A combination of intrarectal lignocaine cream plus periprostatic nerve block improves pain control in transrectal ultrasound guided prostate biopsy: A prospective evaluation

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ABSTRACT

Background: Prostate biopsy is a painful procedure. The aim of this study was to determine which stage of prostate biopsy is most painful and to investigate the effect of intrarectal local anesthetic (IRLA) on the periprostatic nerve block (PNB).

Methodology: Two groups were established in this prospective, randomized controlled study. One received ultrasonic gel + prilocaine during PNB (Group UP) and the other received intrarectal lignocaine gel + prilocaine combination (Group IP). Prior to probe insertion, ultrasonic gel only was applied to the patients in Group UP, while the subjects in Group IP were administered 60 mg of lignocaine gel via the rectal route 5 min before the biopsy procedure. In the subsequent stage, 10 ml of 2% prilocaine was infiltrated 4 ml into each prostate-seminal vesicle junction and 2 ml into the apex of the prostate. Pain evaluation during and after biopsy was explained to the patients, and this assessment was performed using a Visual Analog Scale (VAS).

Results: The mean age of the patients was 63.37 ± 6.61 years. We identified probe insertion as the most painful stage of prostate biopsy. VAS scores during probe insertion were 3.63 ± 0.98 in Group UP and 3.35 ± 0.85 in Group IP (p = 0.001). We observed less pain in patients receiving an IRLA + PNB combination during biopsy (p = 0.001).

Conclusions: Probe insertion is the most painful stage in transrectal ultrasonography guided prostate biopsies, and intrarectal local anesthetic significantly reduces probe insertion-related pain. In addition, a combination of intrarectal local anesthetic and periprostatic nerve block causes less pain than ultrasonic gel and periprostatic nerve block during biopsy.

Key words: Pain; Probe; Prostate; Transrectal prostate biopsy; Lignocaine; Periprostatic nerve block.

INTRODUCTION

Prostate cancer is the most common form of cancer in men, and the prevalence is constantly increasing due to increased prostate-specific antigen (PSA) testing and to growing awareness.¹ In 2012, 1.1 million men were diagnosed with prostate cancer, 70% of these cases being from developing countries.² Mortality rates from prostate cancer are the second highest after lung cancer.³ Although methods such
as digital rectal examination, measurement of serum PSA levels and pelvic magnetic resonance imaging (MRI) can be used in the diagnosis of prostate cancer, definite diagnosis is established by histology-based prostate biopsy. Pain is a major problem occurring in association with transrectal ultrasound guided (TRUS) biopsy performed for diagnostic purposes, in addition to undesired side-effects such as anxiety during the procedure, and bleeding, prostatitis, sepsis, urinary retention, impairment of sexual function, and hemospermia during or after it. Although major progress has been made in techniques with six quadrant TRUS biopsy of earlier years being increased to a standard 12 quadrants and with saturation biopsies being performed on occasion, pain is still a significant problem. Intensive research is still being performed in a search for alternative and effective methods for overcoming pain and associated anxiety in cases scheduled for TRUS biopsy with a preliminary diagnosis of prostate cancer. Previous studies have to date investigated anesthetic techniques including intravenous sedoanalgesia, use of inhalation agents, periprostatic nerve block (PNB), and intrarectal local anesthesia (IRLA) with the aim of improving comfort and reducing pain. Although no ideal anesthetic technique for prostate biopsy has to date been identified, local anesthesia is sufficient for biopsy, and PNB is the most commonly employed local anesthetic technique.

Our primary objective was to assess the effect of IRLA + PNB compared to ultrasonic gel + PNB alone. Since rectal tissues have high absorbance capacities and since the region is close to the prostate nerves, anesthesia in prostate biopsy can be established with IRLA. IRLA reduces pain levels in TRUS guided prostate biopsy. Causes of pain in the prostate include the entry of the ultrasound probe into the rectum, and the biopsy needle perforating the prostate capsule and stroma. So IRLA can provide a more comfortable biopsy by reducing pain during probe insertion and movements.

**METHODOLOGY**

Patient Selection and Evaluation: Seven hundred patients undergoing TRUS biopsy between March 2012, and July 2017, were included in this prospective study (Figure 1). Local Ethical Committee approval (Scientific Research Review Board of Health Sciences University, Samsun Training and Research Hospital, No. 12.03.2012/2837) was granted for the study. All patients were given detailed information about the study protocol (probe insertion, detailed ultrasonographic prostate examination, local anesthetic agent injection, specimen collection from the prostate and probe removal), and all provided written consent to participate. This research was performed as a prospective, randomized, single-center, parallel-group study with balanced randomization [1:1]. Three hundred fifty subjects were randomly enrolled into each of the two groups, one scheduled to receive either prilocaine (Group UP) and the other receiving an intrarectal lignocaine gel + prilocaine (Group IP) combination. Pre- and post-biopsy pain evaluation was also explained to

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**Figure 1: CONSORT flow diagram; (IP: Intrarectal lidocaine gel + prilocaine, UP: Ultrasonic gel + prilocaine)**

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all subjects. This involved an 11-point linear Visual Analog Scale (VAS) (0 = no pain, 10 = very severe pain) based on subjects’ previous experiences. The pain classification employed was no pain, score of 0; mild pain, 0.1 to 3; moderate pain, 3.1 to 7; and severe pain, scores 7.1 to 10.11 Immediately following the biopsy procedure, subjects were asked to state which sub-procedure had involved the worst pain from among rectal probe insertion, local anesthetic agent infiltration, collection of prostate tissue and probe extract.

The procedure of prostate biopsy was subdivided into four stages in this study (probe insertion, local anesthetic infiltration, collection of tissue from the prostate, probe removal), and patients were asked which one was most painful. In addition all the patients were evaluated with detailed medical history, physical examination, routine hematologic analysis, urine analysis, prothrombin time and, partial thromboplastin time. Appropriate treatment was started with anticoagulant therapies being stopped among those patients receiving them.

Inclusion Criteria: Adult patients aged under 80 with PSA values of 2.5–25 ng/ml and with 10 core parts removed from the prostate were included.

Exclusion Criteria: Patients, with PSA values over 25 ng/ml or age over 80 years, were excluded (since the neuropathic component of pain rises significantly with age and, also due to the risk of these subjects experiencing difficulties in expressing themselves). Patients from whom fewer than 10 prostatic core parts were collected, or with pain in the pelvic region before the procedure started (such as chronic pelvic pain or chronic orchialgia), subjects with rectoanal diseases, a history of alcohol or narcotic dependence or using analgesics on a regular basis were also excluded.

Procedure: Antibiotic prophylaxis was established with oral ciprofloxacin (500 mg) initiated three days before the biopsy procedure. This was continued for a further two days post-biopsy, for a total administration time of five days. Biopsies were performed with subjects in the left lateral decubitus position with hip flexion. The procedures were explained while the biopsy was carried out in order to establish cooperation. Prior to probe insertion, ultrasonic gel only was applied to the patients in Group UR while the subjects in Group IP were administered 60 mg of lignocaine gel via the rectal route 5 min before the biopsy procedure. A 6-MHz 74-mm diameter rectal probe was then inserted. Following the insertion procedure, the prostate was visualized. Prostate volume was calculated using the automatic ellipsoid program (height×width×length×0.52) incorporated.
in the ultrasound machine. We then identified asymmetric or hypoechoic regions. In the subsequent stage, 10 ml of 2% prilocaine was infiltrated, 4 ml into each prostate-seminal vesicle junction and 2 ml into the apex of the prostate, with the help of a 7 inch, 22-gauge spinal needle inserted into the sagittal axis (Figure 2).

Approximately 5-7 min following the periprostatic injection, 10 core prostate biopsy specimens were collected using a 25 cm, 18-gauge biopsy needle together with an automatic biopsy gun (Bard® MaxCore®, Bard Peripheral Vascular Ins, Tempe, USA) (Figure 3).

Patients were requested to indicate the levels of pain felt during probe insertion, during the biopsy procedure, and 1 h after the procedure using the VAS about which they had already received detailed instruction.

Statistical Analysis: Data analysis was carried out on SPSS software (Statistical Package for the Social Sciences, V. 20.0; SPSS Inc, Chicago, IL, USA). Data were expressed as mean ± standard deviation (SD), median (min–max) or frequency (%). The Shapiro-Wilk test was used to assess normality of distribution of quantitative results. Numerical variables were compared using the independent samples t-test. Ordinal variables were compared using the Mann-Whitney U test, and categorical variables using the chi square or Fisher exact tests, as required. All analyses were planned as intention to treat. P values < 0.05 were regarded as statistically significant.

RESULTS

The mean ages of the patients in groups UP and IP were 63.7 ± 6.7 (49-80) years and 63.2 ± 6.8 (45-80) years, respectively. Prostate volumes were 38.7 ± 9.9 (20.1-69.5) ml and 38.6 ± 9.1 (20.2-69.8) ml, respectively. No statistically significant differences were observed between groups UP and IP in terms of age, body mass index (BMI), education level, PSA levels, prostate volume or length of procedure (p > 0.05) (Table 1).

The majority of patients in both groups described probe insertion as the most painful phase of the biopsy procedure that we divided into four stages (rectal probe insertion, local anesthetic agent infiltration, collection of prostatic tissue and removal of the probe). Probe insertion was the most painful part of the prostate biopsy procedure according to 239 (68.2%) patients in Group UP, 232 (66.2%) in Group IP and 471 (67.3%) of the total 700 patients in both groups. The least painful procedure was probe removal. However, 5 (0.7%) patients, 3 (0.9%) in Group UP and 2 (0.6%) in Group IP nevertheless described probe removal as the most painful stage (Table 2).

Table 1: Demographic and clinic characteristics of the patients (BMI: Body mass index, PSA: Prostate specific antigen)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group UP N = 350</th>
<th>Group IP N = 350</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.7 ± 6.7 (49-80)</td>
<td>63.2 ± 6.8 (45-80)</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>28.1 ± 4.6 (21.4-44.9)</td>
<td>28.3 ± 5.1 (21.3-43.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Schooling level [(n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>189 (54%)</td>
<td>173 (49.4%)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>98 (28%)</td>
<td>105 (30%)</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>63 (18%)</td>
<td>72 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>8.1 ± 5.2 (2.56-24.98)</td>
<td>8.1 ± 5.3 (2.54-24.92)</td>
<td>0.89</td>
</tr>
<tr>
<td>CL grade (1,2,3)</td>
<td>7, 9, 4</td>
<td>16, 3, 1</td>
<td>0.015</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>38.7 ± 9.9 (20.1-69.5)</td>
<td>38.6 ± 9.1 (20.2-69.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Biopsy time (min)</td>
<td>2.94 ± 0.9 (2-7)</td>
<td>2.91 ± 0.9 (2-7)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Table 2: According to patients, most painful part of the biopsy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group UP</th>
<th>Group IP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>350</td>
<td>350</td>
<td>700</td>
</tr>
<tr>
<td>Probe entry</td>
<td>239 (68.2%)</td>
<td>232 (66.2%)</td>
<td>471 (67.3%)</td>
</tr>
<tr>
<td>Local anesthetic infiltration</td>
<td>77 (22%)</td>
<td>78 (22.3%)</td>
<td>155 (22.1%)</td>
</tr>
<tr>
<td>Specimen retrieval</td>
<td>31 (8.9%)</td>
<td>38 (10.9%)</td>
<td>69 (9.9%)</td>
</tr>
<tr>
<td>Removal of probe</td>
<td>3 (0.9%)</td>
<td>2 (0.6%)</td>
<td>5 (0.7%)</td>
</tr>
</tbody>
</table>

Table 3: The mean VAS scores by groups (VAS: Visual analog scale); [Data shown as mean ± SS, (Max-min)]

<table>
<thead>
<tr>
<th>VAS evaluation time</th>
<th>Group UP N = 350</th>
<th>Group IP N = 350</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>While placing the probe</td>
<td>3.63 ± 0.98 (1-7)</td>
<td>3.35 ± 0.85 (1-7)</td>
<td>0.001</td>
</tr>
<tr>
<td>During the biopsy</td>
<td>2.60 ± 0.81 (1-7)</td>
<td>2.39 ± 0.85 (1-7)</td>
<td>0.001</td>
</tr>
<tr>
<td>After 1 hour</td>
<td>1.03 ± 0.83 (0-4)</td>
<td>1.06 ± 0.67 (0-4)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Intrarectal lignocaine cream periprostatic nerve block

Group UP and 3.35 ± 0.85 in Group IP (p = 0.001) (Table 3). No patient in either group reported VAS = 0 (no pain) or VAS = 7.1-10 (very severe pain) during probe insertion. Number of patients reporting mild pain (VAS = 0.1-3) during probe insertion was 226 (64.6%) in Group UP and 197 (56.2%) in Group IP.

VAS scores immediately after biopsy were 2.60 ± 0.81 in Group UP and 2.39 ± 0.85 in Group IP (p = 0.69). One hundred ten (31.4%) patients in Group UP and 21 (6%) in Group IP described the biopsy procedure as moderately painful (VAS = 3.1-7).

VAS scores 1 h after prostate biopsy were 1.03 ± 0.83 in Group UP and 1.06 ± 0.67 in Group IP (p = 0.69). One hundred ten (31.4%) patients in Group UP and 114 (32.5%) in Group IP felt no pain (VAS = 0) 1 h after.

Prostate cancer was identified at histopathological analysis in 146 (20.9%) patients, 72 from Group UP and 74 from Group IP.

DISCUSSION

Prostate cancer is the most commonly diagnosed solid tumor in men.1 The widespread use of PSA for prostate cancer screening has led to a dramatic increase in the number of transrectal biopsies. Prostate biopsy performed under the guidance of TRUS is the standard diagnostic method in the diagnosis of prostate cancer. TRUS biopsy is becoming increasingly used in routine urology practice across the world in the diagnosis of prostate cancer. Detection rates are constantly improving, and the prevalence is currently estimated to range between 4.5/100,000, and 111.6/100,000.12,13 Pain is a particularly important problem, in addition to complications such as post-biopsy bleeding, prostatitis, sepsis, urinary retention, impaired sexual function and hypospermia.4 The International Association for the Study of Pain (IASP) describes pain as an uncomfortable sensory and emotional/affective and cognitive experience arising from real or potential tissue injury.14 Due to the invasive nature of prostate biopsy, pain is inevitable. Patients undergoing prostate biopsies are generally awake, albeit under local anesthesia, and the procedure is performed on an outpatient basis. While some patients report little or no discomfort, others experience severe pain. One previous related study reported that over half of patients experienced moderate to very severe pain despite pre-procedural use of intrarectal lignocaine. There is no general consensus that TRUS biopsy is a source of significant pain and discomfort. Mkinen et al. reported that 18% of patients undergoing biopsies refuse rebiopsies.15 Pain during TRUS biopsies is associated with probe insertion, intrarectal movements of the probe, and the tissue collection procedure itself. Probe insertion and biopsy core collection have been described as the main causes of pain in most previous studies. There are two causes of pain in prostate biopsy. The first derives from pain during insertion and movements, and the second from the needle perforating the rectum and prostate capsule.9 Predicting the causes of pain, we divided prostate biopsy into four separate stages (rectal probe insertion, local anesthetic agent infiltration, collection of prostatic tissue and removal of the probe) and investigated which would involve the most pain. Probe insertion was the most painful procedure in both groups. A total of 68.2% (n = 239) of patients in Group UP and 66.2% (n = 232) in Group IP described probe insertion as the most painful stage in prostate biopsy. When the two groups were assessed together, 471 (67.3%) of our 700 patients described probe insertion as the most painful phase. The second most painful stage after probe insertion according to our patients was local anesthetic infiltration. A total of 22.1% (n = 155) of our entire patient group, 22% (n = 77) of those in Group UP and 22.3% (n = 78) of those in Group IP described local anesthetic infiltration as the most painful stage of prostate biopsy. Sixty-nine (9.9%) of our 700 patients (31 in Group UP and 38 in IP) described collection of prostate tissue as the most painful stage. One of the causes of pain in prostate biopsy is the puncturing of the nerve fiber-rich prostate capsule and stroma.16 Only 9.9% of our patients described tissue collection as the most painful stage. Considering that prostate tissue was collected after PNB, it may be concluded that PNB is a good technique for prostate biopsy.

Probe-associated friction will occur in the anal canal during probe insertion, and pain will occur due to damage to the mucosa. The pressure placed on the anal canal by the probe and the pressure on the canal caused by the movement of the probe will stimulate the nerve fiber-rich dentate line and cause pain with a somatic sensation.9 Rectal tissues have high absorption capacities and the region can be easily anesthetized with IRLA.7 The most commonly applied local anesthesia method in prostate biopsy is PNB.6 However, PNB has no effect on pain occurring during probe insertion. Local analgesic methods such as IRLA, anti-inflammatory suppository, lignocaine gel/spray and glyceryl trinitrate ointment have therefore been applied to the anal region in order to reduce probe pain before PNB.17-20 The pain level during probe insertion in the group receiving IRLA...
in our study (Group IP) was 3.35 ± 0.85, compared to 3.63 ± 0.98 in the group using standard ultrasound gel (Group UP). The use of IRLA significantly reduced pain during probe insertion (p = 0.001). Similarly, Stirling et al.21 also reported that the use of IRLA significantly reduced pain during prostate biopsy. Low-diameter rectal probes may possibly cause less pain since they alleviate erosion of the anal canal mucosa and also cause low-severity pressure inside the anal canal. Considering that patients experienced moderate pain during probe insertion despite our application of local anesthetic with intrarectal lignocaine, we think that the use of more flexible rectal probes with a smaller diameter may represent an alternative method in terms of reducing pain during probe insertion. Indeed, Fabiani et al.22 reported that the use of a small-diameter probe significantly reduced pain during probe insertion.

A form of pain relief should be administered before the biopsy procedure. The method of pain control may be either i.v. sedation, intrarectal local analgesia or periprostatic infiltration of local anesthetic such as 1% lignocaine, depending on the preference of the clinician.20 In recent years, some anesthetic techniques were introduced for TRUS-guided prostate biopsies performed in office setting but intrarectal local analgesia and PNB are still the most commonly used anesthesia techniques. Because of its low cost and safely application properties intrarectal lignocaine gel was first and mostly used technique. A significantly reduced VAS score of pain due to probe insertion was shown in pooled analysis results of previous studies using intrarectal lignocaine gel. This result could be attributed to the short-lasting analgesic activity of lignocaine gel with an insufficient coverage for the whole biopsy procedure.21,22 Two separate placebo-controlled studies by Noh et al.23 and Giannarini et al.24 found statistically significant difference in pain tolerance between ultrasonic gel and intrarectal 2% lignocaine- prilocaine gel applications. A prospective study including 75 patients showed that intrarectal 10 ml 2% lignocaine gel was more effective in pain management in comparison to placebo.25

The combined use of IRLA + PNB can reduce pain, not only during probe insertion, but also during prostate biopsy. Pain during probe insertion will increase patients’ stress and anxiety, and this will in turn cause worsened pain during biopsy.19 A VAS value of 2.39 ± 0.85 during biopsy was reported in Group IP in this study. The corresponding value in Group UP was 2.60 ± 0.81. The VAS value in the patients using IRLA + PNB was significantly lower. Noh et al.23 compared an intrarectal lignocaine-prilocaine cream + PNB combination with PNB alone and reported VAS values of 2.22 ± 0.89 and 3.02 ± 1.15, respectively, and concluded that IRLA + PNB was superior. Another meta-analysis by Tiomg et al.,26 including 20 centers and 1,685 patients, also revealed similar results which was PNB decreased pain significantly in comparison to placebo group during prostate biopsy procedure. Previous studies have also reported that an IRLA + PNB combination reduces pain in a safer and more effective manner than PNB alone.20,24,25,27,28 In that respect, our study is compatible with the previous literature.

VAS values in our study 1 h after biopsy were 1.03 ± 0.83 in Group UP and 1.06 ± 0.67 in Group IP. There was no statistically significant difference between the groups. In a study using an IRLA + PNB combination, Wang et al.29 reported a 1-h post-biopsy VAS score of 1.1 ± 1.1. Iremashvili et al.30 determine a 1-h post-biopsy score of 1.13 ± 0.74. Our VAS values 1-h after biopsy were close to those reported in previous studies. In addition, our own and other studies showed that PNB provided effective analgesia in the early period after biopsy.

Limitations

This study has a number of limitations. Anxiety may have prevented patients from responding to the questions objectively. Pain is specific to the subject involved, and measurement is therefore problematic. There are also no standardized pain measurement techniques. Pain perception may also fluctuate from day to day. Pain scores are subjective, and pain may also fluctuate in connection with subjects’ mental and emotional states. We found the most painful stage of prostate biopsy to be probe entry. Our findings may not be very objective because this outcome was derived from the patients’ expression of pain.

Strengths of the Study

The number of enrolled patients was high, and the standardized surgical procedure performed was carried out by a single experienced surgeon.

CONCLUSIONS

This study shows that probe insertion is the most painful stage of prostate biopsy, that pain during insertion decreases with the use of intrarectal local anesthetic and that an intrarectal local anesthetic plus periprostatic nerve block combination significantly reduces pain during biopsy. In addition, we determined that periprostatic nerve block is an effective and tolerable technique in transrectal ultrasound guided guided prostate biopsies. We
Intrarectal lignocaine cream periprostatic nerve block recommend the intrarectal local anesthetic plus periprostatic nerve block combination to all our colleagues for transrectal ultrasound guided prostate biopsies.

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Authors’ Contribution: EA: Conduction of study, data collection, and manuscript editing.
SA: Concept, literature search, and manuscript editing.

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