Oncology: Prostate/Testis/Penis/Urethra

Combination of Oral Tramadol, Acetaminophen and 1% Lidocaine Induced Periprostatic Nerve Block for Pain Control During Transrectal Ultrasound Guided Biopsy of the Prostate: A Prospective, Randomized, Controlled Trial

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Purpose: Prostate biopsy for diagnosing cancer can be painful. Tramadol is a centrally acting analgesic used to treat many pain disorders. We determined whether administering oral tramadol and acetaminophen combined with 1% lidocaine induced periprostatic nerve block would significantly decrease the pain experienced by patients during standard 10-core transrectal ultrasound guided needle biopsy of the prostate.

Materials and Methods: A total of 60 men who presented for diagnostic prostate biopsy were randomized to receive placebo plus periprostatic 1% lidocaine as the control group of 30 or 75 mg tramadol/650 mg acetaminophen orally plus periprostatic 1% lidocaine as the experimental group of 30 before undergoing biopsy. Immediately after biopsy each patient was asked to rate the pain on a linear 10-point scale and a standard 6-point faces pain scale. Complications of pain medication administration in each group were noted and compared.

Results: Pain medication administration was well tolerated by each study group except for lightheadedness/dizziness and itching in 1 patient each in the experimental group, and lightheadedness/dizziness in 1 patient in the control group. Overall patients in the experimental group reported a mean decrease ± SD in the pain score of 2.3 ± 2.4 on the scale of 1 to 10 (p = 0.0008) and 1.11 ± 1.25 on the scale of 0 to 5 compared with scores in controls (p = 0.0009).

Conclusions: Administering 75 mg tramadol/650 mg acetaminophen orally with periprostatic 1% lidocaine before transrectal ultrasound guided prostate biopsy is a safe, easy and effective method of controlling pain during the biopsy procedure.

Key Words: tramadol, lidocaine, prostate, biopsy, pain

Ultrasound guided prostate biopsy is the procedure of choice for diagnosing prostate cancer. However, 19% to 25% of men who undergo this procedure find it painful.1–3 Approximately 20% of men report that the pain associated with the procedure is significant and they would refuse to undergo the procedure again without some form of analgesia.1

During the last 5 years our approach to prostate biopsy has evolved from traditional sextant biopsy to several extended techniques involving the gathering of 8 to 12 biopsy core samples. These extended techniques have allowed us to obtain more biopsy samples, ie achieve better prostate sampling, in each case and, thus, increase our prostate cancer detection rate by 20% to 40%.4,5 However, they may have also resulted in more patients reporting increased pain and discomfort during the procedure. We will test the approach to easing such pain and discomfort has been the administration of various analgesics before prostate biopsy.6–10 The current standard for prebiopsy analgesia is periprostatic injection of 1% lidocaine,11 although men who receive it still report persistent pain and discomfort. Therefore, other analgesic approaches are needed to decrease pain during the biopsy procedure.

Tramadol is a centrally acting analgesic used for many pain disorders. This drug uniquely combines μ opioid receptor binding activity with the inhibition of serotonin/norepinephrine reuptake. Acetaminophen has been proved to enhance the therapeutic efficacy of tramadol.12 In a study of 585 patients who received tramadol after major abdominal surgery pain at rest and during movement decreased significantly, as rated on a verbal numerical scale.13 In light of these data we hypothesized that the combined administration of a readily available tramadol/acetaminophen drug and periprostatic 1% lidocaine before standard 10-core TRUS biopsy would significantly decrease the pain experienced by patients during biopsy. Ultracet® capsules were chosen as the tramadol/acetaminophen drug because of availability and ease of administration.

PATIENTS AND METHODS

Patients and Selection Criteria
This double-blind, prospective, randomized, controlled trial was approved by our institutional review board. Patients presenting to the urology clinic at University of Florida and Shands Jacksonville between January 2005 and July 2005 were eligible for study inclusion. Pretreatment evaluations...
included medical history, physical examination (height, weight and digital rectal examination), and measurement of free and total PSA (Abbott Laboratories, Abbott Park, Illinois). The indication for TRUS guided needle biopsy of the prostate was PSA greater than 4.0 ng/ml and/or abnormal digital rectal examination results. Inclusion criteria were all patients who were eligible for prostate biopsy and willing to provide informed consent. Excluded from study were patients who had a known allergy to tramadol or acetaminophen, or a history of epilepsy or any other seizure disorder. Also excluded were patients who had received selective serotonin reuptake inhibitors, tricyclic antidepressants or other tricyclic compounds, opioids, monoamine oxidase inhibitors or neuroleptics within the previous 3 months and those who had compromised hepatic function (ie bilirubin 1.5 mg/dl or greater and serum glutamic pyruvic transaminase 2.5 times or greater the upper limit of normal) or compromised renal function (ie serum creatinine 1.8 mg/dl or greater, or creatinine clearance less than 40 ml per minute).

Of the 63 eligible candidates who were asked to participate in the study 60 agreed and provided informed consent. These 60 men were randomized into 2 groups, including 1 of 30 who received placebo plus periprostatic 1% lidocaine as the control and the other of 30 who received 75 mg tramadol/650 mg acetaminophen before periprostatic 1% lidocaine using a blocked randomization plan. Any anticoagulation or aspirin therapy regimens were discontinued 7 days before the biopsy procedure.

**Study Protocol and Biopsy Technique**

One to 10 days before planned biopsy each patient was given a package containing 3 doses of 500 mg levofloxacin, a Fleet Enema®, 1 dose of 75 mg tramadol/650 mg acetaminophen and written instructions on when to administer them. Each patient was to self-administer levofloxacin as prophylactic antibiotic therapy once on the day before, once on the day of and once on the day after the biopsy procedure. On the morning of biopsy each patient was to self-administer the Fleet Enema®. Three hours before the scheduled time of biopsy each patient was to self-administer the 75 mg tramadol/650 mg acetaminophen, so that a peak serum drug level would be attained by the time that the biopsy procedure was under way.

At the scheduled time each patient was brought to the biopsy suite and placed in the lateral decubitus position. A well lubricated 7.5 MHz transrectal probe (B-K Medical Systems, Wilmington, Massachusetts) was placed into the rectum to visualize the prostate. Sagittal and transverse views of the prostate were obtained and ultrasonographic abnormalities and gland dimensions were noted. Three-dimensional volume was calculated by multiplying gland height in cm by width in cm by depth in cm and dividing the product by 0.51. A 22 gauge spinal needle was used to inject 5 ml 1% lidocaine lateral to the right seminal vesicle and another 5 ml 1% lidocaine lateral to the left seminal vesicle.

A modified version of the 5-region prostate biopsy schema (5-region minus 3 mid gland biopsies) was used to obtain enough samples to allow a diagnosis of cancer, if present. Before removing the ultrasound probe at the end of the procedure the prostate was again visualized sagittally and transversely to search for any signs of hematoma. Additionally, digital rectal examination was performed to assess hematoma. All biopsies were performed in a standardized manner by one of us (CJR).

**Data Collection**

Within 10 minutes of biopsy procedure completion the patients were presented with 2 visual pain scales and asked to rate the pain. The scales were a linear, 10-point visual analog pain scale and a standard 6-point faces pain scale of 0—“no hurt,” 1—“hurts little bit,” 2—“hurts little more,” 3—“hurts even more,” 4—“hurts whole lot,” 5—“hurts worst.” All patients were monitored for possible complications during and after the procedure, including any deviations from the protocol and any instances of postprocedural fever, urinary retention, persistent bleeding or other complications. In addition, each patient was telephoned daily after the procedure until he no longer reported any pain or other side effects, eg hematuria or blood in stool.

Seven study violations were noted. After being randomized 2 patients in the experimental group and 3 in the control group never underwent prostate biopsy and were lost to followup. Since no pain data were collected from these patients, they were excluded from statistical analysis. One patient in the experimental group required periprostatic injection of an additional 10 ml lidocaine and 1 in the control group did not receive the entire 10 ml lidocaine injection periprostatically. The patient who did not receive the entire 10 ml lidocaine and the one who received a second lidocaine injection were still analyzed on an intent to treat basis.

**Statistical Analysis**

Before the trial was initiated it was determined that 30 patients would have to be enrolled in each study arm to detect a decrease in the pain score of 1.0 at an SD of 1.2, a significance of 5% and a power of 88.8%. This effect was chosen because any smaller effect would be neither clinically nor substantively significant, and because this magnitude of effect was considered reasonable to expect in the field of pain research. The end points of prostate biopsy feasibility and pain threshold were analyzed by ANOVA and Student’s t test, respectively. Data were analyzed with SAS® statistical software. All normally distributed, continuous variables are described as the mean ± SD. Patient age was compared between the groups by ANOVA. Other variables, including pain scores, were compared using nonparametric tests, ie the Kruskal-Wallis, chi-square and Fisher exact tests, as appropriate. Analysis was based on intent to treat.

**RESULTS**

A total of 28 men in the experimental group and 27 in the control group completed the study. The table lists demographics. The 2 study groups were well matched and statistically similar in terms of age, race, PSA and prostatic volume.

Patients in the experimental group tolerated well the prescribed tramadol/acetaminophen doses. The only reported symptoms of discomfort were dizziness and lightheadedness in 2 patients, itchiness in 1 and euphoria in 1. Patients in the control group reported similar symptoms with similar frequency, ie dizziness and lightheadedness,
and itching in 1 each (p > 0.05). However, patients in the experimental group reported a mean pain score decrease of 2.3 ± 2.4 on the scale of 1 to 10 and a decrease of 1.11 ± 1.25 on the scale of 0 to 5 compared to the control group (standard t test, p = 0.0008 and 0.0009, respectively, figs. 1 and 2). Overall mean pain scores using the visual linear scale were 1.43 ± 1.89 in the experimental group and 3.74 ± 2.84 in the control group. The faces pain scale mean was 2.2 ± 1.5 in the experimental group and 1.09 ± 0.95 in the control group. Data collected 3 days after the procedure showed no significant differences between the groups. In the treatment group no men reported any pain after 3 days. In the placebo group 3 men reported pain (3 or less on the 10-point scale) after 3 days. However, chi-square analysis showed that the difference between the groups was not significant (p = 0.08).

No significant morbidity was noted in either study group. Rectal bleeding that developed during the biopsy procedure in 1 control (2%) required monitoring in the clinic immediately after the procedure. Bleeding subsided without intervention within 30 minutes. All instances of rectal bleeding, hematuria and hemospermia were self-limiting and did not result in any hospitalizations or additional office visits. On followup telephone calls no patient in either study group reported any significant postprocedural pain or complications.

DISCUSSION

Men undergoing TRUS guided needle biopsy of the prostate for diagnosing prostate cancer routinely report pain and discomfort during the procedure. Our current findings clearly demonstrate that oral administration of 75 mg tramadol/650 mg acetaminophen 3 hours before periprostatic injection of 1% lidocaine as a nerve block can significantly decrease such pain, as reported on 2 pain scales without causing any additional complications. Our findings also indicate that this combination is safe and easy to administer.

Periprostatic nerve block with 1% lidocaine is considered the gold standard for analgesic anesthesia before office based prostate biopsy. Other approaches to analgesia in this setting are intrarectal lidocaine, intraprostatic 1% lidocaine, pudendal nerve block, intravenous ketorolac and periprostatic bupivacaine. Routinely the intravenous medications are not readily available in an office setting in the United States. All were more difficult to administer and none provided better analgesia than the periprostatic nerve block.

Additionally, Obek et al found that intravenous tramadol acting alone is more efficacious than placebo but it did not perform as well as perirectal lidocaine injection or perirectal lidocaine injection plus perirectal and perianal lidocaine gel. These studies show the value of what has become the gold standard for TRUS prostate biopsy, that is local analgesic control using 1% lidocaine. Our study shows that this trusted technique should not be substituted, but rather augmented with other available analgesic techniques to produce optimal results.

Despite its prospective, randomized and controlled design our study had several limitations. 1) It was based on the clinical experience of a single urologist and slight differences in the way that other surgeons administer periprostatic blocks may lead to different results. 2) Because pain reporting is essentially subjective, some could argue that a larger sample size would have made it possible to determine a smaller difference in reported pain. 3) Some could argue that the pain scales that we used did not encompass the quality or duration of pain experienced by our study population. Often during pain reporting sessions patients would comment that the pain experienced was not significant but the

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<th>Characteristic</th>
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<tr>
<td>Median age ± SD (range)</td>
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<td>66 ± 11.0 (62–73)</td>
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<tr>
<td>Other</td>
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<td>Median ng/ml serum PSA ± SD (range)</td>
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<td>5.02 ± 19.2 (0.57–102)</td>
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<td>Mean prostate vol (cm³)</td>
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<td>33.93</td>
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Fig. 1. Visual analog pain scores on scale of 1 to 10 points

Fig. 2. Digital visual pain scores on scale of 1 to 5 points
procedure was uncomfortable due to positioning, instrumentation or the general unpleasantness of the biopsy procedure. 4) A tramadol alone arm was not included. It is possible that tramadol alone may result in a significant pain decrease.

CONCLUSIONS

Our current study shows that the techniques currently used to control pain during TRUS guided needle biopsy procedures can be improved on. In particular the oral administration of 75 mg tramadol/650 mg acetaminophen 3 hours before periprostatic nerve block and biopsy appears to provide more effective pain control than periprostatic nerve block alone without causing any additional complications or side effects.

ACKNOWLEDGMENTS

The blocked randomization plan used in the experimental group was developed at University of Florida and Shands research pharmacy. Mr. Jude Richard reviewed the manuscript.

Abbreviations and Acronyms

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<th>Description</th>
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<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
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REFERENCES