Timing interval from peri-prostatic block to biopsy impacts procedural pain

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Introduction: *To compare visual analog scale (VAS) pain scores between patients with a 2-minute versus 10-minute delay of peri-prostatic lidocaine injection prior to transrectal ultrasound-guided prostate biopsies (TRUS-bx).*

Materials and methods: *Eighty patients who underwent standard 12-core TRUS-bx by a single surgeon were prospectively randomized into four different treatment arms: bibasilar injection with a 2-minute delay, bibasilar injection plus a single apical injection with a 2-minute delay, bibasilar injection with a 10-minute delay, and bibasilar injection plus a single apical injection with a 10-minute delay. Patients were asked to report their level of pain on the VAS (0-10, with 10 indicating unbearable pain) at the following intervals: probe insertion (baseline), after each core, and post-procedure. The primary outcome measure was mean VAS score across all 12 cores minus baseline VAS score, which we refer to baseline-adjusted mean VAS score.*

Results: *Baseline-adjusted mean VAS score was significantly higher for the 2-minute delay group compared to the 10-minute delay group (mean: -0.7 versus -1.6, $p = 0.025$). Subset analysis of biopsies 1-3, 4-6, 7-9 and 10-12 also demonstrated higher baseline-adjusted mean VAS scores in the 2-minute delay group (all $p \leq 0.043$).*

Conclusions: *Lower TRUS-bx VAS scores can be achieved by extending the time from lidocaine injection to onset of prostate biopsy from 2 to 10 minutes.*

Key Words: biopsy, lidocaine, prostate neoplasms, trans-rectal ultrasound, visual analog scale

Introduction

Approximately 65%-90% of men undergoing transrectal ultrasound-guided prostate biopsies (TRUS-bx) report discomfort or anxiety associated with this procedure.[1-3] Therefore, several attempts have been made to ameliorate the pain and anxiety of standard TRUS-bx.

The implementation of local anesthesia was first investigated as a therapeutic measure to lessen pain during TRUS-bx in 1996 when Nash et al authored the seminal paper in examining the use of lidocaine injection during TRUS-bx. A meaningful reduction in pain scores associated with peri-prostatic injection of 1% lidocaine prior to initiation of biopsy was discovered.[4]

Motivated by the shift from sextant to 12-core biopsies, more recent publications have focused on the effect of site, dosage, and method of administration of lidocaine injection on 10-point visual analog scale (VAS) pain scores during standard TRUS-bx.[5-13] Although the efficacy of peri-prostatic lidocaine injection in terms of site, dosage, and method of administration has been previously described in prospective, randomized control trials elsewhere, the time from lidocaine injection to TRUS-bx has not been thoroughly investigated.

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We examined the effect of delaying the onset of TRUS-bx following peri-prostatic lidocaine injection in a single-center, prospective, randomized clinical trial. The primary aim of our study was to evaluate whether extending the time period from lidocaine injection to initiation of TRUS-bx from 2 minutes to 10 minutes results in a reduction in patient-reported VAS pain scores. As a secondary aim, we examined whether VAS pain scores differed between patients receiving a bibasilar injection and those receiving a bibasilar injection plus a single apical injection.

Materials and methods

Study patients

A total of 80 patients who underwent a TRUS-bx from September 2011 to June 2014 at our institution by a single surgeon were included in this prospective, single-center randomized study. Institutional Review Board (IRB: 11-003635) approval was acquired prior to study initiation. Informed consent was obtained from each patient prior to enrollment. Indications for biopsy included elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). Exclusion criteria included previous TRUS-bx within the past year, history of chronic prostatitis, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, allergy to lidocaine, hemorrhagic diathesis, active urinary tract infection, anti-coagulant use, history of daily narcotic use, current prescription of oral/topical analgesic, non-prescription analgesic use on day of biopsy, or active anorectal disease (inflammatory bowel disease or hemorrhoids).

Randomization

Patients were assigned to treatment groups using a computer-based randomization via the dynamic allocation method of Pocock and Simon.[14] With a primary aim of comparing outcomes according to delay in TRUS-bx after lidocaine injection (2 minutes versus 10 minutes) and a secondary aim of comparing outcomes according to number/location of injection (bibasilar injection vs. bibasilar injection plus a single apical injection), we randomized patients into 1 of 4 different treatment groups: 1) 2-minute delay with bibasilar injection, 2) 10-minute delay with bibasilar injection, 3) 2-minute delay with bibasilar injection and a single apical injection, and 4) 10-minute delay with bibasilar injection and a single apical injection. The effect of delay after lidocaine injection on outcomes was evaluated by comparing groups 1 and

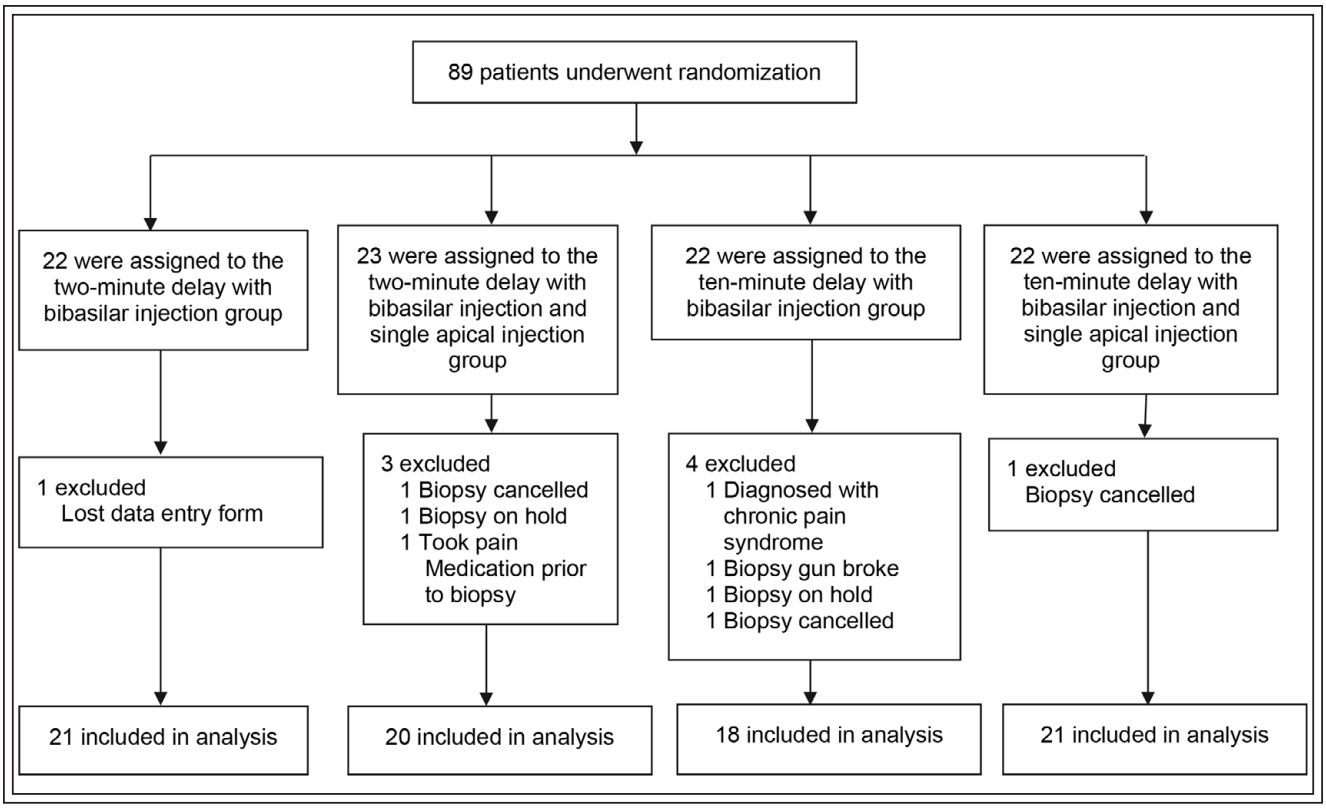

Figure 1. CONSORT diagram.

3 (2-minute delay group) to groups 2 and 4 (10-minute delay group), while the effect of number/location of lidocaine injections on outcomes was examined by comparing groups 1 and 2 (bibasilar) to groups 3 and 4 (bibasilar, single apical). In total, 21 patients were randomized to the 2-minute delay with bibasilar injection group, 18 were randomized to the 10-minute delay bibasilar injection group, 20 were randomized to the 2-minute delay with bibasilar injection and single apical injection group, and 21 were randomized to the 10-minute delay with bibasilar injection and single apical injection group, Figure 1.

TRUS-bx procedure

The TRUS-bx was completed with the patients in the left lateral decubitus position using the Bruel and Kjaer Falcon system accompanied with a B&K 8808 electronic curved array biplane ultrasound probe (BK Ultrasound Corp., Denmark). Dependent on randomization, a total of 12 cc of 1% lidocaine via a 28-gauge 20 cm needle was injected under ultrasound guidance into the peri-prostatic space bilaterally at the prostatic base and posterior apical location with a 2- or 10-minute delay. The probe was removed and reinserted for patients with a 10-minute delay. A 12-core biopsy using an 18-gauge Tru-Cut biopsy gun (Bard Magnum Corp., AZ, USA) was performed in standard fashion. Biopsies were taken in the following order: right base, right mid, right apex, left base, left mid, left apex, right lateral base, right lateral mid, right lateral apex, left lateral base, left lateral mid, and left lateral apex (Biopsy #: 1-12).

Pain measurements and outcomes

The VAS, an 11-point numerical scale with 0 indicating no pain and 10 indicating the worst pain imaginable, was utilized as a measurement of pain quantification secondary to its low-cost, reproducibility, and wide-spread acceptance in prostate literature.[15] Pain scores were elicited and recorded by male nurses at probe insertion, after each of the 12 different biopsies, and 5 minutes after procedure completion.

We initially planned to use the mean VAS score across all 12 biopsies as our primary outcome measure. However, because the difference in baseline VAS score between these 2 groups was greater than expected, Table 1, we modified our approach and instead examined the mean VAS score across all 12 biopsies minus baseline VAS score as our primary outcome, which we refer to as "baseline-adjusted mean VAS score." Secondary outcome measures included baseline-adjusted (ie, with the baseline subtracted from) mean VAS score across biopsies 1 to 3, 4 to 6, 7 to 9, and 10 to 12 and post-procedural (5 minutes after completion).

Data analysis

All analyses were performed on the basis of the intention-to-treat principle after applying exclusion criteria. Continuous variables were summarized using the sample mean and range. Categorical variables were summarized using number and percentage. In evaluation of the primary study aim, we compared the baseline-adjusted mean VAS score between the 2-minute delay and 10-minute delay groups using a Wilcoxon rank sum test. In a sensitivity analysis adjusting for the potential confounding influence of baseline characteristics, we additionally performed a series of van Elteren stratified Wilcoxon rank sum tests[16] where we stratified individually for different baseline characteristics.

Comparisons of secondary VAS outcomes between the 2-minute delay group and 10-minute delay group and comparisons of all outcomes between the bibasilar and bibasilar plus single apical injection groups were also made using Wilcoxon rank sum tests. For the primary outcome measure (baseline-adjusted mean VAS score), we examined whether an interaction exists between delay after lidocaine injection, Figure 2, and number/location of injections received using a permutation test based on the interaction test statistic from a 2-way analysis of variance.[17] P values of 0.05 or lower were considered statistically significant, and all tests were 2-sided. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Inc., Cary, NC, USA) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

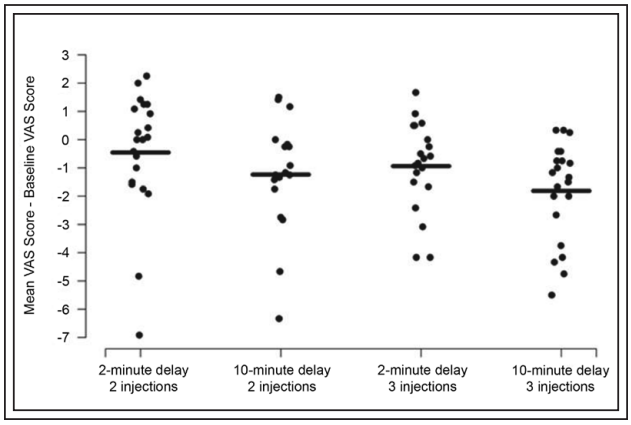

Figure 2. Baseline-adjusted mean VAS score according to delay after lidocaine injection and number/location of injections. The sample mean is shown with a solid horizontal line.

Results

Characteristics of the overall cohort

The mean age of the resultant sample of 80 patients was 65 years (range: 42-90 years), with a median body mass index (BMI) of 29.5 (range: 22.3-52.1). The majority of patients (92.4%) were Caucasian. Eleven patients (13.8%) stated that they regularly take non-prescription analgesics (not taken the day of biopsy). Mean VAS pain scores for all 960 cores (80 patients and 12 biopsies per patient) was 1.7, and only 16% of patients reported a pain score greater than 4 for any of their 12 biopsies.

Comparison of outcomes between 2-minute and 10-minute delay groups

A total of 41 men were randomized to the 2-minute delay group, and 39 men were randomized to the 10-minute group. Patients in these 2 treatment groups were comparable with respect to age, BMI, most recent PSA, prostate volume, smoking status, family history of prostate cancer, 5α-reductase inhibitor use, regular non-prescription analgesic, hypertension, and digital rectal examination, Table 1. As previously stated, there was a greater than expected difference in baseline VAS scores between the 2-minute delay and 10-minute delay groups (2-minute delay: mean 2.5; 10-minute delay: mean=3.1).

A comparison of primary and secondary outcomes between the 2-minute delay and 10-minute delay groups is shown in Table 2. With respect to the primary outcome of baseline-adjusted mean VAS score, this was significantly higher for the 2-minute delay group compared to the 10-minute delay group (mean: -0.7 versus -1.6, $p = 0.025$), indicating heightened pain in the 2-minute delay group. This significant difference was consistent when adjusting individually for baseline patient characteristics (all $p \leq 0.05$).

Baseline-adjusted mean VAS scores across biopsies 1-3, biopsies 4-6, biopsies 7-9, and biopsies 10-12 were all significantly higher in the 2-minute delay group compared to the 10-minute delay group (all $p \leq 0.043$). No statistically significant difference in baseline-adjusted VAS score was observed 5 minutes after procedure completion between the 2 groups (mean:-0.5 versus -1.0, $p = 0.23$).

TABLE 1. **Patient characteristics according to delay after lidocaine injection**

Variable	**2-minute delay (n = 41)**	**10-minute delay (n = 39)**
Age	64.7 (47.1, 90.3)	65.4 (41.9, 83.1)
Race		
Caucasian	37 (92.5%)	36 (92.3%)
African American	3 (7.5%)	3 (7.7%)
Body mass index	29.4 (23.1, 52.1)	29.6 (22.3, 42.2)
Most recent PSA (ng/mL)	14.9 (0.6, 361.5)	6.4 (2.6, 26.5)
Prostate volume (grams)	37.6 (14.7, 75.7)	37.2 (14.8, 102.0)
Number of lidocaine injections		
2 injections at prostate base only	21 (51.2%)	18 (46.2%)
2 injections at prostate base and 1 injection at apex	20 (49.9%)	21 (53.9%)
Smoked > 100 cigarettes in life	16 (40.0%)	15 (38.5%)
Currently smoke cigarettes	3 (7.3%)	1 (2.6%)
Family history of prostate cancer	12 (30.8%)	17 (44.7%)
Ever taken dutasteride	0 (0.0%)	0 (0.0%)
Ever taken finasteride	1 (2.4%)	0 (0.0%)
Regular non-prescription pain-killer use	6 (14.6%)	5 (12.8%)
Hypertension	17 (41.5%)	13 (33.3%)
Abnormal digital rectal exam	14 (34.1%)	10 (25.6%)
Baseline VAS at probe insertion	2.5 (0, 7)	3.1 (0, 8)
> 2	14 (34.1%)	18 (46.2%)

VAS = visual analog scale

TABLE 2. **Comparison of VAS scores according to delay after lidocaine injection**

Variable	2-minute delay (n = 41)	10-minute delay (n = 39)	p value
Primary endpoint			
Mean VAS score across all 12 biopsies minus baseline VAS score	-0.7 (-6.9, 2.3)	-1.6 (-6.3, 1.5)	0.025
Secondary endpoints			
Mean VAS score during biopsies 1-3 minus baseline VAS score	-0.7 (-7.0, 2.7)	-1.5 (-6.0, 2.0)	0.023
Mean VAS score during biopsies 4-6 minus baseline VAS score	-0.3 (-7.0, 3.0)	-1.3 (-6.3, 3.0)	0.020
Mean VAS score during biopsies 7-9 minus baseline VAS score	-0.9 (-7.0, 3.7)	-1.8 (-7.0, 2.3)	0.021
Mean VAS score during biopsies 10-12 minus baseline VAS score	-0.9 (-6.7, 3.7)	-1.6 (-6.3, 2.0)	0.043
VAS score 5 minutes after procedure completion minus baseline VAS score	-0.5 (-6.0, 3.0)	-1.0 (-6.0, 2.0)	0.23
Primary and secondary endpoints without subtracting baseline VAS score			
Mean VAS score across all 12 biopsies	1.8 (0.0, 4.1)	1.5 (0.0, 4.3)	0.080
Mean VAS score during biopsies 1-3	1.8 (0.0, 4.7)	1.5 (0.0, 5.3)	0.13
Mean VAS score during biopsies 4-6	2.2 (0.0, 6.3)	1.8 (0.0, 7.0)	0.10
Mean VAS score during biopsies 7-9	1.6 (0.0, 4.7)	1.3 (0.0, 4.7)	0.087
Mean VAS score during biopsies 10-12	1.7 (0.0, 5.0)	1.4 (0.0, 5.0)	0.18
VAS score 5 minutes after procedure completion	2.1 (0.0, 5.0)	2.1 (0.0, 7.0)	0.92

VAS = visual analog scale. The sample mean (range) is given. P values result from a Wilcoxon rank sum test. Information was unavailable regarding VAS score 5 minutes after procedure completion in one 2-minute delay patient

Comparison of outcomes between bibasilar injection and bibasilar plus single apical injection groups

In total, 39 men were randomized to the bibasilar injection group, while 41 men were randomized to the bibasilar plus single apical injection group. There were no notable imbalances in baseline patient characteristics between these 2 patient groups. Table 3 shows a comparison of outcomes between the 2-injection and 3-injection patient groups. No statistical significance was achieved when comparing bibasilar injection and bibasilar plus single apical injection groups (mean: -0.8 versus -1.4, p = 0.11). There was a similar lack of a statistically significant difference between the bibasilar and bibasilar plus single apical injection groups for all secondary outcomes.

Discussion

The four main factors impacting the onset of sensory anesthesia include concentration and volume of drug administered, proximity of the injection to the nerve plexus, degree of ionization of the drug, and the actual time required for onset of action. The onset of action for lidocaine is rapid and may be as low as 2 minutes to about 5 minutes.[18] The duration of nerve blockade is directly dependent on lipid solubility and protein binding. Lidocaine belongs to a class of anesthetics with an intermediate duration of action and an elimination half-life on average of 45-120 minutes.[18]

Given the trend toward 12-core TRUS-bx, new methods altering the dosing, site and method of peri-prostatic lidocaine administration have evolved.[5-13] However, the time from lidocaine injection to TRUS-bx in the aforementioned publications varied from 2 minutes to 15 minutes,[5-8,11-13] with two articles failing to specify.[9,10]

Prior studies examining the dosage of lidocaine[8,13] concluded sufficient anesthetic effect, in the absence of toxicity, with 10 mL of 1% lidocaine, as utilized in our study. Although the site and number of injections have been debated in prospective, randomized clinical trials,[5-13] the design of most trials incorporates peri-prostatic infiltration at the base of the prostate bilaterally with or without an apical infiltration site.

Prior to this study, our standard practice involved initial lidocaine injection, followed by transrectal ultrasound guided prostatic volume measurement,

TABLE 3. **Comparison of VAS scores according to number/location of injections**

Variable	2 injections at the prostate base only (n = 39)	2 injections at the prostate base and 1 injection at the apex (n = 41)	p value
Primary endpoint			
Mean VAS score across all 12 biopsies minus baseline VAS score	-0.8 (-6.9, 2.3)	-1.4 (-5.5, 1.7)	0.11
Secondary endpoints			
Mean VAS score during biopsies 1-3 minus baseline VAS score	-0.8 (-7.0, 2.7)	-1.4 (-6, 1.3)	0.11
Mean VAS score during biopsies 4-6 minus baseline VAS score	-0.6 (-7.0, 3.0)	-1.0 (-5.3, 3.0)	0.13
Mean VAS score during biopsies 7-9 minus baseline VAS score	-1.0 (-7.0, 3.7)	-1.6 (-6.0, 1.7)	0.082
Mean VAS score during biopsies 10-12 minus baseline VAS score	-0.9 (-6.7, 3.7)	-1.5 (-5.3, 1.7)	0.21
VAS score 5 minutes after procedure completion minus baseline VAS score	-0.6 (-6.0, 3.0)	-0.8 (-6.0, 2.0)	0.35
Secondary endpoints without subtracting baseline VAS score			
Mean VAS score across all 12 biopsies	1.8 (0.1, 4.1)	1.5 (0.0, 4.3)	0.29
Mean VAS score during biopsies 1-3	1.8 (0.0, 4.7)	1.6 (0.0, 5.3)	0.34
Mean VAS score during biopsies 4-6	2.0 (0.0, 6.3)	1.9 (0.0, 7.0)	0.72
Mean VAS score during biopsies 7-9	1.7 (0.0, 4.7)	1.3 (0.0, 4.3)	0.28
Mean VAS score during biopsies 10-12	1.7 (0.0, 5.0)	1.4 (0.0, 5.0)	0.35
VAS score 5 minutes after procedure completion	2.0 (0.0, 5.0)	2.1 (0.0, 7.0)	0.97

VAS = visual analog scale. The sample mean (range) is given. P values result from a Wilcoxon rank sum test. Information was unavailable regarding VAS score 5 minutes after procedure completion in one 2-injection patient.

and finally, TRUS-bx. Initially, we felt 1 to 2 minutes (time required during measurement of prostatic volume) was appropriate for sufficient lidocaine diffusion and exertion of anesthetic effects. However, after investigation of lidocaine pharmacokinetics, it appears the onset of action is long enough and variable enough to warrant a delay in TRUS-bx with the expectation of improving pain scores.

We report that extending the length of time from lidocaine injection to onset of TRUS-bx from 2 minutes to 10 minutes is associated with a decrease in patient self-reported pain. On average, patients who were randomized to the delay group reported baseline-adjusted VAS scores that were approximately 1 unit lower. Therefore, we have adopted delaying the onset of TRUS-bx from lidocaine injection in our practice.

With respect to our secondary treatment comparison of interest, we failed to identify a statistically significant difference between bibasilar injections versus bibasilar injections plus a single apical injection in terms of patient-reported pain scores. Further study on the effect of utilizing an additional single apical injection on patient-reported pain is warranted.

Baseline probe insertion yielded VAS pain scores of 2.5 and 3.1 in the 2-minute and 10-minute delay groups, respectively. If probe insertion represents the height of pain perceived, reinsertion of the probe for the 10-minute delay group would result in increased VAS scores in the 10-minute group. Although we did not record a VAS score upon reinsertion, when comparing the mean VAS score and mean VAS score minus baseline VAS score at biopsy #1 (indirectly represents the effect of probe insertion as biopsy 1 is taken within seconds of probe insertion), we found the 10-minute delay group had lower VAS scores (mean: 1.0 versus 1.4, and accounting for baseline VAS: -2.0 versus -1.1) and biopsies 1-3 were significantly different, resulting in lower pain scores for the 10-minute delay group (p = 0.023). Likely, the anal sphincter has become relaxed upon initial probe insertion, and reinsertion may not be perceived as painful. In addition, the effects of lidocaine diffusion and analgesia may also account for this finding.

Our study has several limitations. First, Caucasians constituted more than 90% of our study population. The results of this study cannot be extrapolated to patients of other races. The single-site, single-surgeon protocol utilized in this study may further compromise the generalizability of our conclusions. However, this protocol eliminates individual surgeon and institutional variations of TRUS-bx technique as variables in the analysis.

Delaying onset of TRUS-bx for 10 minutes following peri-prostatic lidocaine injection results in lower VAS pain scores than when TRUS-bx is done 2 minutes following lidocaine injection. □

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