

Intrarectal Lidocaine-Diltiazem-Meperidine Gel for Transrectal Ultrasound Guided Prostate Biopsy

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Background: TRUS-guided needle biopsy of the prostate gland is the current standard method used for diagnosis of prostate cancer. Pain control during this procedure is through the use of i.v. sedation or local anaesthetic (LA), depending on clinician preference.

Objectives: The aim of this study was to evaluate the effectiveness of intrarectal lidocaine, lidocaine-diltiazem and lidocaine-meperidine-diltiazem gel for anesthetizing transrectal ultrasound guided prostate biopsy.

Patients and Methods: In a randomized double-blind clinical trial, 100 consecutive patients were divided into three groups. The patients received one of the gels before transrectal ultrasound guided prostate needle biopsy: group A, intrarectal and perianal lidocaine, gel 1 g; group B, intrarectal lidocaine gel, 1 g, + perianal diltiazem, 1 g; group C, intrarectal lidocaine gel, 1 g, + meperidine, 25 mg, and perianal diltiazem, 1 g. Visual analog pain scale was used to estimate pain during probe insertion and biopsy. Heart rate and blood pressure during probe insertion and biopsy were recorded too.

Results: The mean of visual analog pain scale was 4.5 in group A, 3.5 in group B, and 2.0 in group C during probe insertion (P value = 0.01). The mean of visual analog pain scale was 5.1 in group A, 3.5 group B, and 2.5 in group C during biopsy (P value = 0.001). The groups were comparable for patients' age, weight, serum prostate-specific antigen (PSA), and prostate size (P > 0.05). No side effects of meperidine and lidocaine including drowsiness, dizziness, tinnitus and light-headedness or requiring assistance for activity were noted.

Conclusions: Lidocaine-meperidine-diltiazem gel provides significantly better pain control than lidocaine-diltiazem gel and lidocaine gel alone during transrectal ultrasound guided prostate biopsy and probe insertion. This mixture gel is safe, easy to administer and well accepted by patients.

Keywords: Benign Prostatic Hyperplasia; Pain

1. Background

Transrectal ultrasound guided prostate biopsy has been the gold standard technique for early detection of prostate cancer (1), although identification of specific molecular markers for prostate cancer may lead to its earlier detection (2). As intravenous opioids have side effects (3), some authors have recommended periprostatic nerve block (4) and perianal-intrarectal lidocaine-prilocaine cream which provide better pain control than the two modalities alone for prostate biopsy anesthesia (5); but some have advised lidocaine (4, 6) or bupivacaine as a single agent (7). These latter studies have suggested that rectal administration of lidocaine gel is a safe, simple modality, without any discomfort for patients (8). Not only local anesthetic agents but also intravenous anesthetic drugs (ketamine) (9) or opioids (10) that have local anesthetic effects have been used for local anesthetizing at urologic procedures.

In this study, we compared the effects of lidocaine gel alone, lidocaine gel plus diltiazem and lidocaine-meperidine-diltiazem in anesthetizing patients for transrectal

ultrasound guided prostate biopsy. As calcium channel blockers such as diltiazem that cause relaxation of gastrointestinal smooth muscle have been shown to reduce resting anal sphincter pressure (11-13), we chose topical diltiazem to be added for groups B and C. Topical diltiazem has been an effective and safe treatment for anal fissure in people who have had failed topical glyceryl trinitrate (11, 12). As meperidine owns a local anesthetic property and can be absorbed to the mucosa (14, 15) of the rectum; we added this drug to group C.

2. Objectives

The aim of this study was to evaluate the effectiveness of intrarectal lidocaine, lidocaine-diltiazem and lidocaine-meperidine-diltiazem gel for anesthetizing transrectal ultrasound guided prostate biopsy.

3. Patients and Methods

After being approved by the Ethical Committee of Teh-

ran University of Medical Sciences and registered in Iranian Registry of Clinical Trials (IRCT) center (number IRCT201211153773N7), this double-blinded randomized clinical trial was conducted on 100 patients awaiting transrectal ultrasound guided prostate biopsy in a teaching hospital from October 2012 to October 2013. Patients had the first experience from a prostate biopsy; it was considered that any previous painful experience from the procedure could have interfered with the present evaluation of pain. An informed written consent was obtained from the patients. Patients younger than 65 years of age, > 40 kg, with raised serum prostate-specific antigen (PSA), and abnormal digital rectal examination, were enrolled in this study. The exclusion criteria were coagulation disorders, hemorrhoidal diseases, severe cardiac or hepatic diseases, local anesthetic and opioids contraindication, and opioids addiction. Males were divided into three groups using a block random allocation process. Group A (38 patients) received lidocaine gel 2% 50 mL (1 g) intrarectal and perianal, group B received lidocaine gel 2% 50 mL (1 g) intrarectal and perianal plus diltiazem cream 1 g (36 patients); group C received similar to group B + meperidine 25 mg which was added to the gel (26 patients). The mixing procedure of meperidine and diltiazem with lidocaine gel (group C): First, perianal diltiazem cream 1 g was applied in the form of application of diltiazem cream on and around the anus. Second, two lidocaine gel tubes were mixed by 25 mg meperidine (prediluted in water and reached to 5 mL) as follows: after pouring the first lidocaine gel tube into a 50-mL syringe, meperidine was poured to the syringe. Then, the second lidocaine gel tube was added to the syringe. No diltiazem was added to the syringe containing meperidine and lidocaine gel. Therefore, no diltiazem was administered intrarectally; only diltiazem was applied on anus to relax its muscle. The gels were made by Sina Darou Company (Iran). The ultrasound probe was made by "Prosound" company (Japan). The mixture was administered 20-60 minutes before the biopsy. The drugs were administered by a physician; another physician who was unaware of the group allocation estimated the pain level. The patients were blinded to the composition of drugs. Visual analog pain scale was used to estimate the pain during probe insertion and biopsy. Heart rate and blood pressure during probe insertion and biopsy were recorded. Males were observed for effects of opioid (meperidine) or lidocaine

overdose: drowsiness, dizziness, requiring assistance for normal activities or tinnitus and light-headedness. Males had 15-20 samples obtained at the time of biopsy.

For reducing the infection rate, all the males received a standard antibiotic prophylaxis: ofloxacin 300 mg twice daily for three days, started eight hours before the procedure, although simple use of povidone-iodine for cleaning the rectum before transrectal ultrasound guided prostate biopsy has been reported to reduce the infection rate as well (16). The patients were asked to attempt to retain the gel. For comparing different main outcomes across the groups, we used one way analysis of variance. SPSS version 17 was used for statistical analysis. $P < 5\%$ was regarded significant.

4. Results

There was no statistical significance in prostate volume, weight, age, PSA levels and blood pressure between the three groups. Since the patients were asked to attempt to retain the gel, no patient expelled it. The patients' characteristics are summarized in Table 1. The mean systolic blood pressures during probe insertion were 151 ± 26 mmHg in group A, 151 ± 17 mmHg in group B and 153 ± 20 mmHg in group C, which were not significantly different (P value = 0.961). The mean systolic blood pressures during the biopsy were 147 ± 24 mmHg in group A, 145 ± 24 mmHg in group B and 145 ± 20 mmHg in group C, which were not significantly different (P value = 0.867). The mean heart rates during probe insertion were 78 ± 16 beat/minute in group A, 79 ± 14 in group B and 83 ± 15 in group C, which were not significantly different (P value = 0.651). The mean heart rates during biopsy were 84 ± 14 beat/minute in groups A and B and 70 ± 16 in group C, but they were not significantly different (P value = 0.01).

The mean visual analog scale (VAS) during probe insertion were 4.5 ± 1.6 in group A, 3.5 ± 1.7 in group B and 2 ± 2.2 in group C (P value = 0.01). The mean VAS scores during the biopsy were 5.1 ± 2.1 in group A, 3.5 ± 2.3 in group B and 2.5 ± 2.2 in group C (P value = 0.001), which were significantly different. No side effects of opioids (meperidine) and lidocaine including drowsiness, dizziness, requiring assistance for activity along with tinnitus and lightheadedness from one hour before the procedure until two hours after were noted (overall three hours).

Table 1. Patients' Demographic Characteristics and Basal Hemodynamic Values ^{a,b}

Variable	Males	Group A	Group B	Group C	P Value
Weight, kg	71	72	72	70	0.764
Age, y	66	67	64	67	0.479
Prostate volume, mL	54	55	59	47	0.064
PSA level, ng/mL	21	23	13	27	0.1
Base heart rate	77	76	77	78	0.891
Base systolic blood pressure, mmHg	146	151	144	143	0.136

^a Abbreviation: PSA, prostate specific antigen.

^b Data are presented as mean.

5. Discussion

Our data suggested that the lidocaine-meperidine-diltiazem mixture was significantly superior to the lidocaine-diltiazem gel and lidocaine gel alone for pain control during transrectal ultrasound guided prostate biopsy. Intrarectal local anesthetic gel is the easiest and most noninvasive method to reduce the transrectal biopsy pain. The results of previous studies have been ambiguous, and the volume, concentration and timing of administration have not been standardized (17). Pain during prostate biopsy has two components. Firstly, it originates from ultrasound probe insertion and secondly, it raises from the biopsy punctures. Luscombe and Cooke (18) reported that for 27% of males, probe insertion pain was as bad as or worse than the pain from needle biopsies. Several procedures are being undertaken routinely, but the use of anesthesia staff will obviously increase the cost. Therefore, providing a safe anesthesia without the use of anesthesia staff may be preferred in terms of financial matters. Some procedures, e.g. combination of perianal-intrarectal lidocaine-prilocaine cream and periprostatic nerve block can be administered without the use of anesthesia staff, but injection discomfort and time assignment are the disadvantages. Transrectal gels may be administered easily and safely and it is a noninvasive procedure. As usual, males who are candidates for prostate biopsy are old and there is a clinically significant reduction in the intensity of pain perception with increasing age (19). Therefore, the use of only topical anesthesia for most males scheduled for prostate biopsy, especially the old ones, seems to be logical.

Cantiello (20) et al. has reported their study with Antrolin cream (trademark filed in Italy with the Ministry of Health) in addition to periprostatic nerve blocker with lidocaine and naropin. The cream was a mixture of 1.5% lidocaine and 0.2% nifedipine which are calcium channels blockers located along the anal sphincter fibro-muscular cell membranes, achieving muscle relaxation. The aim of cream administration was to provide pain control during probe insertion. The authors found that pain during probe insertion might be significantly reduced using Antrolin. We administered a calcium channels blocker (diltiazem) in groups B and C in purpose of lessening the perceived pain in comparison to lidocaine gel alone; the result was significant.

Limitations: lipid-soluble opioids such as fentanyl may be administered; they could have stronger analgesic effects, although the physician who is usually an urologist should learn more about the new lipid-soluble opioids; an instrument able to precisely dissolve opioid in gel is also required. Since these patients are rather old, an instrument measuring the pain i.e. Bispectral index (BIS) (or newly recognized as brain function assessment) or perfusion index (21) which represents a noninvasive measure of peripheral perfusion are suggested. The latter instrument has been used to determine proper manage-

ment of pain, especially in patients unable to communicate their discomfort, although currently they can only be used in extremities. Measuring the plasma opioid (before and after opioids administration) assuring the opioid effect is another suggestion.

Lidocaine-meperidine-diltiazem mixture provides a significantly better pain control than lidocaine-diltiazem gel or lidocaine gel alone during transrectal ultrasound guided prostate biopsy. These intrarectal gels were safe, easy to administer, and well accepted by the patients.

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Authors' Contributions

Design and study collection: Farsad Imani, Yasaman Moghaddam, Seyed Reza Hosseini. Management: Farsad Imani, Yasaman Moghaddam, Seyed Reza Hosseini. Analysis of the data: Farsad Imani, Seyed Reza Hosseini. Preparation, review, and approval of the manuscript: Reza Shariat Moharari, Farhad Etezadi, Mohammad Reza Khajavi, Farsad Imani, Yasaman Moghaddam, Seyed Reza Hosseini.

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