A Prospective Randomized Trial Comparing a Combined Regimen of Amikacin and Levofloxacin to Levofloxacin Alone as Prophylaxis in Transrectal Prostate Needle Biopsy.

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Purpose: We investigated whether addition of amikacin to levofloxacin-based antimicrobial prophylaxis reduces febrile urinary tract infections after transrectal ultrasound-guided prostate needle biopsy (TRUSB).

Materials and Methods: A total of 447 patients undergoing TRUSB were prospectively randomized into two groups. The 230 patients in Group A were given one oral dose of levofloxacin 400 mg prior to TRUSB; the 217 patients in Group B each received the same dose of levofloxacin and one 200 mg intravenous dose of amikacin. Patients' characteristics were assessed prior to TRUSB and their symptoms were checked after the TRUSB.

Results: Both regimens were well tolerated with no side effects. No statistically significant difference in patients' characteristics, or in incidence of inflammation- or infection-related symptoms was seen between the two groups; nor any significant difference among those who developed fever and those who did not. Two Group A patients and one Group B patient developed febrile urinary tract infections. Accountable pathogens determined by urine and blood cultures were fluoroquinolone-resistant E.coli and extended-spectrum β-lactamase-producing E.coli. All pathogens isolated were levofloxacin-resistant, amikacin-susceptible species.

Conclusion: Although the present study was under-powered by unexpectedly low overall incidence of febrile urinary tract infections, addition of one intravenous administration of amikacin to one oral administration of levofloxacin showed no advantage compared with levofloxacin alone as antimicrobial prophylaxis in TRUSB. Strikingly, all pathogens isolated from febrile patients were sensitive to amikacin in vitro. Therefore, further understanding of amikacin's drug kinetics in the prostate is necessary to develop a more efficient drug delivery system for amikacin.

Keywords: antibiotic prophylaxis; methods; bacterial infections; prevention & control; prostatic neoplasms; diagnosis; anti-bacterial agents; administration & dosage.

INTRODUCTION

Currently, transrectal ultrasound-guided prostate needle biopsy (TRUSB) is accepted as a standard procedure for pathologic diagnoses of prostate cancer. However, TRUSB is an invasive procedure with complications such as pain, dysuria, hematuria, hematospermia, rectal bleeding, urinary retention, non-febrile and febrile urinary tract infection (UTI), and sepsis. Infectious complications, especially acute prostatitis and sepsis may result in severe morbidity, and even death.[1] Hence, antibiotic prophylaxis is routinely administered to lower incidence of infectious complications after TRUSB.[2-4] Fluoroquinolone (FQ) antimicrobial agents are widely used as prophylaxis due to their broad spectrum of activity against gram-positive and gram-negative bacteria. Moreover, FQs are available orally, have a widely acceptable safety profile, and penetrate well into the prostatic cytosol.[5-7] Until the early 2000s, multiple randomized studies have shown FQs to be effective in lowering the incidence of infectious complications after TRUSB.[2,8-10] However, wide use of FQs has led to development of FQ-resistant bacteria, such as extended-spectrum β-lactamase (ESBL)-producing coliforms.[11] A number of studies during the last decade have shown a trend of increasing FQ resistance in cases of bacterial infections after TRUSB.[11-13] Several studies have tested alternative antibiotic prophylaxis regimens, or combinations of other antibiotics with FQs to lower the incidence of these complications. The American Urological Association (AUA) guideline for antimicrobial prophylaxis for TRUSB recommends

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FQs or cephalosporins as the agents of first choice, and lists aminoglycosides, aztreonam, or trimethoprim-sulfamethoxazole (TMP-SMX) as alternatives to FQs.[14] Aminoglycosides have also been recommended as alternative antimicrobials for preoperative prophylaxis for a number of other surgical procedures in the guideline. Amikacin (AMK) is a low-cost aminoglycoside drug available in Japan, and has a good sensitivity profile against ESBL-producing coliforms.[12,15] However, there is no report of a prospective randomized study on the combined use of AMK and FQs for TRUSB. The aim of this prospective study is to assess whether the addition of AMK to levofloxacin (LVFX)-based antimicrobial prophylaxis reduces febrile UTI after TRUSB.

MATERIALS AND METHODS

Study Patients

From November 2007 to December 2009, patients undergoing TRUSB at Nishi-Kobe Medical Center and Japanese Red Cross Otsu Hospital, two tertiary referral hospitals 80 km apart, were recruited to the study. These patients had standard indications for TRUSB, such as abnormal findings on digital rectal examination and/or elevated serum prostate specific antigen (PSA) levels. Patients with indwelling urethral catheters, untreated UTI, current use of antibiotics, severe heart disease, abnormal liver function (aspartate transaminase (AST) and alanine transaminase (ALT) > × 2.5 upper limit of normal), abnormal renal function (serum creatinine > 1.2 mg/dL), immunosuppressive status, or histories of hypersensitivity to FQs or aminoglycosides were excluded. We calculated that with a two-sided alpha of 0.05, a power of 0.8, and expected reduction in incidence of febrile UTI from 2% in the Group A control arm to 0.5% in the Group B, we needed 201 samples for each arm. All Patients were sufficiently informed of the aims of this trial and all possible complications. The 447 patients who agreed to this trial gave written consent documents to be enrolled in this study, which was approved by Institutional Review Boards at each hospital (IRB Approval Number 200904 for Nishi-Kobe Medical Center, and 109-2009 for Japanese Red Cross Otsu Hospital).

Methods

Patients were prospectively randomized into two groups using a computer-generated random number table. Group A received a single oral administration of LVFX (400 mg), two hours before TRUSB. Group B received the same dose of LVFX two hours before TRUSB and a single intravenous administration of AMK (200 mg), 30 minutes before TRUSB. This trial was performed as a single blind trial: the patients were not informed of the group they were randomized to. Patient characteristics, including age, serum PSA, prostate volume, International Prostate Symptom Score (IPSS), quality of life (QoL) score, presence of dysuria, comorbidities, history of previous TRUSB, use of anticoagulant agents, antimicrobials, or steroid drugs, were assessed prior to TRUSB. For analgesia, each patient had a diclofenac sodium suppository (50 mg) 30 minutes before the procedure. We established an intravenous line before each TRUSB to prepare for hypotensive side effects, and performed each TRUSB using a disposable automated biopsy gun with 18-gauge biopsy needles. All biopsies were carried out using a systematic approach in which 10 specimens were taken from each patient. Of note, the method of bowel preparation was not predetermined in the current study. As a result, all the patients who underwent TRUSB at the Nishi-Kobe Medical Center took sennoside orally (24 mg, before sleep), and were administered an enema (glycerine enema 120 mL, under 70 years old/ glycerine enema 60 mL over 71 years old) on the day of TRUSB, whereas the patients at Japanese Red Cross Otsu Hospital did not receive any bowel preparation. All the other procedures were identical between the two institutions. Patients were instructed to record symptoms associated with their TRUSBs, including pain at TRUSB, gross hematuria, rectal bleeding, hematospermia, perineal discomfort, urination pain, difficulty voiding, urinary retention, fever, and symptomatic adverse drug events, using provided check sheets, which were collected at 2-4 weeks after each TRUSB. Patients were instructed to contact the office immediately if any problems occur, especially febrile symptoms (body temperature higher than 38.0°C). Urine and blood cultures were collected immediately from patients who developed febrile symptoms, and the patients were immediately treated with meropenem. Antimicrobial susceptibility was evaluated by Clinical and Laboratory Standards Institute (CLSI) broth microdilution method, and a bacterial isolate was considered non-susceptible to an antimicrobial agent when it tested resistant, intermediate, or non-susceptible. Multiple drug resistance was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. The primary endpoint of the present study was incidence of febrile UTI in each group. Secondary endpoints were incidence of non-febrile symptoms, tolerability, and safety of the combined regimen, and determination of variables associated with febrile UTI. Results were analyzed using JMP 9 software (SAS Institute Inc, Cary, North Carolina, USA); P

Table 1. Complications after transrectal ultrasound-guided prostate needle biopsy.

Variables	Group A	Group B	*P* Value
	Single-dose LVFX	Single-dose LVFX + AMK iv.	
	(n = 230)	(n = 217)	
Pain at TRUSB, no.	40	28	.160 †
Hematuria, no.	77	72	.865 †
(mean duration of symptoms, days)	3.64	3.32	
Rectal bleeding, no.	40	44	.464 †
(mean duration of symptoms, days)	1.33	1.33	
Hematospermia, no.	13	11	.812 †
Perineal discomfort, no.	34	25	.265 †
(mean duration of symptoms, days)	1.38	1.62	
Urination pain, no.	9	9	.933 ††
(mean duration of symptoms, days)	4.33	2.89	
Feeling of residual urine, no.	19	17	.903 †
(mean duration of symptoms, days)	4	3.35	
Difficulty voiding, no.	3	8	.179 ††
(mean duration of symptoms, days)	1	1	
Urinary retention, no.	3	2	.935 ††
(mean duration of symptoms, days)	4.33	3	
Fever > 38°C	2	1	.950 ††
(mean duration of symptoms, days)	3.5	5	
Symptomatic adverse drug event, no.	0	0	-----

Abbreviations: TRUSB, transrectal ultrasound-guided prostate needle biopsy; LVFX, levofloxacin; AMK, amikacin; iv, intravenous.
† Chi-square test; †† Fisher's exact test.

values were calculated with Student's *t*-test, chi-square test and Fisher's exact test, and $P < .05$ was considered significant.

RESULTS

There was no significant difference in incidences of non-infectious complications after TRUSB, such as pain at TRUSB, gross hematuria, rectal bleeding, and hematospermia. Moreover, we could not detect any significant difference in incidences of symptoms related to inflammation or infection including perineal discomfort, micturition pain, difficulty voiding, urinary retention, and fever (**Table 1**). Two patients from Group A and one patient from Group B developed febrile symptoms. Urine and blood cultures were collected immediately from these patients, and the patients were promptly treated with intravenous administration of meropenem. Table 2 shows details of the three patients and results of their urine and blood cultures. The history of previous TRUSB is reported as one of the significant risk factors of febrile UTI. In the present study, 46/230 (20.0%) in group A, and 38/217 (17.5%) in group B had prior TRUSB, however, the three patients who developed febrile symptoms had not undertaken TRUSB previously.

All three patients were diagnosed with acute prostatitis; none progressed to septic shock, and all were cured with intravenous meropenem. Accountable pathogens, as determined by urine and blood cultures were FQ-resistant E.coli in two cases and ESBL-producing E.coli in another. All pathogens isolated were LVFX-resistant, AMK-susceptible species (**Table 2**). Both regimens were well tolerated with no side effects. No patient had deterioration of renal function. No patient was lost to follow up. There was no statistically significant difference in patients' characteristics between the two groups before TRUSBs (**Table 3**). Overall, prostate cancer was detected in 208 (46.5%) cases by TRUSB. Prostate cancer detection rates were similar between the two groups (105 [45.6%] of 230 in group A, 103 [47.4%] of 217 in group B).

The survey of urine culture results from all the symptomatic UTI patients in the two hospitals between 2006 and 2009 showed that the detection rate of LVFX-resist-

Table 2. Characteristics of the patients who developed febrile urinary tract infection, and results of urine / blood cultures.

Variables	Patient 1 (vs. afebrile patients)	Patient 2	Patient 3	*P* Value
Group	A	A	B	–-----
Age, years	78	68	75	.282 †
PSA, ng/ml	6.88	14.1	13.7	.00106 †
Prostate volume, cc	35	45.8	62.4	.636 †
Antimicrobial history	–-----	–-----	–------	.850 ††
Comorbidities	Re-biopsy	Dysuria	Dysuria; use of anticoagulant agents; diabetes mellitus; hypertension	–-----
Complications after TRUSB	Hematuria; feeling of residual urine	Urination pain	Urination pain; urinary retention	–-----
Prostate cancer detection	+	+	+	0.0625 ††
Interval from biopsy to febrile symptom, days	1	3	1	–-----
Organism isolated (source)	E. coli (urine)	E. coli (urine and blood)	ESBL-producing E. coli (urine)	–-----
Antimicrobial sensitivity				
Levofloxacin	Resistant	Resistant	Resistant	–-----
Amikacin	Sensitive	Sensitive	Sensitive	–-----

Abbreviations: TRUSB, transrectal ultrasound-guided prostate needle biopsy; E. coli, Escherichia coli.
† Chi-square test; †† Fisher's exact test.

ant E.coli among all E.coli had increased from 17.2% in 2006 to 22.2% in 2009, and that of ESBL-producing E. coli from 3.80% to around 10% (**Figure 1**). AMK showed a very high sensitivity rate (99.0%) to coliforms from urine cultures of all UTI patients. Furthermore, AMK showed almost similar sensitivity rate (97.1%) to ESBL producing E.coli (**Figure 2**).

DISCUSSION

Introduction of PSA testing into clinical practice led

Figure 1

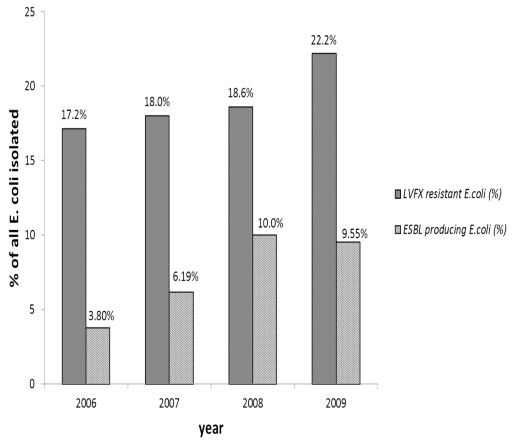

Figure 1. Ratios of LVFX-resistant E.coli and ESBL-producing E.coli to all E.coli isolated from urine cultures of patients with UTI at the two hospitals.
Abbreviations: LVFX, levofloxacin; E. coli, Escherichia coli; ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection.

Figure 2

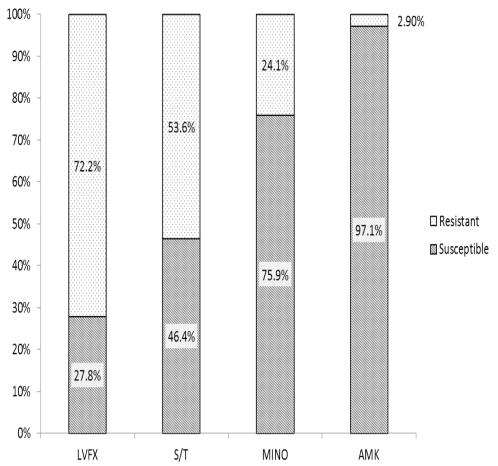

Figure 2. Drug susceptibility of extended-spectrum β-lactamase producing E.coli at the two hospitals.
Abbreviations: AMK, amikacin; LVFX, levofloxacin; MINO: minocycline; S/T, sulfamethazine /trimethoprim.

Table 3. Patient characteristics.

Variables	Group A	Group B	*P* Value
	Single-dose LVFX	Single-dose LVFX + AMK iv.	
	(n = 230)	(n = 217)	
Age, years (mean ± SD)	69.4 ± 7.82	69.5 ± 7.38	.994 †
PSA, ng/mL (median)	7.90 (IQR 5.38-13.85)	7.51 (IQR 5.58-14.25)	.771 †
Prostate volume, cc (mean ± SD)	41.3 ± 22.7	41.0 ± 24.2	.886 †
IPSS score (mean ± SD)	12.2 ± 7.60	11.5 ± 7.16	.543 †
QoL score (mean ± SD)	3.28 ± 1.54	3.17 ± 1.56	.916 †
Presence of previous TRUSB	46	38	.465 ††
Dysuria	73	69	.924 ††
Use of anticoagulant agents	30	24	.557 ††
Long term use of antimicrobials	1	4	.334 †††
Use of steroid drugs	5	1	.0856 †††
Diabetes mellitus	21	31	.106 ††
Hypertension	69	63	.807 ††
Cardiovascular disease	21	18	.656 ††
Respiratory disease	5	9	.486 †††
Liver disease	2	3	.667 †††
Renal disease	2	3	.667 †††
Cerebrovascular disease	11	6	.363 †††
Number of prostate cancers detected	105	103	.603 ††

Abbreviations: TRUSB, transrectal ultrasound-guided prostate needle biopsy; LVFX, levofloxacin; AMK, amikacin; PSA, prostate specific antigen; QoL, Quality of Life; SD, standard deviation; IPSS, International Prostate Symptom Score; IQR, interquartile range; iv, intravenous.
† Student's *t*-test; †† chi-square test; ††† Fisher's exact test.

to a dramatic increase in TRUSBs. About 700,000 patients are diagnosed with prostate cancer worldwide annually.[16] E.coli is the major cause of symptomatic infection after TRUSB.[17] Although prophylactic antimicrobial administrations lower the risk of infection after TRUSB,[18] no standard antimicrobial prophylaxis regimen has been established, and a variety of antimicrobial prophylaxis regimens are administered without clear evidence,[4,19] FQs are the most widely used antimicrobial in TRUSB, and is recommended as a first-line agent for prophylaxis in both AUA and European Association of Urology (EAU) guidelines.[14,20] In the United States and Europe, ciprofloxacin (CPFX) is commonly used, whereas in Japan LVFX is popular. Increasing resistance to FQs and wide emergence of ESBL-producing E.coli has been reported,[11-13] which would pose more patients receiving FQs alone as prophylaxis before TRUSB at risk of developing febrile UTIs. Because of these increases in FQ-resistant coliforms, the urgent need to develop new prophylactic strategies have been emphasized.[21-23] Batura and colleagues examined resistance rates of organisms which were isolated from rectal swab during TRUSBs to CPFX, co-amoxiclav, and AMK, and found AMK to have the lowest resistance rate (0.22%) compared to CPFX (10.6%) and co-amoxiclav (13.3%).[15] Furthermore, a recent survey of 3000 patients who underwent TRUSB in France showed that the resultant pathogen for acute bacterial prostatitis were 95% resistant to FQs, and only 5% resistant to AMK.[24] The resistance rates of these pathogens to third-generation cephalosporin, gentamicin, and imipenem were 25%, 55%, and 0% respectively. These results suggest the possible advantage of adding AMK to conventional FQ-based regimen, although it has never been tested in a prospective randomized controlled trial. Batura and colleagues have retrospectively reviewed the addition of AMK to their conventional regimen (CPFX + co-amoxiclav + metronidazole) and reported decreased incidence of febrile infections, from 3.9% to 1.4%.[23] However, two patients in their study, who received AMK as a part of combined regimen, also developed febrile infections from AMK-sensitive coliforms. In the present study, although all organisms isolated from patients developing

acute prostatitis were resistant to LVFX and sensitive to AMK, patients with combined regimen also developed acute prostatitis, and there was no overall benefit of the combined regimen. These results underscore the theoretical efficacy of AMK to LVFX-resistant E.coli, however, the clinical ineffectiveness of combining AMK to LVFX in prophylaxis of TRUSB associated febrile UTI suggests suboptimal drug delivery or tissue penetrance of AMK to prostate tissue.

There is no report on the optimal dosage or administration method of AMK as prophylaxis in TRUSB. Goto and colleagues reported a high concentration of AMK in the prostate tissue after a single dose (200 mg, intramuscularly).[25] However, Özden and colleagues reported ESBL-producing isolates had a significant reduction in activity for most antimicrobial agents, including FQs and AMK.[11] Further studies to elucidate the precise drug kinetics of AMK in the prostate could lead to a more efficient drug delivery method for AMK.

The reported incidence of febrile infection is similar between CPFX and LVFX: 0.1–3% in CPFX,[2,3,26] and 0.6–5% in LVFX.[27-29] Although we expected the incidence of febrile UTI to be 2% in the LVFX group (group A) in power calculation, in the present study, only 3 (0.67%) of 447 cases developed febrile UTI. This low incidence of overall febrile UTI in the present study lowered the power of the study, and might partially explain the lack of significant difference between the two groups. Increasing sample size may detect smaller difference due to addition of AMK; however, at the cost of a larger number needed to treat (NNT), which would limit its clinical benefit.

Prostate volume, history of previous TRUSB, and use of antimicrobials have been reported to be associated with febrile UTIs after TRUSB;[12,13,30] however, we could not detect any clinical variables statistically associated with febrile UTIs except PSA, which was higher in the febrile patients (**Table 2**).

Although there was no difference in clinical variables between the two hospitals, all febrile UTIs occurred in patients at Japanese Red Cross Otsu Hospital. To identify any possible cause, we reviewed all the maneuvers associated with TRUSB at the two hospitals, and found that the only difference was the way of bowel preparation prior to TRUSB. All the patients who developed acute prostatitis did not receive any bowel preparation. The combined antimicrobial prophylaxis protocol was adopted for one year following the end of patient recruitment for this study. During this one-year period, another four febrile UTI cases occurred, exclusively in the patients not receiving any bowel preparation, suggesting a possible prophylactic role of bowel preparation in TRUSB. Kim and colleagues reported that using enemas significantly decreased the incidence of acute prostatitis (15 [1.6%] of 913 in enema group, and 3 [30%] of 10 in no enema group).[31] On the contrary, Carey and colleagues have retrospectively reviewed the usefulness of enemas in TRUSB, and found no significant difference in the incidence of acute prostatitis (10 [4.4%)] of 225 in enema group, 6 [3.2%] of 185 in no enema group).[32] Therefore, a well-designed randomized study is necessary to confirm the role of bowel preparation in TRUSB.

Figure 3

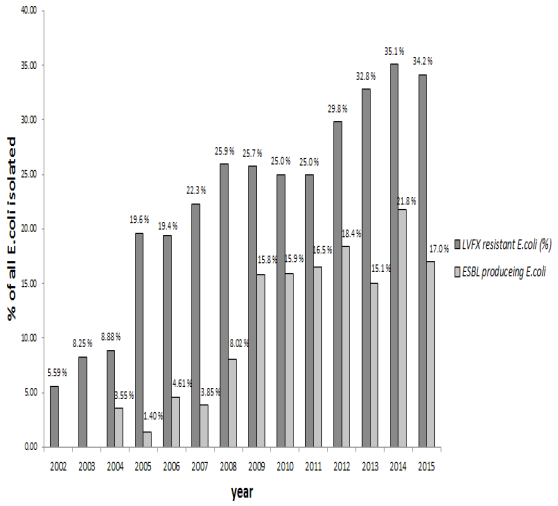

Figure 3. Ratios of LVFX-resistant E.coli and ESBL-producing E.coli to all E.coli isolated from urine cultures of patients with UTI between 2002 and 2015 at Japanese Red Cross Otsu Hospital.

Abbreviations: LVFX, levofloxacin; E. coli, Escherichia coli; ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection.

FQ resistant E-coli continue to be a growing threat for patients undergoing TRUSB. The rate of LVFX resistant E-coli among all the E-coli isolated from urine samples has been increasing even after 2009 at Japanese Red Cross Otsu Hospital, and is approaching 35% in 2015 (**Figure 3**). Considering the cost of treating TRUSB induced sepsis, newer prophylactic methods are certainly needed, and multiple studies to improve efficacy of prophylaxis including personalized approach based on pre-biopsy rectal swab are underway.

CONCLUSIONS

There is a strong rationale to add AMK to conventional FQ-based regimens, since FQ-resistant coliforms show strong sensitivity to AMK in vitro. However, in the present randomized control study, addition of a single

intravenous administration of AMK to single oral administration of LVFX did not show any advantage compared with LVFX alone as an antimicrobial prophylaxis in TRUSB. More strikingly, all the pathogens isolated from febrile patients were sensitive to AMK. Therefore, further understanding of drug kinetics of AMK in the prostate is necessary to develop a more efficient drug delivery method for AMK. Factors other than antimicrobial prophylaxis, such as bowel preparation, should also be considered in the future studies.

CONFLICTS OF INTEREST

None declared.

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