Preventing Pain During Office Biopsy of the Prostate

A Single Center, Prospective, Double-Blind, 3-Arm, Parallel Group, Randomized Clinical Trial

Richard A. Ashley, MD
Brant A. Inman, MD
Jonathan C. Routh, MD
Amy E. Krambeck, MD
Sameer A. Siddiqui, MD
Lance A. Mynderse, MD
Matthew T. Gettman, MD
Michael L. Blute, MD

Department of Urology, Mayo Clinic, Rochester, Minnesota.

BACKGROUND. A prospective, double-blind, 3-arm, parallel group, randomized clinical trial was performed to compare 3 anesthetic techniques for preventing pain during prostate biopsy.

METHODS. A total of 243 men undergoing a 12-core prostate biopsy were randomized to 1 of 3 anesthetic methods: 1) seminal vesicle-prostatic base blockade, 2) intraprostatic blockade, and 3) apical-rectal blockade. Pain was estimated with the 10-point visual analog scale. Multivariate logistic regression evaluated factors predictive of pain. The Kruskal-Wallis test analyzed overall group comparisons and the Steel-Dwass test assessed between-group comparisons in pain scores. Proportional odds ordinal logistic regression quantified the ability of covariates and treatment arms to predict biopsy pain. These values are presented as odds ratios with confidence intervals (OR, 95% CI).

RESULTS. From November 2005 to June 2006, 81 men were randomized to 3 study arms. Lidocaine administration was the most painful element of the procedure, while probe insertion was the least. Apical biopsies were routinely more painful than mid-gland biopsies, which were more painful than base biopsies. The apical-rectal blockade was the most painful to administer, but has lasting effects and led to better pain control than the prostatic base-seminal vesicle blockade. Similarly, the intraprostatic blockade was more effective than the prostatic base-seminal vesicle blockade. Besides pain reported at the time of anesthetic injection, no difference was identified between the intraprostatic and apical-rectal blockades.

CONCLUSIONS. Mid and apical biopsies of the prostate are more painful than base biopsies. The seminal vesicle-prostatic base blockade is less effective than intraprostatic and apical-rectal blockade at controlling pain. Cancer 2007; 110:1708–14. © 2007 American Cancer Society.

KEYWORDS: prostate, biopsy, pain, anesthesia.

Each month, approximately 50 office-based ultrasound-guided transrectal needle biopsies of the prostate are performed at our medical center on men with an elevated prostate-specific antigen (PSA) or an abnormal digital rectal exam (DRE). The pain and short-term morbidity associated with prostate biopsy has been carefully described.1,2 Like many biopsy centers, we have instituted periprostatic anesthesia along with a topical intrarectal anesthetic jelly in hopes of improving the biopsy experience of our patients.3–5 Although comfort levels have improved with these 2 agents, biopsy-associated pain has not been eliminated and there remains ample room for innovation.

Recent attempts at ameliorating biopsy-associated pain have resulted in changes to both the type of anesthetic agent used and
the anatomic site of injection. To date, the best analgesic cocktail and injection method for prostate biopsy remain undefined. The goals of this randomized, clinical trial were to 1) identify the stages of the biopsy protocol that result in the most pain, and 2) determine the optimal location for local anesthetic delivery for a 12-core prostate biopsy in the office setting.

MATERIALS AND METHODS

Trial Design and Participants

The study was designed as a single-center, prospective, double-blind, 3-arm, parallel group, randomized clinical trial comparing 3 prostate anesthesia techniques: seminal vesicle-prostatic base blockade, intra-prostatic blockade, and prostatic apex-rectal tissue blockade. The protocol was approved by the Mayo Clinic Institutional Review Board and patient recruitment took place from November 2005 to June 2006.

Men were eligible for the study if they were referred to the prostate biopsy suite for a nonsaturation office biopsy procedure to rule out the presence of prostate cancer in the setting of an elevated PSA or abnormal DRE. We excluded men with a history of daily narcotic use, chronic prostatitis and chronic pelvic pain, pelvic floor tension myalgia, and other chronic pain syndromes that could bias patient pain perception. For safety reasons, we also excluded men with active anorectal disease (such as inflammatory bowel disease and hemorrhoids), active urinary tract infection, or allergy to local anesthetic.

Treatment Allocation and Concealment

Informed consent was obtained by a study nurse that was uninvolved with treatment allocation, administration, or outcome assessment. This nurse recorded risk factors and administered a quality of life survey to consenting patients before biopsy. Patients were then randomized in the biopsy suite to 1 of 3 treatment arms using a computerized randomization procedure with blocking. A block size of 6 was used and remained fixed throughout the study. Patients and nurses assessing outcomes were blinded to treatment group assignment. Although efforts were made to conceal the treatment allocation from the study nurses assessing treatment outcome, it is possible that nurses experienced with transrectal ultrasound (TRUS) may have deciphered the treatment allocation by observing the injection process on the imaging screen. There were no treatment crossovers and no dropouts; therefore, the present analysis is necessarily intent-to-treat.

Biopsy and Anesthetic Procedures

All biopsy sessions took place in an outpatient biopsy suite typical of most office urology practices. The procedures were performed by 4 senior-level urology residents that had performed over 100 TRUS-guided prostate biopsies before study commencement. All patients received oral quinolone antibiotic therapy the day before prostate biopsy and this was continued for 4 days after biopsy. If endocarditis prophylaxis was indicated, intravenous antibiotics were administered 30 minutes before the procedure. Each patient was instructed to perform a prebiopsy rectal enema using Fleet phosphosoda. Vital signs were assessed by a nurse and then 10 mL of topical 20% benzocaine jelly was administered intrarectally and left in place for 5 minutes before TRUS probe insertion. With the patient in the prone, jackknife position, a B&K 8808 model side-fire biplanar TRUS probe (B-K Medical, Denmark) was used to image the prostate and its surrounding structures. A 22-gauge, 15-cm spinal needle with was used to inject 10 mL of 1% lidocaine anesthetic without epinephrine using 1 of the following techniques (Fig. 1):

- Group 1 (Seminal vesicle-prostatic base blockade): Injection of 5 mL of lidocaine between the seminal vesicle and base of prostate, while drawing the TRUS and anesthetic toward the apex of the gland and the needle toward the rectal wall. Adequacy was confirmed by the “Mount Everest sign.” This

![Initial needle placement for administration of anesthetic.](image)

FIGURE 1. Initial needle placement for administration of anesthetic. (1 = seminal vesicle-prostatic base blockade, 2 = intra-prostatic blockade, 3 = apical-rectal blockade).
was then repeated on the opposite side of the gland.

- Group 2 (Intraprostatic blockade): Insertion of the needle through the lateral prostate gland, from the apex to the base, and infiltration of the gland with 5 mL of lidocaine along the entire length of the prostate as the TRUS and anesthetic were drawn from the base to the apex. Adequacy was confirmed by the increase in gland echogenicity that occurred as the anesthetic was administered. This was then repeated on the opposite side of the gland.

- Group 3 (Apical-rectal blockade): Insertion of the needle into the prostate apex with infiltration of the apical and periapical tissues with 5 mL of lidocaine, while drawing the TRUS probe and anesthetic inferiorly into the rectal tissue. Adequacy was confirmed by an apical wheal of anesthetic at the apex and surrounding tissues. This was then repeated on the opposite side of the gland.

After injection, a timer was set for 2 minutes to allow full anesthetic effect. The prostate volume was then estimated via TRUS and the gland was scanned for anatomic abnormalities. After the 2-minute wait time, 12 prostate biopsies were obtained using a standardized template: 2 apical, 2 midregion, and 2 base biopsies were taken from both the right and left lobes of the prostate with the needles angled toward the lateral peripheral zones and anterior-apical horns. Any hypoechoic lesions identified were included in the 12-core sampling. After the biopsy procedure, patients were examined to rule out rectal or urethral trauma and hemorrhage. Vital signs were then reevaluated and the patient was allowed to leave the biopsy suite when ready and stable.

Outcome Assessment

The primary clinical outcome evaluated was patient-reported pain on a standard 10-point visual analog scale (VAS). During prespecified timepoints during the biopsy procedure, patients were instructed by a study nurse to rate their current level of pain from 0 to 10 on the VAS. The outcome assessment intervals of pain were: during TRUS probe insertion, during local anesthetic infiltration, during each biopsy procurement (1 through 12), and at the termination of the biopsy session.

Statistical Analyses

A sample size of 81 patients per group was estimated with a 3-group analysis of variance (ANOVA) test with the following assumptions: detection of a minimum 0.4 point deviation by a single group from the grand mean pain score, a measurement variance in pain score of 0.9, an \( \alpha \) level of 0.05, and 80% power.\(^3,4,7-14\)

Histograms of the overall distributions of pain scores for each timepoint were consistently right-skewed and indicated the need for nonparametric testing (Fig. 2). Therefore, the Kruskal-Wallis test was used to test for overall group differences and the Steel-Dwass test, a post-hoc nonparametric multiple comparisons procedure,\(^15\) was used to test for between-group differences in pain scores. In addition, proportional odds ordinal logistic regression models were created to quantify the ability of covariates and treatment arms to predict biopsy pain. The ordinality and proportional odds assumptions were verified graphically as described by Harrell.\(^16\) Because of sparse data at certain pain levels, adjacent pain level categories were collapsed so that at least 15 measures were available per pain level. This left 4 timepoints with 5 ordinal pain levels and 2 timepoints with 6 ordinal pain levels.

RESULTS

Figure 2 demonstrates the recruitment, randomization, and patient retention dynamics for this study and Table 1 details the clinical features of the 243 men evaluated. Important clinical factors appeared evenly distributed among the 3 study arms, suggesting no random covariate imbalance between the groups. In particular, there were no differences with respect to age, body mass index (BMI), prebiopsy PSA, prostate volume, family history of prostate cancer, DRE status, the number of prior biopsies, or prior pathology. The overall cancer detection rate was 47.4% for the entire cohort.

In the study, 16% (40 of 243) of men reported a pain score \( \geq 5 \) at some point during the biopsy
A multivariate ordinal logistic regression model could not identify any clinicopathologic variable that reliably predicted escalating patient pain during the biopsy procedure, although older men appeared to tolerate lidocaine injection better and men with larger prostates tolerated the base biopsies better (Table 2). Overall, the most painful part of the procedure was lidocaine injection, followed by the apical biopsies, midprostate biopsies, base biopsies, probe insertion, and the end of the procedure (Fig. 3).

The overall Kruskal-Wallis ANOVA demonstrated important differences in pain scores between the groups at all timepoints except TRUS probe insertion (Table 3). Between-group comparisons, adjusted for multiple testing by the Steel-Dwass method, are also presented in Table 3. These data suggest that the seminal vesicle-prostatic base blockade was the least effective method of delivering prostatic analgesia. Although no statistical difference in efficacy existed between intraprostatic and apical blockades for most timepoints, injecting lidocaine at the prostatic apex to obtain the apical blockade was significantly more painful than the intraprostatic technique. To visually demonstrate these differences in treatment efficacy, proportional odds ordinal logistic regression was used to calculate odds ratios and their 95% confidence intervals for worsening pain control between the study arms and these results are plotted in Figure 4.

Complications occurring during the study included: urethral catheterization in 3 patients for either severe hematuria or for urinary retention, syncope in 1 patient, and a skin rash due to quinolone therapy in 1 patient.

**DISCUSSION**

The prostate biopsy remains 1 of the most common procedures performed in the urologist’s office. The technical aspects of the procedure undoubtedly cause significant anxiety and fear of pain in many patients. Patients requiring repeat biopsy could be particularly prone to having an unpleasant and painful biopsy experience. Caring physicians are duty-bound to ensure that prostate biopsy is a well-tolerated procedure that causes as little emotional and physical trauma as possible.

One way to improve the prostate biopsy experience is to reduce the pain caused by the passage of the biopsy needles through the rectal wall and into the prostate. To this end, we examined whether different techniques for obtaining prostatic analgesia could provide superior pain relief during biopsy procedure in a moderately sized, double-blind, randomized trial. Patients were treated uniformly according to strict preestablished biopsy protocols to ensure as little variability in biopsy technique as reasonably possible. Rigorous control was maintained for the quantity and location of anesthetic injected, the waiting time before biopsy procurement, the method of prostate imaging and volume measurement, the timing and sequence of prostate biopsy, and the fashion in which the pain outcomes were elicited and recorded. However, given that 4 individuals performed the biopsies over 8 months, it is probable that some degree of procedural variation existed. We did not detect, however, any systematic change in pain outcomes when patients were stratified by month of procedure or by treating physician.

Contrary to prior studies that have suggested that insertion of the ultrasound probe is the most painful part of the biopsy procedure, we consistently found that this was the least painful manipulation experienced by our patients. This difference may be explained by our use of a side-fire probe (instead of an end-fire probe), our systematic application of benzocaine jelly, and our use of the prone-jackknife position (instead of the lateral decubitus position).

**TABLE 1**

Baseline Clinicopathologic Variables by Study Arm

<table>
<thead>
<tr>
<th></th>
<th>Seminal vesicle-prostatic base blockade, n = 81</th>
<th>Intraprostatic blockade, n = 81</th>
<th>Apical-rectal blockade, n = 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median IQR</td>
<td>Median IQR</td>
<td>Median IQR</td>
<td>Median IQR</td>
</tr>
<tr>
<td>Age, y</td>
<td>65 60–71</td>
<td>66 59–72</td>
<td>65 58–71</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9 25.0–31.9</td>
<td>28.4 26.4–30.9</td>
<td>28.3 25.7–31.9</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>5.1 3.4–6.4</td>
<td>4.7 3.0–7.0</td>
<td>4.9 3.4–6.7</td>
</tr>
<tr>
<td>Prostate volume, mL</td>
<td>46 32–65</td>
<td>46 33–64</td>
<td>47 32–60</td>
</tr>
<tr>
<td>Count %</td>
<td>Count %</td>
<td>Count %</td>
<td>Count %</td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td>Yes 17 21%</td>
<td>26 32%</td>
<td>25 31%</td>
</tr>
<tr>
<td>Abnormal digital rectal exam</td>
<td>Yes 34 42%</td>
<td>35 43%</td>
<td>35 43%</td>
</tr>
<tr>
<td>Number of previous biopsies</td>
<td>0 65 80%</td>
<td>65 80%</td>
<td>65 80%</td>
</tr>
<tr>
<td>Number of previous biopsies</td>
<td>1 15 19%</td>
<td>15 19%</td>
<td>14 17%</td>
</tr>
<tr>
<td>Number of previous biopsies</td>
<td>&gt;2 1 1%</td>
<td>1 1%</td>
<td>2 2%</td>
</tr>
<tr>
<td>Previously diagnosed prostate pathology</td>
<td>None 65 80%</td>
<td>65 80%</td>
<td>66 81%</td>
</tr>
<tr>
<td>PIN/ASAP</td>
<td>14 17%</td>
<td>14 17%</td>
<td>14 17%</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2 2%</td>
<td>2 2%</td>
<td>1 1%</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; PSA, prostate-specific antigen; BMI, body mass index; PIN/ASAP, prostatic intraepithelial neoplasia/atypical small acinar proliferation.
Injection of the local anesthetic agent was uniformly the most painful part of the procedure in all groups. In this regard, apical blockade appeared to be significantly more painful than the other 2 techniques of prostatic blockade and elicited the highest levels of pain experienced by patients in our study.

After the completion of prostatic analgesia, needle passage into the prostate was fairly well tolerated, with most patients experiencing only mild discomfort. Although not explicitly tested in the current study, our subjective impression is that allowing the elapse of a standardized period of time (2 minutes in the current study) before passing the biopsy needles into the prostate may have an important role in overall pain prevention. This waiting period does not waste time because it can be used to systematically survey the prostate gland and to accurately calculate prostate volumes. It is interesting to note that while our biopsy template proceeded from the prostatic base toward the prostatic apex, allowing the maximum anesthetic dwell time for the apex, this anatomical site was consistently the most sensitive to biopsy. This finding is congruent with prior studies that have also suggested that the apical biopsy is associated with significant pain.7,14,17–19 The discomfort of apical biopsies is related to the anatomic relation between the prostatic apex and innervation of the rectum below the dentate line. We have used the "rectal sensation test,"18 but have not found it helpful when patients are in the prone jackknife position. Therefore, focused administration of local anesthetic at this anatomic location and the use of topical anesthetic jelly in the rectum both seem important for overall pain control.

FIGURE 3. Ordinal distribution of pain scores reported at set intervals during the biopsy protocol.

### TABLE 2
Predictors of Pain Score at Various Biopsy Timepoints by Proportional Odds Ordinal Logistic Regression*

<table>
<thead>
<tr>
<th></th>
<th>Age OR (95% CI)</th>
<th>BMI OR (95% CI)</th>
<th>PSA OR (95% CI)</th>
<th>Prostate volume OR (95% CI)</th>
<th>Inflammation in biopsy specimen OR (95% CI)</th>
<th>Previous prostate biopsy OR (95% CI)</th>
<th>Family history of prostate cancer OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe insertion pain</td>
<td>0.97 (0.94–1.00)</td>
<td>1.03 (0.98–1.08)</td>
<td>0.99 (0.94–1.04)</td>
<td>1.00 (0.99–1.01)</td>
<td>1.50 (0.74–3.04)</td>
<td>2.10 (0.99–4.45)</td>
<td>1.66 (0.87–3.17)</td>
</tr>
<tr>
<td>Lidocaine injection pain</td>
<td>0.96 (0.93–0.99)</td>
<td>1.00 (0.95–1.04)</td>
<td>1.02 (0.98–1.06)</td>
<td>0.99 (0.97–1.00)</td>
<td>1.21 (0.58–2.52)</td>
<td>1.48 (0.68–3.22)</td>
<td>1.27 (0.67–2.38)</td>
</tr>
<tr>
<td>Base biopsy pain</td>
<td>0.99 (0.96–1.03)</td>
<td>1.00 (0.95–1.05)</td>
<td>1.02 (0.98–1.07)</td>
<td>0.98 (0.97–0.99)</td>
<td>0.94 (0.46–1.91)</td>
<td>2.32 (1.01–5.37)</td>
<td>0.84 (0.44–1.59)</td>
</tr>
<tr>
<td>Middle biopsy pain</td>
<td>1.01 (0.98–1.04)</td>
<td>0.97 (0.92–1.02)</td>
<td>1.02 (0.98–1.06)</td>
<td>1.00 (0.98–1.01)</td>
<td>1.31 (0.65–2.64)</td>
<td>0.97 (0.44–2.11)</td>
<td>0.95 (0.50–1.73)</td>
</tr>
<tr>
<td>Apical biopsy pain</td>
<td>0.99 (0.96–1.02)</td>
<td>0.95 (0.90–1.00)</td>
<td>1.01 (0.96–1.06)</td>
<td>0.99 (0.98–1.00)</td>
<td>0.90 (0.45–1.79)</td>
<td>1.11 (0.53–2.34)</td>
<td>0.79 (0.43–1.45)</td>
</tr>
<tr>
<td>End of biopsy pain</td>
<td>0.97 (0.94–1.00)</td>
<td>0.96 (0.92–1.02)</td>
<td>1.02 (0.98–1.06)</td>
<td>1.00 (0.99–1.02)</td>
<td>1.23 (0.61–2.49)</td>
<td>1.02 (0.44–2.35)</td>
<td>1.06 (0.56–2.01)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval. (95% CI); PSA, prostate-specific antigen; BMI, body mass index.

* Data in this table are adjusted for treatment arm, age, BMI, PSA, prostate volume, inflammation, previous prostate biopsy, and family history.

Confirmation of accurate anesthetic infiltration at the prostatovesiculocolonic junction by the development of a “Mount Everest sign” has been reported.3,5,8,10,20 However, infiltration of the nerves at the base of the prostate may not provide optimal pain relief, as shown in the current study. No randomized studies have compared the efficacy of intraprostatic to apical blockade. In this regard, the current study did not identify any significant differences in procedural pain control between these 2 groups, except for the period of anesthetic infiltration. Overall, these results suggest that the intraprostatic and apical blockades are superior to prostatovesiculoseptal blockades in preventing patient pain. It is important to note that we found the apical blockade easier to learn and apply more consistently than the intraprostatic blockade. Future studies will assess the outcomes of the apical-
rectal blockade versus the intraprostatic blockade versus a combination of the 2 methods. In addition, we plan to analyze the quality-of-life differences between each of the study groups to determine whether either anesthetic technique influenced urinary, sexual, or bowel function.

We did not include a placebo group in the current study because previous work has already demonstrated an advantage for prostatic anesthesia.\textsuperscript{3,7,8} Shortcomings of the study include the use of the VAS (instead of more precise instruments) and the possibility of allocation deciphering by the nurses documenting patient-reported outcomes. Although the VAS remains a commonly used tool to assess pain, its accuracy and repeat validity have occasionally been questioned. Given the speed with which the prostate biopsy procedure progresses, we did not think that more involved pain measurement systems would have been practical. While deciphering of the treatment allocation group by experienced nurses may have occurred, we believe that it is unlikely that this affected our results to a significant degree because patients reported their pain scores at predefined intervals and no coaching or counseling was permitted during the biopsy procedure. In addition, all interventions were performed by residents in training. Although each member of the team was proficient in the prostate biopsy procedure, it is possible that variability in technique could have biased our outcomes. Notably, even after multivariate analysis, there was no difference in pain scores among the anesthetics provided by any member of the research team.

Conclusion
In the current era of PSA screening, the number of prostate biopsies is anticipated to increase. Patient tolerance of this procedure can be improved by administering local anesthetic before prostate biopsy. The most painful part of the procedure is the injection of local anesthetic and the least painful is the insertion of the TRUS probe. Apical and intraprostatic blockades appear to provide superior analgesia to the seminal vesical-prostatic base blockade.

TABLE 3
Comparisons of Pain Occurring at Various Timepoints During the Biopsy Procedure

<table>
<thead>
<tr>
<th></th>
<th>Median pain score and interquartile range</th>
<th>Between-group comparisons\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seminal vesicle blockade</td>
<td>Intraprostatic blockade</td>
</tr>
<tr>
<td>Probe insertion pain</td>
<td>1 [0–2]</td>
<td>1 [0–2]</td>
</tr>
<tr>
<td>Lidocaine injection pain</td>
<td>3 [2–4]</td>
<td>3 [2–5]</td>
</tr>
<tr>
<td>Base biopsy pain</td>
<td>1 [1–3]</td>
<td>1 [0–2]</td>
</tr>
<tr>
<td>Middle biopsy pain</td>
<td>3 [1–4]</td>
<td>2 [1–3]</td>
</tr>
<tr>
<td>Apical biopsy pain</td>
<td>4 [2–5]</td>
<td>2 [1–4]</td>
</tr>
<tr>
<td>End of procedure pain</td>
<td>1 [0–3]</td>
<td>1 [0–2]</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; PSA, prostate-specific antigen; DRE, digital rectal exam; BMI, body mass index; VAS, visual analog scale; TRUS, transrectal ultrasound.

\textsuperscript{a} Kruskal-Wallis test.

\textsuperscript{b} Steel-Dwass multiple comparisons test.

FIGURE 4. Odds ratio for increased pain when assessing groups between each other at set timepoints during the biopsy protocol. (SV = seminal vesical-prostatic base blockade, IP = intraprostatic blockade, AP = apical-rectal blockade).
REFERENCES


