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Formalin disinfection of prostate biopsy needles may reduce post-biopsy infectious complications

Nirmish Singla, **Jordon Walker**, **Solomon L. Woldu**, **Niccolo M. Passoni**, **Karen de la Fuente**, **Claus G. Roehrborn**

Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA.

Abstract

BACKGROUND: We sought to determine whether formalin disinfection of prostate biopsy needles between cores reduces post-biopsy urinary tract infections (UTIs).

METHODS: We reviewed a single-surgeon experience of transrectal prostate biopsies from 2010 to 2014. Biopsies were performed in either an operative suite, where 10% formalin was used to disinfect the needle tip between each biopsy core, or an outpatient clinic, where formalin was not used. Our primary outcome was post-biopsy UTI rates, defined as a positive urine culture within 30 days of biopsy. Infection severity was characterized by the need for admission. Patient demographics, prostate size, prior biopsies, prior UTIs, pre-biopsy antibiotics and cultures and post-biopsy cultures were analyzed. Logistic regression was used to assess predictors of post-biopsy UTIs. Statistical significance was defined as $P<0.05$.

RESULTS: A total of 756 patients were included for analysis, including 253 who received formalin disinfection and 503 who did not. Of these, 32 patients (4.2%) experienced post-biopsy UTIs, with 8 requiring admission (all without formalin use). Infection rates were more than double in the group that did not receive formalin (5.2% vs 2.3%, $P = 0.085$). More patients in the formalin group had undergone prior biopsies (73.9% vs 31.8%, $P<0.001$). On multivariable analysis, prior UTI (odds ratio (OR) 3.77, $P = 0.006$) was a significant predictor for post-biopsy infection, whereas formalin disinfection trended towards a protective effect (OR 0.41, $P = 0.055$).

CONCLUSION: Infectious complications following prostate biopsy may be mitigated by the use of formalin disinfection of the biopsy needle between cores.

INTRODUCTION

Over one million transrectal ultrasound-guided (TRUS) prostate biopsies are performed annually in the United States and Europe.[1] Urinary tract infections (UTIs), including both bacteriuria treated with outpatient antibiotics and sepsis necessitating inpatient admission and intravenous antibiotics, are among the most common complications following prostate biopsy.[1] Incidence rates have been increasing in light of emerging fluoroquinolone-resistant

Correspondence: Dr CG Roehrborn, Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, J8.130, Dallas, TX 75390-9110, USA. claus.roehrborn@utsouthwestern.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

bacterial strains.[2] Overall reported UTI rates after biopsy have ranged from 0.1 to 7% in various series,[3–6] with 30-day hospital admission rates ranging from 0.6 to 4.1% of cases.[7] Given the mean estimated cost of $5900 per hospital admission for infectious complications after TRUS biopsy[8] and associated morbidity, there is a need to identify cost-effective strategies to help curb these serious complications.

A number of strategies to decrease UTI rates following TRUS biopsy have been investigated including augmented antibiotic prophylactic regimens tailored to institutional patterns of bacterial susceptibility,[8–12] targeted antibiotics per rectal swab cultures,[2,13–16] routine urine cultures before prostate biopsy[17] and rectal cleansing with topical povidone-iodine preparation,[18,19] enemas[20–22] or bisacodyl suppositories.[23] However, data have been variable with regard to the effectiveness, cost efficiency and ease of implementing these strategies.[1] An alternative simple, cost-neutral method of needle disinfection using formalin between biopsy cores was recently reported.[24] In the present study, we sought to determine whether the use of formalin to disinfect the prostate biopsy needle after each core decreases post-biopsy infectious complications. We secondarily evaluated other predictors of post-biopsy UTIs.

MATERIALS AND METHODS

Following institutional review board approval, we reviewed a single-surgeon experience of consecutive TRUS biopsies performed between 1 January 2010 and 31 August 2014. Biopsies were performed at two separate centers within the same institution, including an operative suite and an outpatient clinic. A standard 12-core biopsy template protocol was utilized in the clinic setting under no sedation, whereas a 32-core saturation biopsy template was used in the operative suite under moderate sedation. Decision to perform TRUS biopsy in the operating room was based on either the need for saturation biopsy or patient request for sedation. In the operative suite, a no-touch formalin disinfection technique was instituted without finger manipulation, in which the distal 3 cm of the biopsy needle, with its outer sheath retracted, was immersed and swirled in 10% formalin before obtaining each core in all patients.[24] The biopsy cores were dislodged into the specimen container while the formalin disinfected the end of the needle. In addition, after the specimen was dislodged, the needle was then swirled in a new fresh formalin container without any tissue. This technique was not performed in any patient within the clinic setting.

All patients received a pre-procedural rectal enema and antibiotic. TRUS biopsy was performed only if patients did not exhibit symptoms of an active UTI and had low clinical suspicion for infection on pre-biopsy urinalysis (absence of leukocyte esterase, nitrites and bacteria and <5 white blood cells per high-power field) based on a clean-catch midstream voided or catheterized specimen with <5 squamous epithelial cells per high-power field. Pre-biopsy urine cultures were not obtained in all such cases, although any patient with concerning symptoms or urinalysis received a complete course of culture-appropriate antibiotics before consideration of biopsy. Next, 5 ml of 1–2% lidocaine was injected near the lateral base at the insertion of the seminal vesicles on each side of the prostate to achieve local anesthesia. A sterile needle guide and needle were used for each procedure.

Indications to proceed with biopsy were based on a shared decision between provider and patient following a discussion of associated risks and benefits in the setting of PSA values, digital rectal examination findings and patient life expectancy. Data including patient demographics and comorbidities, lower urinary tract symptoms, number of prior prostate biopsies, prior UTIs, receipt and type of pre-biopsy antibiotics, pre-biopsy cultures and post-biopsy cultures and sensitivities were collected and analyzed when available. Urine was collected via clean-catch midstream spontaneous voids with retraction of the foreskin in uncircumcised patients or via catheterization and cultured using Colombia CNA (colistin and nalidixic acid) agar with 5% sheep blood and MacConkey agar.

Our primary outcome was post-biopsy UTI rates, defined as any positive urine culture documented within 30 days following biopsy. Post-biopsy urine cultures were generally obtained if a patient sought medical attention for any suggestive signs or symptoms of a UTI, such as dysuria, frequency, urgency, hematuria, fevers or abdominal or flank pain. Infection severity was characterized as either mild (suitable for outpatient management) or severe (requiring inpatient hospitalization for sepsis). Positive post-biopsy urine cultures were treated appropriately with tailored antibiotics, and they were compared with pre-biopsy antibiotic class received and culture results if available.

Patients and infectious outcomes were stratified by whether or not formalin disinfection was employed during biopsy. Independent-sample Mann–Whitney *U*-test and χ^2 test were used to compare continuous and categorical variables, respectively, between the two groups. Univariable and multivariable logistic regression analyses were performed to identify predictors of post-biopsy infections. All statistical analyses were conducted using SPSS version 22.0 (IBM, Armonk, NY, USA). *P*-values are two sided with statistical significance defined for $P<0.05$.

RESULTS

A total of 756 patients were included for analysis, including 253 who received formalin disinfection between cores and 503 who did not. Patient characteristics are summarized in Table 1. In all, 32 patients (4.2%) experienced a UTI within 30 days of biopsy, 8 of whom required hospital admission (1.1%). Infection rates were more than double in the non-formalin group (5.2% vs 2.3%, $P = 0.085$). All 8 patients requiring admission were in the non-formalin group, whereas no patients in the formalin group developed sepsis ($P = 0.057$). Patients who received formalin had slightly larger median prostate size on TRUS (47.0 vs 43.2 g, $P = 0.036$) and were more likely to have had a prior TRUS biopsy performed (73.9% vs 31.8%, $P<0.001$).

The majority of patients received a pre-biopsy fluoroquinolone for antibiotic prophylaxis (93.3%). Rates of prophylactic non-fluoroquinolone administration, including penicillin derivatives, cephalosporin, sulfamethoxazole/trimethoprim, aminoglycoside or other antibiotic class, were not significantly different between the two groups (5.8% in the non-formalin group vs 8.7% in the formalin group, $P = 0.166$). Pre-biopsy urine cultures were only obtained in 252 patients (33.3%); the vast majority of these cultures were obtained in patients who were biopsied in the operative suite (219/253, 86.6%) as part of routine pre-

operative testing rather than in the outpatient clinic setting (33/503, 6.6%). However, urine cultures did not always result before biopsy and thus were not routinely treated or used to guide prophylaxis if the patient was asymptomatic and had low suspicion for UTI on urinalysis. Out of 219 patients in the formalin group, 23 were retrospectively noted to have a positive pre-biopsy urine culture, and of those with sensitivity data available (17 patients), 58.8% had received a class-appropriate prophylactic antibiotic before undergoing biopsy. In contrast, 7/33 patients in the non-formalin group were retrospectively noted to have a positive pre-biopsy urine culture, of whom 71.4% had received a class-appropriate antibiotic before biopsy ($P = 0.669$ vs formalin group).

On univariable logistic regression analysis, use of formalin trended towards a protective effect for post-biopsy UTIs (odds ratio (OR) 0.45, $P = 0.079$), whereas prior UTI (OR 3.40, $P = 0.010$) was a significant predictor for post-biopsy UTIs, as shown in Table 2. Neither use of a non-fluoroquinolone antibiotic (OR 1.46, $P = 0.547$) nor receipt of a class-inappropriate prophylactic antibiotic per positive pre-biopsy urine culture when available (OR 1.86, $P = 0.575$) significantly influenced UTI rates. ORs remained significant on multivariable analysis for prior UTI (OR 3.77, $P = 0.006$) and approached significance for formalin use (OR 0.41, $P = 0.055$).

DISCUSSION

We herein report a reduction in post-TRUS biopsy UTIs by more than 50% using formalin disinfection of the biopsy needle between cores, with a trend toward statistical significance. No patients in the formalin group required hospital admission for sepsis in contrast to eight patients in the non-formalin group. We also demonstrate a protective trend of formalin use in preventing infectious complications, in a multivariable model.

Although our results did not achieve statistical significance using an α-level of 0.05, the potential clinical relevance of our results cannot be overlooked. Arguably, liberalizing our significance threshold to $P<0.1$ (which would yield a statistically significant reduction in UTI and sepsis rates in χ^2 analysis as well as a significantly protective OR on multivariable analysis using formalin) may be justifiable. That is, it may be reasonable to accept a 10% chance for our difference in UTI rates between the formalin and no-formalin groups to be a random finding, given that the added cost, time and complications directly from the intervention (formalin disinfection) were negligible. Formalin disinfection of the needle between biopsies is a no-cost intervention as formalin is already available on the set for the specimen. Furthermore, there appears to be no added harm from implementation of this technique, as demonstrated by Issa *et al.*[24] and by the lack of adverse events in our cohort following formalin disinfection.

To our knowledge, only one other study has reported on this technique of biopsy needle disinfection using formalin between cores.[24] The authors reported similarly favorable outcomes. Their statistical analysis was limited, however, as they did not compare underlying risk factors that may have affected UTI rates against their historical control or perform any regression analyses to identify other potentially confounding predictors of post-biopsy infections. Nonetheless, they did perform an *ex vivo* experiment that showed the total

potential formaldehyde exposure to be ~ 3.9 mg—which they acknowledge as a likely overestimation—for a 12-core prostate biopsy template using 10% formalin needle disinfection.[24] This amount is well within the safe parameters of formaldehyde exposure permitted by the Environmental Protection Agency (0.2 mg kg^{-1} per day).[25] As in their study, we did not encounter formalin-related adverse events even with a 32-core biopsy template, reinforcing its safety for use in this setting.

With respect to cumulative exposure to formaldehyde in patients who undergo repeated biopsy sessions, DNA–protein crosslinks induced by formaldehye in mammalian cells *in vitro* and *in vivo* are removed from normal cells with a half-time of 2–3 h.[26] Furthermore, formaldehyde is eliminated from the plasma with a half-time of ~ 1–1.5 min.[27] Hence, it would be highly unlikely for any considerable amount of formaldehyde to remain between biopsy sessions. As formaldehyde takes days to biodegrade to low levels when dissolved in water,[28] the solution would be expected to remain active throughout the biopsy session, even with 32 cores obtained.

Given that 19–22% of patients undergoing prostate biopsies reportedly harbor fluoroquinolone-resistant bacterial strains on rectal swabs,[2,16] targeting these pathogens while minimizing the emergence of further antibiotic resistance has generated considerable interest. Formalin has been shown to exhibit effective bacteriocidal activity against most pathogens, including *Escherichia coli*, at low concentrations by destroying bacterial fimbriae and pili and inhibiting protein synthesis.[29] In two additional *ex vivo* experiments, Issa et al. [24] found that formalin is effective against fluoroquinolone-resistant strains of *E. coli*, suggesting a promising role for formalin in this setting without promoting antibiotic resistance. Several alternative strategies have been utilized to address this issue with variable efficacy, cost effectiveness and ease of implementation reported. Although some authors have recommended rectal cleansing with topical povidone-iodine,[19] mechanical enemas or biscaodyl suppositories[23] before biopsy, others have found that they these maneuvers did not appear to make any difference in clinically significant UTI rates.[18,20–22] The benefit of routine urine cultures before prostate biopsy also remains unclear.[17]

Augmented antibiotic prophylactic regimens have been shown to reduce overall and fluoroquinolone-resistant UTI rates,[9–12] and Adibi *et al.*[8] showed that with increasing risk of hospital admission for infectious complications, use of more intensive prophylactic regimens becomes more cost effective than standard fluoroquinolone regimens. However, disadvantages of this approach include the potential for increased side effects or intolerance, geographic heterogeneity in bacterial susceptibility patterns and potential emergence of new bacterial resistance. Targeted prophylaxis based on pre-biopsy rectal swab cultures has also been proposed to reduce infectious complications in patients with fluoroquinolone-resistant bacterial strains.[13,15,16] In a single-center, non-randomized cohort, Taylor *et al.*[16] reported a cost saving of ~ $4499 per post-biopsy infectious complication averted using targeted prophylaxis, and they note that 38 men would need to undergo rectal swab in order to prevent 1 infectious complication. However, this approach is likely more expensive and time consuming than empiric antibiotic prophylaxis alone,[14] and there are currently no randomized studies comparing infection rates and costs of targeted prophylaxis using rectal swabs versus standard or augmented prophylaxis.[1] Furthermore, performing routine rectal

swabs may seem impractical, especially given that clinically significant infections have been shown to develop only in a small proportion of patients with fluoroquinolone-resistant bacterial strains.[2] In our cohort, use of non-fluoroquinolone antibiotic prophylaxis was not associated with infection rates.

Our post-biopsy infection rates appear to be concordant with those reported in other studies.[3–7] Proposed risk factors for infections include prior exposure to antimicrobials,[4,30] impaired immunity (high-dose steroid use, diabetes), renal failure, indwelling urethral catheters and recurrent UTIs.[12,31] Although Charlson comorbidity score, which would account for diabetes, renal disease and other immunosuppressive states, did not significantly influence UTI rates in our cohort, a history of UTIs was our strongest predictor on multivariable analysis. Despite repeated antimicrobial exposure in repeat biopsy sessions, Loeb *et al.*[32] noted that a repeat biopsy was not associated with greater risk of infectious complications versus the initial biopsy, which was concordant with our results.

There are limitations to our study including its retrospective nature and single-institution cohort. During the time of patient accrual, awareness of infectious complications increased substantially. The prevalence of quinolone-resistant *E. coli* increased during the same time period, but this affected both groups of patients. Although we may not capture the geographic variability in bacterial susceptibilities from other regions, we would not expect this to affect the efficacy of formalin.[24,29] Furthermore, post-biopsy urine cultures were obtained only if patients subsequently presented to our institution; thus, it is possible that we did not capture patients who may have had positive urine cultures drawn at another facility. However, all patients are scheduled to follow-up in our clinic to review biopsy results, and during this follow-up appointment, any post-procedural issues are discussed.

In addition, there were two different settings in which biopsies were obtained (clinic and operating room). A single surgeon performed all of the biopsies regardless of location, thereby mitigating operator differences in setup and technique; however, other confounding factors may have played a role between the two sites. In particular, there was likely some selection bias, in that patients who underwent biopsy in the operating suite (and hence received formalin) had a significantly greater rate of prior biopsies performed. Pre-biopsy urine cultures were also drawn with much greater frequency for these patients, though were not always used to guide biopsy prophylaxis and have an unproven benefit, as discussed earlier.[17] Furthermore, patients who underwent biopsy in the operating room underwent a 32-core template versus only 12 cores in the clinic setting, although in a large study of nearly 5000 patients, Berger *et al.*[33] did not find a significant association between the number of biopsy cores and complication rates. Ironically, despite the larger median prostate size and greater number of prior biopsies and biopsy cores in the formalin group, formalin use still trended towards a protective effect for post-biopsy UTIs on multivariable analysis in our large cohort, suggesting that it may have had an even stronger OR if a case-matched control group were compared. Prospective studies in a randomized population are indeed warranted.

CONCLUSION

We show that UTI rates following prostate biopsy may be reduced using formalin disinfection of the biopsy needle between cores. On multivariable analysis, formalin use trends towards a protective role in preventing infectious complications. Formalin is an attractive solution to emerging bacterial resistance based on its simplicity, effectiveness, cost neutrality and safety. Although formalin may not replace other principles such as clean technique, sterile equipment processing and use of prophylactic antibiotics, it is practical as an adjunctive maneuver.

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Table 1.

Patient characteristics and infectious outcomes stratified by use of formalin disinfection

	Total	*Formalin used*	*No formalin used*	P-*value*[a]
Patient characteristics				
Total patients	756	253	503	—
Median age (IQR), years	63.8 (58.2–69.2)	63.5 (57.5–68.4)	64.1 (58.4–69.7)	0.145
Median CCI (IQR)	2 (1–3)	2 (1–3)	2 (2–3)	0.011[a]
Median prostate size (IQR), g	45.0 (31.9–65.0)	47.0 (34.8–71.3)	43.2 (30.8–64.0)	0.036[a]
Presence of LUTS (%)	64.6	67.6	63.0	0.228
Prior prostate biopsy (%)	45.9	73.9	31.8	<0.001[a]
Prior UTI (%)	6.9	9.1	5.8	0.095
Use of non-fluoroquinolone prophylaxis before biopsy (%)	6.7	8.7	5.8	0.166
Documented (+) urine culture before biopsy, % (no.)	11.9 (30/252)	10.5 (23/219)	21.2 (7/33)	0.086
Pre-biopsy bacterial genus (no. of patients)	*Escherichia:* 10	*Escherichia:* 5	*Escherichia:* 5	—
	Enterococcus: 11	*Enterococcus:* 11	*Enterococcus:* 0	
	Streptococcus: 3	*Streptococcus:* 3	*Streptococcus:* 0	
	Klebsiella: 1	*Klebsiella:* 0	*Klebsiella:* 1	
	Polymicrobial: 2	Polymicrobial: 1	Polymicrobial: 1	
	Other or not speciated: 3	Other or not speciated: 3	Other or not speciated: 0	
Pre-biopsy CFU counts (%)	<10K: 65.5	<10K: 86.4	<10K: 0	—
	10–49K: 10.3	10–49K: 9.1	10–49K: 14.3	
	50–99K: 3.4	50–99K: 0	50–99K: 14.3	
	>100K: 20.7	>100K: 4.5	>100K: 71.4	
Pre-biopsy culture sensitive to prophylactic antibiotic received, if known, % (no.)	62.5 (15/24)	58.8 (10/17)	71.4 (5/7)	0.669
30-Day outcomes				
Post-biopsy UTI, % (no.)	4.2 (32 patients)	2.3 (6 patients)	5.2 (26 patients)	0.085
Requiring admission, % (no.)	1.1 (8 patients)	0 (0 patients)	1.6 (8 patients)	0.057
Post-biopsy bacterial genus (no. of patients)	*Escherichia:* 14	*Escherichia:* 1	*Escherichia:* 13	—
	Enterococcus: 10	*Enterococcus:* 3	*Enterococcus:* 7	
	Streptococcus: 2	*Streptococcus:* 0	*Streptococcus:* 2	

	Total	*Formalin used*	*No formalin used*	P-*value*[a]
	Polymicrobial: 4	Polymicrobial: 1	Polymicrobial: 3	
	Other or not speciated:	2 Other or not speciated: 1	Other or not speciated: 1	
Post-biopsy CFU counts (%)	<10K: 34.4	<10K: 50.0	<10K: 30.8	—
	10–49K: 12.5	10–49K: 0	10–49K: 15.4	
	50–99K: 18.8	50–99K: 16.7	50–99K: 19.2	
	>100K: 34.4	>100K: 33.3	>100K: 34.6	
Post-biopsy culture sensitive to prophylactic antibiotic received, % (no.)	31.0 (9/29)	0 (0/5)	37.5 (9/24)	0.153

Abbreviations: CCI, Charlson comorbidity index; CFU, colony-forming unit (‘K’ signifies 1000 CFUs); IQR, interquartile range; LUTS, lower urinary tract symptom; UTI, urinary tract infection.

[a]Independent-samples Mann–Whitney *U*-tests were used to compare continuous variables and χ^2 tests for categorical variables. *P*-values were all two sided with statistical significance defined for $P<0.05$ (indicated by asterisk).

Table 2.

Univariate and multivariate logistic regression analyses for predictors of 30-day post-biopsy UTIs

	Variable	*OR (95% CI)*	P-*value*[a]
Univariate analysis	Patient age	1.03 (0.99–1.08)	0.196
	CCI	1.14 (0.93–1.40)	0.216
	Prostate size ⩾40 g	1.45 (0.67–3.13)	0.340
	Presence of LUTS	1.22 (0.57–2.61)	0.612
	Prior prostate biopsy	0.97 (0.47–1.99)	0.928
	Prior UTI	3.40 (1.33–8.68)	0.010[a]
	Use of formalin disinfection	0.45 (0.18–1.10)	0.079
	Use of non-fluoroquinolone prophylaxis before biopsy	1.46 (0.43–4.96)	0.547
	Pre-biopsy culture not sensitive to prophylactic antibiotic received	1.86 (0.21–16.18)	0.575
Multivariate analysis	Prior UTI	3.77 (1.46–9.73)	0.006[a]
	Use of formalin disinfection	0.41 (0.17–1.02)	0.055

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval (95%); LUTS, lower urinary tract symptom; OR, odds ratio; UTI, urinary tract infection.

[a]Statistical significance defined for $P<0.05$ (indicated by asterisk).