failure of ciprofloxacin prophylaxis for ultrasound guided transrectal prostatic biopsy in the era of multiresistant enterobacteriaceae. J Urol 1999;161:222.
3. Kapoor DA, Klimberg IW, Malek GH, Weganke JD, Cox CE, Patterson AL, et al. Single dose oral ciprofloxacin versus placebo for prophylaxis during transrectal prostate biopsy. Urology 1998;52:552-8.
4. 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.
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. Matsumoto T, Kiyota H, Matsukawa M, Yasuda M, Arakawa S, Monden K, et al. Japanese guidelines for prevention of perioperative infections in urological field. Int J Urol 2007;14:890-909.
7. Shandera KC, Thiabault GP, Deshon GE, Jr. Variability in patient preparation for prostate biopsy among American urologist. Urology 1998;52:644-6.
8. Binsaleh S, Al-Assiri M, Aronson S, Steinberg A. Septic shock after transrectal ultrasound guided prostate biopsy. Is ciprofloxacin prophylaxis always protecting? Can J Urol 2004;11:2352-3.
9. Sheikh M, Hussein AYT, Kehinde EO, Al-Saeed O, Rad AB, Ali YM, et al. Patient's tolerance and early complications of transrectal sonographically guided prostate biopsy: prospective study of 300 patients. J Clin Ultrasound 2005;33: 452-6.
10. Png JCD, Tan E, Foo KT. A comparative study of the distribution of ofloxacin and ciprofloxacin in prostatic tissues after simultaneous oral ingestion. BJU 1997;79:781-4.
11. Tal R, Livine PM, Lask DM, Baniel J. Empirical management of urinary tract infections complicating transrectal ultrasound guided prostate biopsy. J Urol 2003;169,1762-5.
12. Lindert KA, Kabalin JN, Terris MK. Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. J Urol 2000;164:76-80.
13. Rodriguez LV, Terris MK. Risk and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of literature. J Urol 1998;160:2115-20.
14. Santucci R, Krieger JN. Gentamicin for the practicing urologist: review of efficacy, single daily dosing and "switch" therapy. J Urol 2000; 163:1076-84.
15. Cormio L, Beradi B, Callea A, Fiorentino N, Sblendorio D, Zizzi V, et al. Antimicrobial prophylaxis for transrectal prostate biopsy: a prospective study of ciprofloxacin vs piperacillin/tazobactum. BJU Int 2002;90: 700-2.
16. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound directed transrectal core biopsy of the prostate. J Urol 1989;142:71-3.
17. Griffith BC, Morey AF, Ali-khan MA, Canby-Hagino E, Foley JP, Rozanski TA. Single dose levofloxacin prophylaxis in patients at low risk. J Urol 2002;168:1021-3.