Complication rates of ciprofloxacin alone vs. ciprofloxacin plus fosfomycin for transrectal prostate biopsy

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ABSTRACT

INTRODUCTION: Infectious complications after transrectal prostate biopsy have been increasing, driven in large part, by rates of antibiotic resistance to conventional prophylaxis, such as ciprofloxacin. This study was designed to compare conventional antibiotic prophylaxis (oral ciprofloxacin) with ciprofloxacin and fosfomycin combination therapy prior to biopsy.

METHODS: This was a retrospective study looking at men between September 2021 and April 2023, who underwent transrectal prostate biopsy at several institutions in Alberta. The primary outcome was infectious complications within 30 days of prostate biopsy. Secondary outcomes included *Clostridium difficile* infections, urinary retention, gross hematuria, diarrhea, emergency room (ER) visits, hospital admissions, and intensive care unit (ICU) admissions. Data was collected on resistance patterns and pathogens isolated in culture.

RESULTS: During the study period, 2168 men underwent transrectal prostate biopsy. A total of 1216 men received ciprofloxacin alone and 877 received fosfomycin and ciprofloxacin. Infectious complications were significantly higher in the ciprofloxacin alone group (5.8% vs. 0.5%, p<0.0001). Thirty-day complications (7.2% vs. 2.1%, p<0.0001), 30-day ER visits (7.1% vs. 1.8%, p<0.0001), and 30-day hospitalizations (2.7% vs. 0.7%, p<0.001) were all higher in the ciprofloxacin alone group. The most isolated pathogen was *E. coli* in 54/60 (90%). Ciprofloxacin resistance in the isolated pathogens was high, with 52/60 (87%) showing resistance to ciprofloxacin and 51/54 (94%) *E. coli* strains resistant. No difference was seen in retention, *C. difficile* infections, bleeding, or diarrhea.

CONCLUSIONS: The addition of fosfomycin for antibiotic prophylaxis prior to transrectal prostate biopsy was associated with significant improvement in infectious complications and healthcare utilization.

INTRODUCTION

Prostate cancer (PCa) is the most common internal malignancy in men and its incidence has been increasing.[1] Transrectal prostate biopsy is a standard method for prostate cancer diagnosis. This procedure has been shown to be safe on population levels, however, there is a risk of postoperative infection and sepsis estimated to be in the 0.1–7.0% and 0.3–3.1% range, respectively.[2] The most significant of these infections can lead to hospitalization, intensive care unit (ICU) admissions, and in some cases, can be life-threatening. As such, antibiotic prophylaxis prior to this procedure is recommended by international guidelines, although there is no standard antibiotic regimen.[2]

Commonly, the antibiotic of choice is a fluoroquinolone, such as ciprofloxacin, owing to their broad spectrum of coverage.[3] In part due to its widespread use, there has been a significant rise in resistance rates, both locally within Canada and around the globe, to fluoroquinolones.[4] Such species as fluoroquinolone-resistant *E. coli* and extended-spectrum beta lactamase (ESBL) are the common bacteria thought to be associated with this. With the rise of resistance, there have been several studies looking at different techniques and methods to decrease infection risk, such as pre-procedural enema, providone iodine rectal preparation, targeted antibiotic prophylaxis, different antibiotic regimens, and transperineal approaches.[5-11]

A transperineal prostate biopsy is the preferred method in European

KEY MESSAGES

- Infectious complications after transrectal prostate biopsy have been increasing, largely due to increasing resistance rates to conventional antibiotic prophylaxis.
- To decrease infectious complications, this study assessed the addition of fosfomycin and found a significant decrease in the rate of post-prostate biopsy sepsis.

countries; however, in North America, transrectal prostate biopsy remains a standard procedure for prostate biopsies. The purpose of this study was to compare standard antibiotic prophylaxis (ciprofloxacin alone) for transrectal prostate biopsy against a combined ciprofloxacin and Fosfomycin-based prophylaxis.

METHODS

This retrospective cohort study was performed on patients biopsied between September 17, 2021, and April 23, 2023, with all patients from several centers in Alberta biopsied during this time included. Human research ethics board approval was obtained (Pro00103525). In total, 2168 men underwent prostate biopsy and were included; 1216 underwent transrectal prostate biopsy with ciprofloxacin alone (500 mg or 1000 mg oral) and 877 underwent prostate biopsy with a combination of ciprofloxacin (500 mg or 1000 mg oral) and fosfomycin (3 g oral). The remainder of the patients (n=75) underwent prostate biopsy with a different antibiotic prophylaxis regimen and were excluded. Traditionally, ciprofloxacin-based antibiotic prophylaxis has been the standard for our center and the prescription was at the discretion of the referring urologist. In recent years, however, owing to high rates of resistance, some urologists at our center have begun adding fosfomycin for antibiotic prophylaxis.

Baseline patient characteristics, antibiotic prophylaxis, 30-day complications and their subtypes, as well as hospital utilization data were collected by retrospective chart review of our provincial medical record. For baseline characteristics, age at the time of biopsy and whether the patient was diabetic or immunocompromised were collected (examples included patients prescribed biologics, steroids, history of organ transplant, or chemotherapy). Subtypes of complications collected included: infections, urinary retention, gross hematuria, *Clostridium difficile* (*C. difficile*) infections, and diarrhea. Complications were determined by the urologist's clinical notes or emergency room (ER) documentations within 30 days of biopsy. Infection rates were supplemented with positive urine or blood cultures, and the bacteria grown, as well as resistance patterns were collected.

The primary outcome of this study was the rate of infectious complications within 30 days of biopsy stratified by antibiotic prophylaxis. Secondary outcomes were rates of urinary retention, gross hematuria, diarrhea, *C. difficile* infections, ER visits, hospital admissions, and ICU admissions. Mean values and standard deviations are reported for continuous variables and categorical variables are reported as frequencies (%). T-tests were used to compare continuous variables between the two groups and Chi-squared test was used to compare the categorical variables. A two-sided p-value of <0.05 was considered significant.

RESULTS

Between September 2021 and April 2023, there were 2168 men who underwent a transrectal prostate biopsy, of which 1216 underwent the biopsy with ciprofloxacin prophylaxis alone and 877 underwent the prostate biopsy with a combination of ciprofloxacin and fosfomycin. Patient demographics and clinical characteristics are presented in Table 1. There was no difference in age, rates of immunodeficiency or diabetes, or prior episodes of post-prostate biopsy sepsis.

There was a significant increase in 30-day complications for the ciprofloxacin-alone cohort, with 7.2% vs. 2.1% experiencing a 30-day complication ($p<0.001$) (Table 2). The study also found that the ciprofloxacin-alone group had a significantly higher rate of ER visits (7.1% vs. 1.8%, $p<0.0001$) and hospitalizations (2.7% vs. 0.7%, $p<0.001$). There were two patients who were admitted to the ICU in this cohort, both of which were in the ciprofloxacin-alone group.

Table 1. Baseline patient characteristics

	Cipro alone (n=1216)	Cipro + fosfomycin (n=877)	p
Age, mean (SD)	65.2 (7.7)	65.1 (6.9)	0.73
Immunocompromised (%)	22 (1.8)	23 (2.6)	0.21
Diabetic (%)	178 (14.6)	130 (14.8)	0.91
History of post-prostate biopsy sepsis (%)	2 (0.2)	1 (0.1)	0.76

SD: standard deviation.

Table 2. 30-day complications

	Cipro alone (n=1216)	Cipro + fosfomycin (n=877)	p
30-day complication (%)	88 (7.2)	18 (2.1)	<0.0001
30-day ER visit (%)	86 (7.1)	16 (1.8)	<0.0001
30-day hospitalization (%)	33 (2.7)	6 (0.7)	<0.001
30-day ICU admission (%)	2 (0.2)	0 (0.0)	0.51

ICU: intensive care unit.

Table 3. Complication types

	Cipro alone (n=1216)	Cipro + fosfomycin (n=877)	p
Infection (%)	70 (5.8)	4 (0.5)	<0.0001
Retention (%)	7 (0.6)	7 (0.8)	0.54
C. diff infection (%)	1 (0.1)	0 (0.0)	1
Bleeding (%)	13 (1.1)	5 (0.6)	0.17
Diarrhea (%)	1 (0.1)	4 (0.5)	0.08

Table 4. Isolated bacterial organism

	Cipro alone (n=57)		Cipro + fosfomycin (n=3)	
	Pathogen	Cipro resistance (%)	Pathogen	Cipro resistance (%)
E. coli ESBL	51 7	48 (94) 7 (100)	3	3 (100)
K. pneumoniae	2	0 (0)	0	0
P. aeruginosa	1	0 (0)	0	0
MRSA	1	0 (0)	0	0
E. faecium	1	1 (100)	0	0
E. faecalis	1	0 (0)	0	0

ESBL: extended-spectrum beta lactamase; MRSA: methicillin-resistant Staphylococcus aureus.

Infection rates was significantly different between the two groups, with the ciprofloxacin-alone group experiencing 70 events (5.8%) vs. the ciprofloxacin and fosfomycin group experiencing four events (0.5%) (odds ratio [OR] 0.08, 95% confidence interval [CI] 0.03–0.21) (Table 3). There were no differences between groups for retention, *C. difficile* infection, bleeding, or diarrhea. Positive blood and urine cultures was significantly different between the two groups. In the ciprofloxacin-alone group, there were 57 (4.7%) positive blood or urine cultures, whereas in the ciprofloxacin and fosfomycin group, there were three (0.3%) (p<0.0001).

The most common isolated pathogen in this cohort was *E. coli* (n=54, 90%), with seven strains of *E. Coli* positive for ESBL (Table 4). Among the pathogens isolated, a high rate of resistance to ciprofloxacin was seen, with 52 pathogens (87%) in this cohort resistant to ciprofloxacin, driven largely by *E. coli* with 51 pathogens (94%) resistant. Fosfomycin susceptibility was not performed for all pathogens, but for 15 that were tested, all were susceptible to fosfomycin.

DISCUSSION

This study demonstrates that in a Canadian cohort, the addition of fosfomycin to antibiotic prophylaxis prior to transrectal prostate biopsy has a significant reduction in infectious complications. A recent multicenter trial in Korea showed that fosfomycin and a fluoroquinolone had a significant improvement in infectious complications when compared to fluoroquinolones alone.[10] Their group found an OR of 0.26 (95% CI 0.09–0.69), similar to this study, which shows an OR of 0.08 (95% CI 0.03–0.21), with both groups having similar infection rates at 0.5% for the fosfomycin and ciprofloxacin cohort.

Another Canadian group studied ciprofloxacin and ciprofloxacin plus fosfomyicin regimens and found a significant improvement in infectious complications with the addition of fosfomycin (1.1% vs. 0.2%).[12] Overall, however, they did find a very low infection rate with the ciprofloxacin alone, which is different from the significant infectious complications that were found in this study (1.1% vs. 5.8%). This study did find a very high rate of fluoroquinolone resistance, with an overall 87% resistance and 94% of the *E. coli* pathogens found to be resistant to ciprofloxacin. This resistance pattern likely accounts for the higher infection rates in this study compared to the other study populations.

The European Commission has suspended the use of fluoroquinolones for perioperative antibiotic prophylaxis and as such the European guidelines recommend against its use.[13] Furthermore, the European Association of Urology recommends that transperineal biopsy should be used to minimize these potential infectious complication risks; however, randomized controlled trials are still needed (and are in progress) comparing infection rates between transrectal and transperineal prostate biopsies.

Limitations

This study does have some limitations. As a retrospective review, we did not have questionnaires or reach out to patients directly, rather relying on our province-wide electronic health record system to assess for urologists' clinical notes, ER visits, and hospital admissions. Patients who sought care at their family physician or out of province would not have been captured in this data set. Furthermore, the ciprofloxacin-alone antibiotic regimen is not standardized, which could affect results. Some patients received 500 mg doses and others 1000 mg, which was at the discretion of the prescribing urologist.

CONCLUSIONS

In comparison with ciprofloxacin alone, the addition of fosfomycin for antibiotic prophylaxis prior to prostate biopsy is associated with a significantly lower rate of infections and healthcare utilization.

COMPETING INTERESTS: Dr. Fung is a co-investigator for NextGen Trial, assessing fusion biopsy and MRI for prostate cancer, supported by Exact Imaging. The remaining authors do not report any competing personal or financial interests related to this work.

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