A RANDOMIZED, CONTROLLED TRIAL COMPARING LIDOCAINE PERIPROSTATIC NERVE BLOCK, DICLOFENAC SUPPOSITORY AND BOTH FOR TRANSRECTAL ULTRASOUND GUIDED BIOPSY OF PROSTATE

N. RAGAVAN,* J. PHILIP, S. P. BALASUBRAMANIAN, J. DESOUZA, C. MARR AND P. JAVLE
From the Michael Heal Department of Urology, Leighton Hospital, Crewe and University of Sheffield (SPB), Sheffield, United Kingdom

ABSTRACT

Purpose: Lidocaine periprostatic nerve block (PPNB) provides good procedural pain relief for transrectal ultrasound (TRUS) prostate biopsy. However, post-procedural pain can be significant. The addition of diclofenac suppository (DS) to lidocaine PPNB might provide additional, particularly post-procedural pain relief. We assessed the procedural and post-procedural pain relief for TRUS biopsy provided by DS, and the combination of DS and lidocaine PPNB compared with lidocaine PPNB alone.

Materials and Methods: A total of 165 patients were randomized into 3 groups, namely group 1—lidocaine PPNB, group 2—DS and group 3—a combination of lidocaine PPNB and DS. In all patients 12 core biopsy was performed. Pain/discomfort at various intervals after the procedure was recorded on a visual analogue scale of 0 to 10 cm.

Results: Biopsy pain was significantly lower in patients who received lidocaine alone or in combination compared with DS alone (median 1.95, IQR 1.08 to 3.12, 3, IQR 1.25 to 5.47 and 1.8, IQR 0.03 to 1.0, respectively, p = 0.018), while evening pain scores were significantly lower in patients who received DS alone or in combination compared with that in patients who received lidocaine alone (median 1.25, IQR 0.38 to 3.0, 0.3, IQR 0.03 to 1.08 and 0.4, IQR 0 to 1.0, respectively, p = 0.001). There were no significant differences in pain/discomfort due to the probe (p = 0.107), that 1 hour after biopsy (p = 0.076) and that on the day after the procedure (p = 0.165). There were no significant differences in hemorrhagic or infective complications among the groups.

Conclusions: The combination of lidocaine PPNB with DS provides additional pain relief during and after prostate TRUS biopsy.

KEY WORDS: prostate; pain; biopsy; ultrasound, high-intensity focused, transrectal; lidocaine

Transrectal ultrasound (TRUS) guided biopsies of the prostate gland is the accepted mode of investigation for the diagnosis of prostate cancer. Irani et al reported that a significant number of patients refused to undergo the procedure again without any anesthesia. Studies have shown that lidocaine periprostatic block is a good form of anesthesia during the procedure and this is routinely practiced in our unit. However, patients have reported pain after the procedure and in the evening. Seymour et al reported that 9% or patients in the local anesthesia group and 14% in the nonlocal anesthesia group used additional analgesia. Diclofenac suppository (DS) has systemic anti-inflammatory and analgesic properties, and its addition to lidocaine periprostatic nerve block (PPNB) might provide additional benefit to patients to provide procedural and post-procedural pain relief. Diclofenac is absorbed rapidly and it attains a peak concentration in less than 40 minutes. It is useful for acute pain relief. Therefore, we performed a randomized, controlled clinical trial to compare the efficacy of 3 forms of analgesia, namely lidocaine PPNB and/or DS, for TRUS biopsy of the prostate.

PATIENTS AND METHODS

Patients and selection criteria. During the 1-year period of June 2002 to May 2003 patients attending urology clinics at a large district general hospital who were scheduled for TRUS biopsy of the prostate were considered for study inclusion. All patients had increased prostate specific antigen (PSA) with or without abnormal digital rectal examination. Patients on warfarin, those with a history of bleeding tendencies and those with known allergy to lidocaine or diclofenac were excluded from study. Informed consent was obtained from all who agreed to participate. One of us (NR) enrolled patients into the trial and randomly assigned them to treatment groups using sealed envelopes containing equal numbers of the 3 treatment arms. Group 1 patients received lidocaine PPNB only, group 2 patients received DS and group 3 patients received a combination of PPNB and DS. Ethical approval was obtained from the Local Research and Ethical Committee (LREC reference M176/02). A total of 165 patients were randomized into 3 groups of 55 each to receive lidocaine PPNB, DS or a combination of PPNB and DS. Antibiotic prophylaxis was administered with 500 mg ciprofloxacin twice daily starting on the day of the procedure and continued for the following 2 days.

Technique. Any of the members of the urology team (NR, JD or PJ), who were experienced with the technique, performed biopsy. An ultrasound machine with a 7.5 MHz probe (Bruel and Kjaer, Decatur, Georgia) was used for the procedure. The periprostatic block was administered with 1% lidocaine using a 22 gauge spinal needle at the basolateral aspect of the gland using 10 ml per side. Although this is slightly more than what other studies have shown, it was routine practice in the department and, therefore, it was also continued during the study. Gland dimensions were then...
measured, thus, allowing few minutes for the local anesthe-
sia to act prior to the actual procedure. Patients randomized
to 100 mg DS alone or the combination were administered
the drug at least 40 minutes before the proposed procedure.
A total of 12 systematic prostatic cores, including 6 laterally
biopsied targets, in addition to conventional parasagittal
biopsies covering the base, mid zones and apexes, were ob-
tained in all patients with an 18 gauge cutting biopsy needle
and spring loaded biopsy gun. All patients were observed for
at least an hour after the procedure and they were dis-
charged home only if they had voided successfully. Patients
were discharged from the hospital with advice to ingest acet-
aminophen as necessary.

Data collection. During the stay in the outpatient unit
patients were counseled about the need to complete the ques-
tionnaire, which included a visual analogue pain score of 0 to
10 cm, regarding 1) pain/discomfort experienced due to the
introduction and presence of the probe, 2) biopsy (pain felt
due to the needle), 3) pain experienced an hour after the
procedure, 4) pain later that evening and 5) pain the day
after biopsy. Scores on the visual analogue scale were meas-
ured with a ruler. Patients also recorded possible complica-
tions and side effects. Specific questions, such as the need to
visit a general practitioner or additional analgesia require-
ments, were also addressed in the questionnaire. A prepaid
addressed envelope was provided for patients to return the
questionnaire to the department.

Statistical analysis. We calculated sample size require-
ments for 2 groups only. To compare the efficacy of diclofenac
alone or combination of diclofenac with lidocaine vs the stan-
dard treatment of lidocaine only we calculated that 51 pa-
tients would be required per group to be able to detect a 1 cm
difference in the visual analogue scale, assuming a mean of
1.6 and SD of 0.9 in the lidocaine group5 with a power of 80%
and a type I error of 0.05. Data analysis was done by an
external investigator (SPB) using SPSS for Windows, version
11.5 (SPSS, Chicago, Illinois). All continuous variables are
described as the mean ± SD if normally distributed and the
median with the IQR if not normally distributed. Patient age
was compared among the groups by ANOVA. Other vari-
ables, including pain scores, were compared using nonpara-
metric tests, including the Kruskal-Wallis, chi-square or
Fisher exact test as appropriate. Post hoc pairwise compari-
sions using the Mann-Whitney test were done if the pain
scores were significantly different in the 3 groups, as shown
by the Kruskal-Wallis test. Analysis was done according to
the intent to treat principle.

RESULTS

Of the 165 patients 147 returned the questionnaire (89%
response). Table 1 lists the baseline characteristics of the 3
patient groups. The groups were similar with respect to pa-
tient age, PSA, prostate volume and the diagnosis of malign-
nancy on TRUS biopsy.

Table 2 shows the pain experienced by patients during and
after the procedure. No significant differences were observed
in pain scores due to the presence of the probe (p = 0.107),
pain 1 hour after the procedure (p = 0.076) and pain the day
following the procedure (p = 0.165). However, a significant
difference among the groups was observed in pain noticed
due to biopsy (p = 0.018) and pain on the evening of the
procedure (p = 0.001). Post hoc pairwise comparisons of
biopsy pain and pain in the evening were done in the 3 groups
using the Mann-Whitney U test. Biopsy pain scores were
significantly lower in patients who received lidocaine PPNB
alone (p = 0.03) or in combination (p = 0.008) compared with
those who received DS alone. Pain scores on the evening of
the procedure were found to be significantly lower in patients
who received DS alone (p = 0.001) or in combination (p = 0.001)
compared with that in patients who received lidocaine PPNB
alone.

Table 3 shows that 40%, 14.5% and 30.6% of the patients in
groups 1 to 3, respectively, used analgesia within 3 days of
the procedure. The questionnaire did not address the dose
and amount of analgesia used by the patients. Patients in
group 2 had minimal post-procedure analgesic use, which
was statistically significant (chi-square test, 2 df, p = 0.019).

DISCUSSION

The introduction of transrectal ultrasound guided biopsies
by Torp-Pedersen et al,6 PSA guided early detection of pros-
tate cancer and the availability of radical treatments for
early prostate cancer has prompted groups at many centers
to perform 12 core biopsy protocols. It is now established that
a significant number of patients experience pain during and
after prostate biopsy.7 Various pain relief modalities have
been investigated, including lidocaine gel,8 enoxaprin9 and
PPNB. PPNB with lidocaine has been investigated by various
groups and shown to be an effective form of anesthesia for
biopsyinsky.10–12 Lido-
was not blinded. We accept that this might have introduced bias in patient responses. All patients were counseled that they would be randomly allocated to 1 of 3 forms of analgesia.

There were no differences in pain/discomfort scores due to introduction or presence of the probe and none of the agents seemed to be effective in this regard. It appears that pain due to biopsy is significantly helped by the use of lidocaine since scores recorded by patient groups 1 (lidocaine alone) and 3 (combination) were much lower than those in group 2 (diclofenac alone). Overall pain scores recorded an hour after the procedure were lower than those of pain felt during biopsy. Of the 3 groups the combination group scores were lowest. However, this did not achieve statistical significance. Pain scores recorded the evening of the procedure in the combination and diclofenac alone groups were lower than those in the lidocaine alone group. This shows that patients with lidocaine alone had rebound pain in the evening and the difference between the groups was statistically significant. It appears that DS with its long duration of action provided significant benefit in these patients.

There were no differences in the pain scores recorded by patients on the day after the procedure. Overall pain scores recorded in the combination group were the least in all of the groups. The combination of PPNB with rectal diclofenac appears to provide the best form of pain relief.

Although pain scores recorded on the day after the procedure were low with no differences among the groups, we still found that a number of patients used analgesia within 3 days of the procedure. Patients in the diclofenac alone group had the lowest analgesic use compared with the combination and lidocaine alone groups (14.6% vs 30.6% and 40%, respectively). It is difficult to explain higher analgesic use in the combination group compared with the group with diclofenac alone. This could have been a chance finding or lidocaine PPNB might have initiated an inflammatory reaction, therefore, necessitating increased analgesic use. It has been suggested that PPNB administration may result in post-inflammatory fibrosis. Further studies are needed to specifically address the issues of longer term pain relief and analgesic use.

We also acknowledge that the study is limited by the lack of blinding patients to the type of analgesia. We also did not stratify patients according to the individual performing the procedure since we believe that the learning process is short and the operator would be an unlikely factor influencing pain severity.

Crundwell et al reported post-procedural complications experienced before the use of periprostatic blocks and Öbek et al reported complications with periprostatic blocks. The incidence rates of bleeding related episodes in our series appear to be more than those reported in other published studies. This may be due to the fact that patients were requested to record even minor amounts of hematoma/blood stained urine and the performance of standard 12 core biopsies in all patients. The duration of bleeding events in our series is comparable to that in another series, in which a combination of brief and long lasting anesthesia was used.

At our hospital routine practice is to advise patients to contact the hospital directly instead of the general practitioner on the day of biopsy, which explains why we had 5 hospital admissions and only 1 patient who visited a general practitioner. There were no serious or life threatening hemorrhagic or infective complications in this study.

Rebound pain after PPNB with lidocaine alone was addressed by Lee-Elliott et al. In a randomized trial comparing lidocaine vs lidocaine and bupivacaine (short and long acting drugs) periprostatic injections the group found that the combination significantly attenuated the 1-hour rebound pain seen after short acting anesthesia alone. Improved pain scores were also sustained during the subsequent week. Mean scores in patients in this study were 1 to 1.5 cm on the visual analogue scale with scores decreasing day by day after biopsy. There were no differences between the groups in analgesic use, although absolute values were not available.

Oral rofecoxib, a nonsteroidal anti-inflammatory drug (NSAID), did not provide better pain relief than placebo for prostatic biopsies. Haq et al compared DS vs placebo as a single agent for prostatic biopsies in a randomized trial and found that rectal diclofenac provided better immediate relief than placebo. They did not address the issue of pain/discomfort felt on the evening or day after biopsy. To our knowledge there are no studies comparing lidocaine PPNB alone, DS alone and the combination after TRUS biopsy of the prostate. Overall pain scores recorded by our patients were lower compared to those in published studies, particularly in the post-procedural period. It may be argued that further decreases in pain provided by additional interventions may not be clinically significant. However, we believe that any degree of pain requiring analgesia should be addressed and DS, which is simple to administer and relatively safe, is helpful in this regard. The alternative option would be to ask the patient to take analgesia as and when necessary, which

<table>
<thead>
<tr>
<th>Pain</th>
<th>Median Lido PPNB (IQR)</th>
<th>Median Diclofenac Suppository (IQR)</th>
<th>Median Combination (IQR)</th>
<th>p Value (Kruskal-Wallis test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>50</td>
<td>48</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Probe</td>
<td>1.95 (1.45–4.05)</td>
<td>3.0 (1.42–4.47)</td>
<td>2.0 (1.03–2.25)</td>
<td>0.107</td>
</tr>
<tr>
<td>Biopsy</td>
<td>1.95 (1.08–3.12)</td>
<td>3.0 (1.25–5.47)</td>
<td>1.8 (0.85–3.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>1-Hr</td>
<td>1.05 (0.37–2.27)</td>
<td>0.6 (0.12–1.67)</td>
<td>0.5 (0.1–1.85)</td>
<td>0.076</td>
</tr>
<tr>
<td>Evening</td>
<td>1.25 (0.38–3.0)</td>
<td>0.3 (0.03–1.08)</td>
<td>0.4 (0.0–1.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Next day</td>
<td>0.35 (0–1.32)</td>
<td>0.2 (0–0.47)</td>
<td>0 (0–1.0)</td>
<td>0.165</td>
</tr>
</tbody>
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**TABLE 2. Pain recorded on visual analogue scale in 3 groups**

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<tr>
<td>No. hematuria (%)</td>
<td>43 (86)</td>
<td>40 (83.3)</td>
<td>38 (77.5)</td>
<td>0.531 (chi-square test)</td>
</tr>
<tr>
<td>Median days hematuria (IQR)</td>
<td>3 (1–4)</td>
<td>1 (1–3)</td>
<td>2 (1–3)</td>
<td>0.107 (Fisher’s exact test)</td>
</tr>
<tr>
<td>No. rectal bleeding (%)</td>
<td>23 (46)</td>
<td>21 (43.7)</td>
<td>24 (48.9)</td>
<td>0.874 (chi-square test)</td>
</tr>
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<td>Median days rectal bleeding (IQR)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.740 (Kruskal-Wallis test)</td>
</tr>
<tr>
<td>No. hemospermia (%)</td>
<td>13 (26)</td>
<td>16 (33.3)</td>
<td>13 (26.5)</td>
<td>0.672 (chi-square test)</td>
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<td>No. fever (%)</td>
<td>1 (2)</td>
<td>2 (4.1)</td>
<td>0</td>
<td>0.322 (Fisher’s exact test)</td>
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<td>No. hospitalization (%)</td>
<td>2 (4)</td>
<td>2 (4.1)</td>
<td>1 (2)</td>
<td>0.871 (Fisher’s exact test)</td>
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<td>No. general practitioner visit (%)</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0.660 (Fisher’s exact test)</td>
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<td>No. analgesic used within 3 days (%)</td>
<td>20 (40)</td>
<td>7 (14.5)</td>
<td>15 (30.6)</td>
<td>0.019 (chi-square test)</td>
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</table>

**TABLE 3. Other outcomes in 3 groups**

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can be acetaminophen or a NSAID depending on physician choice. We prefer to give a NSAID since this is an invasive procedure that is likely to induce some degree of inflammation. The option of DS before the procedure, as in this study, or an oral prescription should be the choice and preference of the patients and treating physicians.

CONCLUSIONS

The combination of DS and lidocaine PPNB provides good additional pain relief during and after biopsy without any increased risk of complications. Pain scores recorded in this study are low. Although we would recommend routine use of this combination, it would be up to the patients and treating physicians to decide the strategy of post-procedural pain relief as routine pre-procedural diclofenac or a separate post-procedural prescription for pain relief.

REFERENCES


EDITORIAL COMMENT

Several years ago (January 2001) we sent out a survey, which was completed by 88 urologists, and found that only 11% used PPNB in an effort to minimize the pain associated with TRUS guided biopsies of the prostate. A third did not prescribe anything to minimize pain. I would hope that the majority of those performing TRUS biopsies now use PPNB since a number of randomized trials, including the current report, indicate that this dramatically decreases pain. This is particularly important since most of us obtain 10 to 12 cores. These authors found that approximately a third of their patients receive additional oral analgesia after biopsy and they suggest that we should routinely prescribe a NSAID or similar analgesia to preempt this minor but annoying sequela. Although patients used to tolerate this anxiety provoking procedure without anesthesia, ie PPNB or other adequate anesthesia, that does not mean that we should be inconconsiderate of their precarious position. Since reading this article, I will not only continue PPNB, but also will prescribe long acting analgesia to be received for 1 or 2 days after the procedure.

Mark S. Soloway
Department of Urology
University of Miami School of Medicine
Miami, Florida