Procedural povidone iodine rectal preparation reduces bacteriuria and bacteremia following prostate needle biopsy

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Introduction: *To determine if a povidone iodine rectal preparation (PIRP) reduces rates of bacteriuria and bacteremia following transrectal ultrasound guided prostate needle biopsy (TRUS PNB).*

Materials and methods: *Men undergoing TRUS PNB were prospectively enrolled in a study comparing the impact of PIRP versus standard of care (two pills of ciprofloxacin 500 mg). Urine, blood, and rectal cultures were obtained 30 minutes post-procedure with colony forming units (CFUs) determined after 48 hours. Patients were called 7 and 30 days post-procedure to evaluate for infections.*

Results: *A total of 150 men were accrued into this study including 95 receiving PIRP and 55 the standard of care. Two-thirds of patients were undergoing an initial biopsy, 19% used antibiotics within the previous 6 months, and median number of biopsy cores was 14. There were no differences between the two cohorts with respect to baseline or biopsy characteristics. In the PIRP cohort, rectal cultures before and after PIRP administration noted a 97.2% reduction in microorganism colonies (2.4×10^5 CFU/mL versus 6.7×10^3 CFU/mL, $p < 0.001$). Mean urine bacterial counts following TRUS PNB were 1 CFU/mL for PIRP versus 7 CFU/mL for standard cohort ($p < 0.001$). Mean serum bacterial counts following TRUS PNB were 0 CFU/mL for PIRP versus 3 CFU/mL for standard of care ($p = 0.01$). One patient in the PIRP cohort (1.1%) developed post-biopsy sepsis while 3 (5.5%) in the standard cohort had an infectious complication (1 UTI, 2 sepsis).*

Conclusion: *A PIRP regimen reduced bacteruria and bacteremia following TRUS PNB.*

Key Words: prostate biopsy, infection, sepsis

Introduction

Transrectal ultrasound-guided prostate needle biopsy (TRUS PNB) is the referent standard for the histologic diagnosis of prostate cancer. Minor procedural complications including pain, dysuria, lower urinary tract symptoms, hematuria, hematospermia, hematochezia, and urinary retention are common, albeit largely self-limiting. Infectious sequelae following TRUS PNB; however, have increasingly become a clinical concern with significant ramifications.[1-3]

Infectious complications including fever, urinary tract infection (UTI), acute bacterial prostatitis, orchiepididymitis, and sepsis have been rising following TRUS PNB.[4,5] The incidence of infectious complications is reported to range from 0.1% to 7% with attributable hospital admissions between 0.6% to 4.1% and an estimated sepsis rate of 0.1% to 0.9%.[6] Escherichia coli is the most common pathogen found in infections following TRUS PNB with most cases attributable to fluoroquinolone-resistant organisms.[5]

Fluoroquinolones penetrate prostatic tissue well and have long-lasting urinary bactericidal activity making them preferred agents for urologic procedures.[7-13]

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Overuse of fluoroquinolones, however, has contributed to fluoroquinolone-resistant bacteria. The SENTRY Antimicrobial Surveillance Program reported *E. coli* quinolone sensitivity to be less than 90% in 20 European countries with increasing resistance worldwide.[14] Urologic literature further highlights that 20%-25% of patients are colonized with fluoroquinolone-resistant *E. coli* in the rectal vault.[15]

With the rising rate of quinolone resistance, there is a great need for alternative prophylaxis strategies for TRUS PNB procedures. Thus far, a few different avenues have been explored. Several groups have demonstrated that the addition of an intravenous or intramuscular agent to oral ciprofloxacin can reduce sepsis post-biopsy.[16,17] Others have incorporated preoperative rectal swab screening of TRUS PNB patients to identify quinolone-resistant organisms.[15] If these organisms are detected, a "targeted" prophylactic antibiotic regimen is used based on the specific sensitivity profile of the tested bacterial strain.[18] If a sensitivity profile is not yet available, at least one group has even advocated for peri-procedural intravenous carbapenems with de-escalation once sensitivities become obtainable for high risk patients. Regardless, the actual process of collecting these rectal swabs, selectively culturing on quinolone selective medium, and then tailoring antibiotics specific to these organisms requires resources that may not be readily available in all clinical practices.

Alternatively, administration of a topical antiseptic to the rectal vault just prior to biopsy may present a more cost-effective and simple strategy to limit TRUS PNB infections. Povidone iodine is a commonly used topical agent that dramatically reduces microorganism colonies when applied to a surgical site. It is highly soluble and less toxic than other similar compounds making it widely suitable for surgical asepsis. The microbiocidal action comes from the polarized form of iodine, which participates in electrophilic reactions with enzymes of the respiratory chain as well as with amino acids of bacterial cell walls.[19] In vitro studies demonstrate a contact kill time of 30-120 seconds for *E. coli*, 60 seconds for *Enterobacter* species, and 15-180 seconds for *Staphyococci*, making it an ideal perioperative preparation agent.

Prior work from our group has highlighted a reduction in clinical infections through the use of a PIRP regimen with TRUS PNB.[20] Due to its promise and efficacy, we designed a prospective study to evaluate the incidence of bacteruria and bacteremia following TRUS PNB in a cohort receiving povidone iodine rectal preparation (PIRP) plus the standard of care versus a cohort receiving only the standard of care.

Materials and methods

Between March 2013 and August 2015, our institution enrolled patients in a prospective, non-randomized, IRB approved study comparing the impact of a peri-procedural PIRP versus standard of care for TRUS PNB cases. Initial study design was proposed as a prospective, randomized although accrual was poor over the first 6 months (8 patients accrued) thereby prompting a change in the design. Thereafter, enrollment into either treatment arm was at the discretion of the treating urologist. In total 150 men were accrued into the study with 95 receiving PIRP and 55 the standard of care.

Antibiotic prophylaxis regimen prior to PNB for all patients was ciprofloxacin 500 mg the night before and morning of the biopsy. Standard of care was defined as oral quinolone antibiotic prophylaxis alone. For patients treated with PIRP, creation of a topical slurry and application to the perianal region and rectal vault was performed as previously described.[4,20] Patients were assigned to the PIRP and standard of care groups at the discretion of the treating urologist in a non-blinded manner. Figure 1 highlights the study design.

For both cohorts, urine and blood cultures were obtained 30 minutes post-procedure and were plated onto nonselective, non-differential Mueller-Hinton agar plates with colony forming units (CFUs) determined after incubation at 37°C for 48 hours. Rectal cultures were obtained by use of sterile culture swabs immediately before (all patients) and 5 minutes post-procedure (in PIRP patients only to quantify changes in microorganism colony counts). The swabs

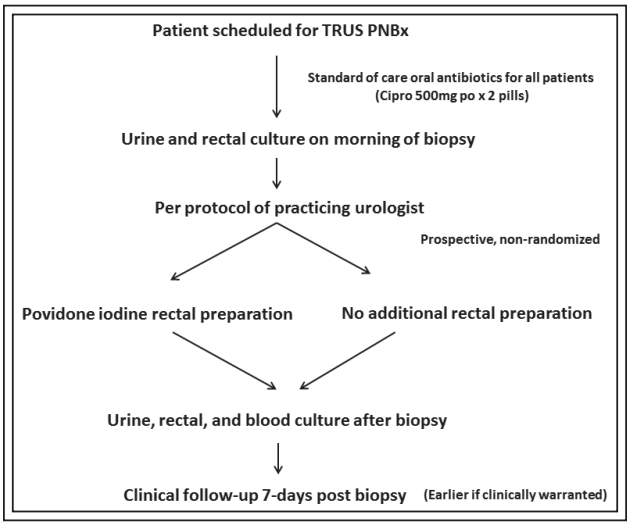

Figure 1. Design for this prospective, non-randomized study.

were then immersed in PBS, vortexed to release the bacteria, and serially diluted on Mueller-Hinton agar plates. CFUs were then determined after incubation at 37°C for 48 hours. All morphological variants of bacterial colonies arising on the plate were included to provide a total count.

Variables of interest collected in the database included age, baseline prostate-specific antigen (PSA), digital rectal exam status, history of prior biopsy, immunosuppression, antibiotic use or hospitalization within the previous 6 months, use of preoperative enema, prostate volume, number of biopsy cores obtained and the presence of cancer on pathology. Infectious post-biopsy complications were defined as fever > 38.5°C with a positive blood and/or urine culture. Post-biopsy infectious complications were further characterized into those requiring hospital admission and intensive care unit (ICU) level care. All patients were called at 7 and 30 days post-biopsy to evaluate for infectious complications.

Statistical analysis was performed with S-Plus Professional version 4.5 (MathSoft Inc., Seattle WA, USA). All p values ≤ 0.05 were considered significant.

Results

A total of 150 men were accrued into this study including 95 receiving PIRP and 55 the standard of care. Median age of eligible patients was 64.0 years, median pre-biopsy PSA was 12.5 ng/mL, 65% were undergoing an initial biopsy, and 19% had a history of antibiotic use within the previous 6 months. Median prostate volume was 45 cm^3 with median number of biopsy cores obtained being 14 (range, 6 to 45). There were no differences between the two cohorts with respect to baseline or biopsy characteristics, Table 1.

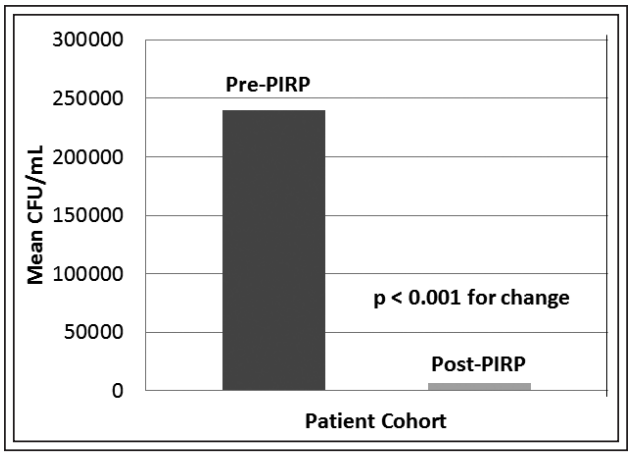

Figure 2. Differences in colony forming units per mL when comparing bacterial counts before and after PIRP treatment.

In the PIRP cohort, rectal cultures before and after PIRP administration noted a mean 97.2% reduction in microorganism colonies (2.4×10^5 CFU/mL versus 6.7×10^3 CFU/mL, $p < 0.001$), Figure 2. Mean urine bacterial

TABLE 1. **Clinical and pathologic characteristics of cohort**

Variable	PIRP + ciprofloxacin	Ciprofloxacin alone	p value
Patients (No., %)	95 (63)	55 (37)	
Age (yrs) (median, range)	64.5 (51-82)	63.0 (48-83)	0.88
Baseline PSA (ng/mL) (median, range)	11.5 (0.5-745)	13.0 (0.4-882)	0.46
Caucasian race (No., %)	84 (88)	48 (87)	0.79
Antibiotic use prior 6 months (No., %)	20 (21)	8 (15)	0.49
Hospitalization prior 6 months (No., %)	8 (8)	4 (7)	1.00
Immunosuppression (No., %)	6 (6)	1 (2)	0.39
Initial biopsy (No., %)	57 (60)	40 (73)	0.16
Biopsy cores (median, range)	14.5 (10-32)	14.0 (6-45)	0.92
Prostate volume (cm^3) (median, range)	42.0 (13.5-98.0)	47.0 (17.3-88.7)	0.77
Prostate cancer at biopsy (No., %)	36 (38)	18 (33)	0.71

PIRP = povidone iodine rectal preparation; PSA = prostate specific antigen

TABLE 2. **Bacteriuria, bacteremia, and clinical infections following TRUS PNB**

Variable	PIRP + ciprofloxacin (No., %)	Ciprofloxacin alone (No., %)	p value
Patients (No., %)	95 (63)	55 (37)	
Urine (CFU/mL) (mean, range)	1 (0-180)	7 (0-375)	< 0.001
Blood (CFU/mL) (mean, range)	0 (0-15)	3 (0-28)	0.01
Clinical UTI	0 (0)	1 (2)	0.37
Clinical sepsis	1 (1)	2 (4)	0.55
Total infectious complications	1 (1)	3 (5.5)	0.14

TRUS PNB = transrectal ultrasound-guided prostate needle biopsy; CFU = colony forming unit; UTI = urinary tract infection

counts following TRUS PNB were 1 CFU/mL for PIRP versus 7 CFU/mL for standard cohort ($p < 0.001$). Mean blood bacterial counts following TRUS PNB were 0 CFU/mL for PIRP versus 3 CFU/mL for standard of care ($p = 0.01$).

One patient in the PIRP cohort (1.1%) developed post-biopsy sepsis while 3 (5.5%) in the standard cohort had an infectious complication (1 UTI, 2 sepsis) ($p = 0.14$). The patient in the PIRP cohort with sepsis was noted to have 1.2×10^5 CFU/mL in the rectal vault following povidone iodine therapy with only a 10% reduction in colony counts from pre-treatment. Additionally, this patient was noted to have 15 CFU/mL of bacteria in blood samples obtained 30 minutes post-procedure. In the standard cohort, the patient developing a clinical UTI had 275 CFU/mL in post-biopsy urine culture and the two sepsis patients had a mean CFU/mL of 18 in the blood post-procedure, Table 2. All clinical infections were quinolone resistant *E. Coli.*

Discussion

Infections following TRUS PNB are presumed to be secondary to translocation of rectal bacterial flora into the highly vascular prostate.[21] While fluoroquinolones have historically provided adequate antimicrobial coverage for TRUS PNB, rising rates of resistance amongst bacteria colonizing the rectal vault necessitate modifications in prophylaxis regimens. Several different approaches have increasingly been utilized to combat this clinical challenge.

Povidone iodine is a cheap, widely available topical antiseptic which is routinely utilized for gynecologic procedures and thus has demonstrated safety on mucosal surfaces. Prior studies have confirmed its ability to reduce infectious complications when applied to the rectal vault prior to biopsy,[4,22-28] Table 3. Some specific studies are discussed below. In 2014, our group retrospectively analyzed data on 570 biopsy patients who received oral and/or parenteral antibiotics (n = 456) versus men receiving PIRP in conjunction with standard preoperative antibiotics (n=114). A reduction in infectious complications was observed when comparing the conventional antibiotic versus PIRP group (1.8% versus 0%), with the largest magnitude of decline occurring in the contemporary sub-cohorts (5.3% versus 0%, $p = 0.03$).[4] Similar observations were noted by Park and colleagues who compared 121 patients receiving a single intravenous injection of a 3rd generation cephalosporin and 5 days of oral cefixime 100 mg BID versus 360 patients who received the same antibiotic regimen in addition to a povidone-iodine suppository just prior to biopsy.[28] The study noted an infectious complication in eight patients (6.6%) in the control group compared to only one (0.3%) in their povidone iodine cohort.

In 2013, AbuGhosh et al[26] prospectively randomized 865 men to rectal cleansing with povidone-iodine or no rectal cleansing before TRUS PNB in patients receiving standard of care ciprofloxacin prophylaxis. The authors noted a 42% relative risk reduction of infectious complications from rectal cleansing with povidone iodine; however, results were not found to be statistically significant, perhaps due to an underpowering of the study. Nonetheless, several more contemporary studies have continued to add to the body of literature implicating a reduction in infections with no additional risk incurred from povidone iodine. Specifically, Hwang et al retrospectively evaluated 814 males who underwent TRUS PNB and found that a povidone iodine enema reduces rates of severe infectious complications.[24] In particular, while there were no significant differences

TABLE 3. **Summary of clinical studies to date investigating topical povidone iodine rectal preparation at time of prostate needle biopsy**

Author (year)	Design	Patient cohorts	Findings
Zhang et al (2017)	Retrospective, single center	Group A = 402 pts. Soap enema only Group B = 413 pts. soap enema + PEG Group C = 315 pts. PEG + PI All received procedural metronidazole	Infectious complications in 48 (4.25%) patients 23 (5.72%) in Group A 20 (4.84%) in Group B 5 (1.59%) in Group C Significant difference among the groups (p = 0.018)
Ryu et al (2016)	Retrospective, single center	Group A = 192 pts. Empiric abx only Group B = 579 pts. PI + empiric abx Group C = 679 pts. PI + targeted abx	Infectious complication rates 3.6% Group A 2.9% Group B 1.3% Group C Incidences of acute prostatitis and bacteremia were significantly lower in group C (p = 0.041 and p = 0.049, respectively) than in the other groups
Huang et al (2015)	Retrospective, single center	Group A = 613 pts. PI + empiric abx Group B = 201 pts. empiric abx only	Infection rate 2.0% 1.5% Group A versus 3.5% Group B (p = 0.083) Severe infections lower in PI group: 0.3% versus 3.5%, p < 0.001)
Pu et al (2014)	Systematic review	7 trials, 2049 pts.	PI significantly reduced fever, bacteriuria, and bacteremia compared to control RR 0.31 95% CI 0.21-0.45, p < 0.00001
Gyorfi et al (2014)	Retrospective, single center	570 men Group A = 456 pts. empiric abx only Group B = 114 pts. PI + empiric abx	1.8% Group A versus 0% Group B 97% reduction in rectal colony counts in PI group
Abughosh et al (2013)	Prospective, randomized, single center	865 men randomized to Group A = 421 pts. PI + empiric abx Group B = 444 pts. empiric abx	31 pts. (3.5%) with infections 2.6 % Group A versus 4.5% Group B (p = 0.15) 42% relative risk reduction in PI group
Kanjanawongdeenham et al (2009)	Prospective, randomized, single center	100 men randomized to Group A = 50 pts. PI + empiric abx Group B = 50 pts. empiric abx Routine blood culture post-procedure per protocol	Positive blood cultures: Group A: 2/50 (4%) Group B: 9/50 (18%)
Park et al (2009)	Retrospective, single center	481 men Group A = 360 pts. w/PI suppository and empiric abx Group B = 121 pts. empiric abx only	Infection rates: Group A: 0.3% Group B: 6.6% 99.9% reduction in rectal colony forming units after PI treatment

PEG = polyethylene glycol; PI = povidone iodine rectal enema

in the total number of infectious complication rates (1.5% versus 3.5%, p = 0.083), their study showed a significant reduction in the number of severe infectious complications such as bacteremia and sepsis (0.3% versus 3.5%, p = 0.001) in the povidone iodine group.

Admittedly, a limitation of many of these prior studies is their retrospective design and potential underpowering to fully highlight a reduction in clinical infections. Indeed, a systematic review of over 2000 patients from Pu and colleagues does implicate PI significantly reduced fever, bacteriuria, and bacteremia compared to control RR 0.31; 95 % CI 0.21-0.45, p < 0.00001].[25] To better support these retrospective data, we performed this prospective study evaluating not only clinical infections, but also bacteriuria and bacteremia post-procedure. We believe our work is novel in demonstrating that reduction of microorganism colonies on rectal biopsy from PIRP correlated with statistically significant differences in mean urine and blood bacterial counts when comparing PIRP to the standard of care. Specifically, we observed that in patients treated by PIRP, there was an over 97% reduction in rectal microorganism colony counts. Furthermore, mean rates of bacteriuria (1 versus 7 CFU/mL, p < 0.001), bacteremia (0 versus 3 CFU/mL, p = 0.01), and clinical infections (1.1% versus 5.5%) were lower in the PIRP cohort. Collectively, these observations lend objective evidence that local therapies such as povidone-iodine are effective in limiting the translocation of bacteria into the blood and urine following TRUS PNB.

Reduced bacterial counts in the blood and urine would intuitively account for the lower rate of clinical infectious complications following TRUS PNB. Supporting these observations are data from our failures. Specifically, in our one sepsis case from the PIRP cohort, the patient had 4×10^4 bacteria remaining in the rectal vault post-treatment. Additionally, following the biopsy, this patient had 15 CFU/mL of bacteria in the blood which was the highest from this treatment cohort. It is unclear if this bacterial persistence in the rectal vault was simply due to inadequate topical therapy or microbial resistance to the povidone iodine. Similarly, for all three patients developing infections in the standard cohort, elevated urinary and blood bacterial counts were noted following biopsy.

Whilst the above data provides strong evidence supporting local rectal cleansing with povidone iodine, it is important to acknowledge alternative regimens. Certainly, some groups have recommended using a combination of oral and parenteral antibiotics as prophylaxis in select higher risk patients, such as those having undergone previous biopsy.[16,17] Complicating this strategy is that fluoroquinolone-resistant organisms are typically multi-drug resistant, thereby necessitating escalation of adjunctive antibiotics for effectiveness.[29] Furthermore, one has to question whether this increased use of systemic antibiotics simply exacerbates the antibiotic resistance challenges we face at present.

A potentially more refined method of prophylaxis involves rectal swab screening of TRUS PNB preoperatively to identify quinolone-resistance organisms. In this strategy, if quinolone-resistant organisms are detected, a "targeted" prophylactic antibiotic regimen is used based on the bacteria's sensitivity profile. Detection of fluoroquinolone-resistant *E. coli* can be achieved by obtaining a rectal swab from a patient and culturing the specimen on a fluoroquinolone embedded agar.[15] A previous study conducted by Taylor et al[18] reported no cases of infectious complications in a group of 112 men undergoing TRUS PNB using this technique, which was significantly reduced in comparison to a group of 345 men with nine infectious complications undergoing the traditional prophylaxis. However, while proven to be effective, the method of obtaining these rectal swabs preoperatively, culturing on plates embedded with specific media, and tailoring antibiotic therapy can be costly and time consuming for many practices. Furthermore, this strategy fails to identify mixed flora or ESBL *E. coli,* which accounted for up to 38% of the infectious complications in prior studies.[4]

We acknowledge several limitations to this study. Firstly, the study was prospective, albeit non-randomized, and therefore the two cohorts have different index number of patients. Additionally, blinding was not possible as the provider was the one to directly apply the PIRP in order to ensure consistency among preparations and collection of pre-biopsy rectal cultures. Secondly, the smaller patient population size was powered to detect differences in bacteriuria and bacteremia but likely not sufficient to detect a significant difference in the incidence of clinical complications between the two cohorts. Finally, although electronic medical records were rigorously maintained and patients were polled about infectious complications, it is possible that subclinical infectious complications may be underreported and infectious complications that were treated at outside facilities could have been missed.

Conclusion

A PIRP regimen yields decreased rates of bacteruria, bacteremia, and clinical infections following TRUS PNB. This approach presents a potentially cheap and reducible strategy to reduce infections without the need for rectal culture swabs or additional systemic, antibiotics. □

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