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Periprostatic Lidocaine Infiltration and/or Synthetic Opioid (Meperidine or Tramadol) Administration Have No Analgesic Benefit during Prostate Biopsy

A Prospective Randomized Double-Blind Placebo-Controlled Study Comparing Different Methods

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Key Words
Prostate · Biopsy, prostate · Pain, prostatic · Analgesia

Abstract
Objectives: To examine in a prospective, randomized, double-blind, placebo-controlled study the analgesic effect of periprostatic nerve block and/or intravenous synthetic opioid administration during a 12-core prostate biopsy. ***Patients and Methods:*** Patients were prospectively randomized to receive unilateral periprostatic lidocaine administration and/or intravenous synthetic opioid (meperidine or tramadol) administration. Placebo groups received sterile normal saline. Unilateral infiltration was performed and biopsy was begun on this side. The degree of pain was recorded using the visual analog scale/numeric analog scale (VAS/NAS) score before the procedure, during probe introduction into the rectum, during unilateral periprostatic nerve blockade, during the first 6-core biopsy and during the second 6-core biopsy, and 30 min after biopsy completion. ***Results:*** Most of the patients had mild or moderate pain (VAS/NAS <6) during the actual biopsy procedure. However, no significant differences existed between the groups with regard to the pain scores at any time ($p > 0.05$). Compared with pain scores, no significant differences existed between the first 6-core (blocked side) and second 6-core biopsies ($p > 0.05$). ***Conclusion:*** Periprostatic lidocaine infiltration and/or intravenous synthetic opioid analgesics are not beneficial in significantly reducing pain during biopsy. We think that most of the patients do have pain during biopsy, however the intensity of pain is tolerable and does not require analgesics.

Introduction

The procedure of transrectal ultrasound-guided biopsy of the prostate has evolved into a standard procedure for the diagnosis of prostate cancer. Although it has been reported that the method is well tolerated [1, 2], pain from the procedure itself is one of the most common side effects [3, 4].

Recent studies have been contradictory. Some have reported that anesthesia by periprostatic local injection of lidocaine or intrarectal administration of lidocaine gel reduced the patient's discomfort [5–7]. In contrast, others have demonstrated that injection of local anesthetics lateral to the seminal vesicles or intrarectal lidocaine admin-

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istration before prostate biopsy were not effective in diminishing biopsy-associated pain [8–11].

There are important methodological issues which need to be considered during a trial assessing the patient's perception of pain and the effect of drugs on pain during biopsy. The conflicting results referred to above can be explained in part by differences in design and pain assessment, the variable number of biopsy cores obtained, and the absence of a double-blind study. The measurement of pain is important and the level of pain intensity is also critical in that it determines whether pain is sufficient enough to require analgesics [12].

This prospective, randomized, double-blind, placebo-controlled study examined the patient's perception of pain and its intensity during a 12-core prostate biopsy, and the efficacy of periprostatic nerve block and/or intravenous synthetic opioid administration to significantly alter pain.

Patients and Methods

From October 2001 to May 2002, we performed a prospective randomized double-blind study in 54 consecutive men undergoing transrectal ultrasound-guided 12-core prostate biopsy. The indications for biopsy included abnormal rectal palpation and/or elevated prostate-specific antigen value. Patients were excluded from the study if they had had a prior transrectal prostate biopsy, had allergies to any study medications (lidocaine, tramadol and meperidine), chronic opioid use, bleeding diathesis, and those receiving anticoagulation therapy or suspected of having a urinary tract infection. Patients received prophylactic oral ciprofloxacin 500 mg the night before and the morning of the biopsy, followed by 500 mg orally twice daily for 2 days. A Fleets enema was self-administered the night before the procedure.

After the patients had provided informed consent, they were randomized into 6 groups (table 1). Thirty minutes before introduction of the ultrasound probe into the rectum, patients received either intravenous tramadol (1 mg/kg) or meperidine (0.5 mg/kg) or saline (placebo). Patients were placed in the lateral decubitus position, and the probe inserted. Ten minutes before performance of prostate biopsies, all patients were randomized to receive 5 ml 1% lidocaine or saline (placebo) injected unilaterally (right side) into the periprostatic nerve plexus under ultrasound guidance using a 12.7-cm 22-gauge needle [5]. The syringe was aspirated before injection to ensure that a vascular structure was not entered. An ultrasonographic wheal viewed in the sagittal plane was created by injecting lidocaine or saline between the rectal wall and the base of the seminal vesicles. No injection was performed on the contralateral side (left). All procedures were performed by the same urologists (M.B., B.C.). The drugs injected were assigned randomly by the anesthesiologist (Ş.A.), and neither the patient nor the urologists were aware of which drug had been administered.

Transrectal ultrasound-guided prostate biopsy was performed using a 7.5-MHz transrectal probe (Siemens Sonoline, Germany) and a total of 12 biopsies were taken using an automatic spring-loaded 18-gauge needle. All biopsies were begun on the right side of the prostate which had received the lidocaine or saline injection (for block).

Table 1. Groups according to the analgesia methods

	Periprostatic nerve blockade	Intravenous medication
Group 1 (n = 9)	Placebo	Placebo
Group 2 (n = 9)	Lidocaine	Placebo
Group 3 (n = 9)	Lidocaine	Meperidine
Group 4 (n = 9)	Lidocaine	Tramadol
Group 5 (n = 9)	Placebo	Meperidine
Group 6 (n = 9)	Placebo	Tramadol

Pain scores were recorded using a visual analog scale/numeric analog scale (VAS/NAS). According to the VAS/NAS, 0 corresponded to no pain and 10 to the greatest pain imaginable. For analysis, numbers are given to the verbal categories: a total pain score of 0 was evaluated as 'no pain', a score from 1 to 3 as 'mild pain', a score from 4 to 6 as 'moderate pain', and any score greater than 6 as 'severe pain'. Sedation scores were recorded using 5-point sedation scale (1 = fully awake and orientated, 2 = drowsy, 3 = eyes closed but rousable to verbal command, 4 = eyes closed but rousable to mild physical stimulation, 5 = eyes closed and unrousable to mild physical stimulation).

Pain scores, blood pressures, heart pulse rates, respirations per minute, arterial oxygen saturations and sedation scores were recorded before the procedure, during probe introduction into the rectum, during unilateral periprostatic nerve blockade, during the first 6-core biopsy (right side), during the second 6-core biopsy (left side) and 30 min after biopsy. Again pain scores were obtained at these time points by verbal response.

We performed statistical analysis of pain scores using Freidman and Mann-Whitney U tests. Sedation scores, blood pressures, pulse rates, respirations per minute and arterial oxygen saturations were analyzed using the Mann-Whitney U test to detect a statistical difference between groups. A p value of <0.05 was considered statistically significant.

Results

The mean age of the study group was 63.1 ± 8.1 years. No significant differences were found between the groups with regard to mean age, mean blood pressures, mean pulse rates, mean respirations per minute, mean arterial oxygen saturations and mean sedation scores (data was not shown). All patients were cooperative and no patient had a sedation score >2 during procedure. There were no adverse effects of injections.

The pain score data are listed in table 2. No significant differences existed between the groups with regard to the pain scores (mean ± SD) at any time ($p > 0.05$). Most of the patients had pain during the actual biopsy procedure (fig. 1), however, the patients' perceptions of pain during

Table 2. VAS/NAS score data (mean ± SD)

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Basal	0	0	0	0	0	0
Probe introduction	0.6 ± 0.2	0.8 ± 1.0	0.4 ± 0.3	0.4 ± 0.6	0.3 ± 0.2	0.2 ± 0.7
Periprostatic injection	0.8 ± 1.2	0.3 ± 1.0	1.2 ± 2.3	1.1 ± 1.3	0.3 ± 0.2	0.2 ± 0.7
First 6 core	2.9 ± 2.6	3.3 ± 2.7	3.1 ± 2.0	2.8 ± 1.2	3.0 ± 2.4	3.3 ± 3.1
Last 6 core	3.2 ± 1.3	3.0 ± 1.9	2.7 ± 2.1	2.2 ± 1.0	2.8 ± 1.7	3.2 ± 2.2
After biopsy	1.3 ± 1.5	1.5 ± 1.7	1.3 ± 1.0	1.2 ± 0.7	1.6 ± 0.9	1.7 ± 1.3

The differences between groups are not statistically significant ($p > 0.05$).

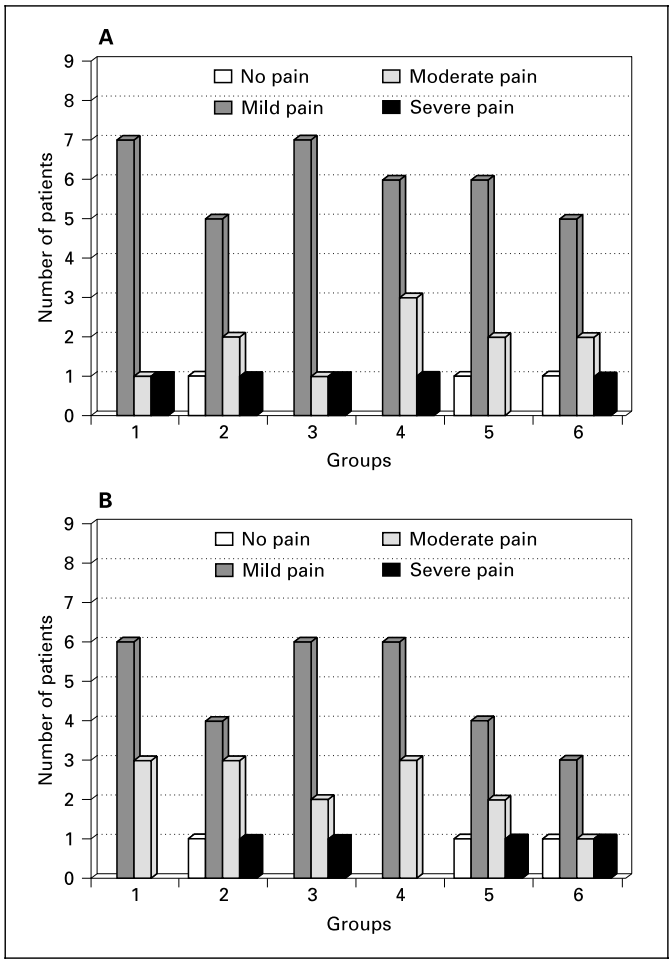

Fig. 1. Pain scores during the actual biopsy including the first 6 core (**A**) and second 6 core (**B**).

these periods were mild or moderate (mean VAS/NAS <6). Comparison of pain scores, no significant differences existed between the first 6-core (blocked side) and second 6-core biopsies ($p > 0.05$).

Discussion

Transrectal ultrasound-guided biopsy of the prostate is the standard method for diagnosing prostate cancer. This is associated with some discomfort, and pain from the procedure itself is one of the most common side effects [3, 4]. According to the experience reported by Aus et al. [2] most of the patients had no or mild discomfort following the biopsy. On the other hand, there have been a number of studies that evaluated the patient's perception of pain and studied the benefit of local or topical anesthesia [5, 6].

Previous data have shown that periprostatic nerve blockade is the most preferable method to reduce the pain induced by transrectal ultrasound-guided prostate biopsy. Soloway and Öbek [5] published their experience based on 50 patients who received infiltration of 5 ml of 1% lidocaine into three points in the periprostatic neurovascular plexus. They noted that only 1 of the 50 men had significant discomfort and all patients who had undergone previous biopsies indicated that there was a dramatic difference when receiving periprostatic nerve block. A double-blind placebo-controlled randomized study reported by Leibovici et al. [13] supported those findings. In contrast, in a randomized double-blind study, Wu et al. [8] showed that periprostatic block had no significant effect in reducing the pain from a 12-core biopsy. In our study, a 12-core prostate biopsy was taken from all patients, and one of the methods we used for reducing pain during procedure was periprostatic lidocaine administration. Since the measurement of subjective pain intensity is important and several components influence its perception from the patient's perspective, in contrast to most of the previous studies we have performed unilateral nerve block. Therefore, we had the chance to compare the pain intensities between in the blocked and non-blocked sides in the same patient. We thought that patients might have experienced pain from the procedure while the biop-

sy was taken from non-blocked side firstly. For this reason, we started the prostate biopsy from the nerve-blocked side in order to avoid experiencing the patient's tolerance of pain. We have shown that the pain scores during biopsy were not significantly different between the blocked and non-blocked sides of the same patient. The other method used in our study was intravenous administration of meperidine or tramadol. Meperidine is a strong synthetic opioid analgesic. Tramadol is a weak synthetic, centrally acting analgesic, and it has both opioid and non-opioid properties. By injection, tramadol is one tenth as potent as morphine. Both of these analgesics are still widely used to reduce pain [14]. We also found that neither periprostatic nerve blockade with lidocaine nor intravenous meperidine or tramadol administration was different from the placebo group according to the patient's perception of pain. Empirically, combinations of local anesthetic and opioids were found to work well [15], however, we did not find any difference in pain scores between the patients receiving periprostatic lidocaine infiltration plus intravenous meperidine or tramadol administration and the patients receiving intravenous saline placebo.

It has been reported that analgesics, sedation and/or narcotic medication may alleviate much of the discomfort associated with transrectal biopsy. Zisman et al. [16] found that less pain was noted during biopsy by patients who self-administered anxiolytics than by those who did not. Our findings do not support these data and there was no significant difference in pain intensity reported by the men in the synthetic opioid groups. It seems unlikely that local anesthesia and local anesthesia plus meperidine or tramadol administration would have improved the pain score during prostate biopsy. The results of our trial question the value of these methods for reducing pain during prostate biopsy.

In summary, the ways of reducing pain associated with this procedure are controversial. Although recent studies have recommended that all prostate biopsies should be done with the patient under local anesthesia, few urologists perform this method to decrease pain [17]. However, recently published data indicate that only 11% of the urologists in United States perform periprostatic nerve block [18]. The statistical analysis of our trial demonstrated that periprostatic infiltration and/or intravenous synthetic opioid analgesics are not beneficial for reducing pain during biopsy. A debatable issue is whether all levels of pain intensities during transrectal ultrasound-guided prostate biopsy can be prevented. While we think the intensity of pain during biopsy is tolerable, elimination of all pain is a worthy goal. Another problem is that our trial might yield different outcomes if performed in different cultures or populations with different pain tolerances and expectations.

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