Evaluation of the efficacy of a combination of diltiazem and periprostatic nerve block in pain control during transrectal ultrasound guided biopsy of the prostate: A randomized controlled trial

Tarun Jindal M.S., Satyadip Mukherjee MCh, Gopa Biswas M.D.¹, Soumendra Nath Mandal MCh, Dilip Karmakar MCh.

Department of Urology and ¹Department of Pharmacology, Calcutta National Medical College, Kolkata, India

Type of article: Research article

Running title: Diltiazem and PPNB in prostate biopsy

Corresponding author

Dr Tarun Jindal

Department of Urology,

Calcutta National Medical College,

Kolkata, India

Phone: 09674444929

E-mail: drtarunjindal@gmail.com
Abstract

**Background**: The choice of analgesia during prostate biopsy remains controversial. The pain has dual origin, one from the insertion of probe and secondly due to the biopsy per se. Periprostatic nerve block (PPNB) is currently the gold standard modality to decrease pain of prostate biopsy but it does not alleviate the pain of probe insertion. We tested the efficacy and safety of combination of diltiazem gel and PPNB for pain control during transrectal ultrasound guided prostate biopsy.

**Methods**: 73 patients who were to undergo their first prostate biopsy were randomized to receive either 2 ml of 2% topical diltiazem gel or placebo 15 minutes before prostate biopsy. All the patients then had a PPNB using 1% lignocaine. A 10-point visual analogue score was used to record the pain immediately after the insertion of the probe and during biopsy. Any adverse effects were also recorded.

**Results**: There was no significant difference in the mean age and prostate volumes between the groups. There was a significantly lower mean pain score due to probe insertion in those who received topical diltiazem as compared to placebo group ($P<0.0001$). There was no significant difference between the pain scores during the biopsy per se between the two groups.

**Conclusions**: Topical diltiazem significantly reduces the pain of probe insertion during prostate biopsy and can be effectively used as an adjuvant to PPNB.

**Key words**: Prostate, Biopsy, Diltiazem, Pain

**Trial registration**: The Clinical Trials Registry- India CTRI/2012/09/003027
Background

Prostate biopsy is one of the commonly performed procedures for the diagnosis of prostate carcinoma. It is usually performed as an office procedure under ultrasound guidance using a trans-rectal probe [1]. As this procedure is associated with pain, it is a cause of significant anxiety for the patient [2,3]. Various methods for pain reduction have been described ranging from simple application of anaesthetic gels to complex nerve blocks [4,5]. Presently periprostatic nerve block (PPNB) is the gold standard method used for pain control during transrectal ultrasound (TRUS) guided biopsy of the prostate. It has been extensively evaluated and has been found to be very effective [6,7].

It has been found that the pain during the TRUS biopsy of the prostate has dual origin, firstly the pain of insertion of the ultrasound probe into the rectum which is due to the stretching of the anal sphincter and secondly due to the insertion of the biopsy needle in the prostate [2,8]. It has been found that the pain due to the insertion of probe is higher than the pain of the biopsy per se [9,10]. PPNB effectively reduces the pain due to the insertion of needle in the prostate but it is ineffective in decreasing the pain of the insertion of the probe into the rectum [2,8,11].

In order to reduce the pain of the probe insertion, we should add drugs that have effect of the anal sphincter. Diltiazem is a drug which has been used in the treatment of anal fissures. It acts by relaxing the anal sphincter [12]. Hypothetically, if we combine diltiazem with PPNB, pain due to both aforementioned reasons can be alleviated.

We, in this study, evaluated the efficacy of addition of diltiazem to PPNB in the management of pain during TRUS guided biopsy of the prostate.
Methods

The study was conducted over a period of six months extending from January 2012 to June 2012. Ethical clearance was obtained from the Ethical committee of Calcutta National Medical College. The patients who were to have their first prostatic biopsy due to clinical or biochemical suspicion of carcinoma prostate were included in the trial. The exclusion criteria included history of active anal diseases, anal fissures, haemorrhoids, rectal ulcers, chronic pelvic pain syndrome, prostodynia, active urinary tract infection, coagulopathies, neuropathies, uncontrolled diabetes, ingestion of aspirin or clopidogrel or any other antiplatelet drugs, use of narcotics and analgesics, antihypertensive medications, known allergy to diltiazem or lignocaine, low systolic blood pressure (<100 mm Hg), severe renal, cardiac or hepatic illness. A written informed consent was taken from all the patients in the study.

Pre-procedural preparation was done by administration of oral ciprofloxacin, twice daily, from the day before the biopsy and was continued for another four days. Patients were also administered an enema in the morning of the day of biopsy. They were randomised with the help of a computer programme in to two groups. Group 1 received 2 ml of a non medicated lubricating gel perirectally and intrarectally (placebo) while group-2 received 2 ml of 2% diltiazem gel perirectally and intrarectally. These gels were applied fifteen minutes before the biopsy procedure by a single person (S.M.). The patients were blinded regarding the type of medication applied.

The biopsies were performed in the left lateral decubitus position by a single operator (T.J). He was blinded towards the gels applied peri and intrarectally. The biopsies were performed using a 7.5 MHz, hand held probe of the Philips HD-7 ultrasound system (Netherlands). First a digital rectal examination was performed followed by transrectal ultrasound of the prostate.
PPNB was administered using a 22-G, 16 cm long spinal needle. The procedure was started on the right side first with the identification of the junction between the prostate and the seminal vesicle. 5 ml of 1% lignocaine was instilled in this area raising an “ultrasonic wheal”. Similar procedure was the performed on the left side. Biopsy was started 5 min after the PPNB. An 18-G, 26 cm long, spring loaded biopsy gun was used. Twelve core biopsies were taken in all the cases which included six para-sagittal and six lateral biopsies with one core each from apex, mid zone and the base of the prostate.

Pain scoring was done at the time of insertion of the ultrasound probe and at the time of biopsy. The standard ten point visual analogue scale was used for determination of pain with a score of zero meaning no pain while that of ten meaning unbearable pain.

The patients were observed for two hours to note any immediate complications and were then followed up for one week to record any late complication.

The statistical analysis was done using student’s t-test for independent variables. The p-value was considered as significant when it was less than 0.05. The data was analysed using the SPSS software, version 19.0.
Results

A total of 73 patients, 35 in group-1 and 38 in group-2, who fulfilled the study criteria, were included in the trial. The mean age, volume of the prostate and serum PSA values were similar in both the groups (Table 1). The time taken for PPNB and during biopsy was also similar in both the groups.

The mean pain scores during insertion of probe into the rectum were significantly lower in the patients who received diltiazem (group-2) as compared to those receiving non medicated gel (2.6 v/s 4.22, p<0.0001). Figure 1 shows the distribution of pain scores during the time of insertion of the probe in both the groups of patients. The categorisation has been done as pain score between 1-3 meaning mild pain, 4-6 meaning moderate pain and 7-9 meaning severe pain. There were no patients with a pain score of 0 (no pain) or 10 (severe unbearable pain) in either of the groups. The mean pain scores during the time of biopsy were similar in both the groups (Table 2).

No significant immediate post procedural complications were noted in either of the groups. 16 patients, eight in each group noted mild complications on follow up. These included hematuria (n=12), hematospermia (n=8), hematochezia (n=11) and dysuria (n=9). All these were self limiting and did not require hospital admission.
TRUS-guided biopsy of the prostate is the established standard test for the diagnosis of prostate cancer. With the availability of PSA as a biochemical marker for prostatic cancer, more and more patients across the world are being subjected to prostate biopsy. Though it is a technically simple and safe procedure, it is associated with significant pain thus necessitating the use of some form of anaesthesia or analgesia. Various agents have been tried for this purpose including the application of anaesthetic gels like lignocaine, eutectic mixture of lignocaine and prilocaine, sedoanalgesia, intrarectal administration of diclofenac, oral cyclooxygenase-2 inhibitors like rofecoxib etc. Sedation with nitrous oxide, entonox, midazolam, propofol etc. have also been tried [1,4-6,13-15]. Significant controversy exists in the literature regarding the choice of analgesia for TRUS biopsy of the prostate. PPNB is now emerging as the gold standard modality for pain control during TRUS biopsy. This method was first described by Nash et al and popularised by Soloway et al [16,17]. It includes bilateral injections of an anaesthetic agent (usually lignocaine or bupivacaine) at the junction of the base of the prostate and the seminal vesicles where the neurovascular bundle innervating the prostate is present. This effectively decreases the pain of needle insertion into the prostate.

The pain during prostatic biopsy has dual origin. It originates due to the insertion of the transducer probe into the rectum as well as due to the insertion of the biopsy needle in the substance of the prostate. It has been found that much of the apprehension of the patients who are to have the biopsy is related to the anal route of this manoeuvre. It has been reported in various studies that the introduction of the probe in the rectum is in fact the most painful part of the procedure. PPNB, unfortunately, is ineffective in reduction of the pain of probe insertion [2,8-10].
The pain of the probe insertion is due to the stretching of the anal sphincter and can be reduced to some extent by drugs that relax anal sphincter. Nitroglycerine relaxes the anal sphincter and has been used in the past to decrease the pain of prostate biopsy. Rochester et al compared the effect of application of nitroglycerin paste before prostatic biopsy and reported significant reduction in pain [18]. McCabe et al reported their experience with the use of nitroglycerin gel along with PPNB. They noted significant reduction in the pain scores during TRUS biopsy [2]. One major issue in both these studies was the significantly high incidence of headaches which may not be acceptable to the patients as well as the urologist [2,18]. Hence, a drug which relaxes the anal sphincter without the risk of significant complications can prove to be an ideal adjuvant to the PPNB.

Diltiazem is a calcium channel blocker. It has been used in the treatment of anal fissures and acts by relaxing the sphincter by calcium mediated mechanism[12]. It has a large therapeutic index and is not associated with complications like headaches, sudden drop in blood pressure, etc. [2,19] We have previously evaluated the efficacy and safety of a combination of diltiazem along with lignocaine gel for prostate biopsy and have compared it with nitroglycerin. Our results revealed that diltiazem reduced the pain of prostatic biopsy and was safe as compared to nitroglycerin [20]. Due to its safety profile and clinical efficacy, we used diltiazem in the present study. To the best of our knowledge, study is the only one in the literature that evaluates the efficacy of combination of diltiazem and PPNB in the reducing the pain of prostatic biopsy.

We evaluated the pain scores at each step of prostatic biopsy instead of assessment at the end of the procedure. This was done in order to avoid the “recall bias” which has been a common problem in the previous studies [21]. Our results indicate that diltiazem reduces the pain of probe insertion. The mean pain scores of the group of patients receiving diltiazem was significantly lower than the group that did not receive it (2.6 v/s 4.22, p<0.0001). However,
addition of diltiazem did not have any effect on the pain during the biopsy per se as the mean pain scores in both the groups are similar (2.02 v/s 2.15, p=0.48).

Diltiazem administration was not associated with any significant complications. None of the patients experienced headaches, fall of blood pressure etc. The total number of complications were similar in both the groups and were self limiting in nature.
Conclusions

Our results indicate that addition of diltiazem to PPNB is effective in reduction of the pain of insertion of probe during the time of prostatic biopsy. It is safe and not associated with any untoward side effects. It can be effectively used in combination with PPNB during prostate biopsy.
List of abbreviations

PPNB: Periprostatic Nerve Block

TRUS: Trans Rectal Ultrasound

VAS: Visual Analogue Scale
Competing interests

The authors declare that they have no competing interests
Authors' contributions

TJ contributed by conceiving the methodology, design, collecting the data, analysing and interpreting it. He also wrote the manuscript. SM, SNM, DK contributed to the editing and final approval of the manuscript.
References


20 Jindal T, Mandal SN, Mukherjee S, Karmakar D: Comparison of the efficacy and safety of topical diltiazem and nitroglycerine for pain relief during transrectal ultrasound guided biopsy of the prostate. *Int Braz J Urol* 2012, 38:405-10.

**Figure legends**

**Figure 1:** Graph demonstrating the distribution of pain scores in the two groups at the time of insertion of rectal probe
Table 1: Patient characteristics, mean time for nerve block and biopsy in the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (non-medicated gel + PPNB)</th>
<th>Group 2 (Diltiazem gel + PPNB)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>35</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>70 (52-86)</td>
<td>70.26 (51-90)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean volume of the prostate (cc)</td>
<td>85.05 (40-124)</td>
<td>79.57 (40-127)</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean PSA value (ng/ml)</td>
<td>22.45 (6-35)</td>
<td>19.23 (6-34)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean time taken for PPNB (sec)</td>
<td>222 (160-278)</td>
<td>213.7 (160-279)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean time taken for biopsy (sec)</td>
<td>403.6 (287-496)</td>
<td>389.6 (291-500)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

PPNB- Periprostatic nerve block
Table 2: Pain scores during the biopsy procedure in the two groups of patients

<table>
<thead>
<tr>
<th>Group 1 (non-medicated gel + PPNB)</th>
<th>Group 2 (Diltiazem gel + PPNB)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pain score during the insertion of the probe (VAS 1)</td>
<td><strong>4.22 (2-6)</strong></td>
<td><strong>2.60 (1-5)</strong></td>
</tr>
<tr>
<td>Mean pain scores during the time of biopsy (VAS 2)</td>
<td><strong>2.02 (1-3)</strong></td>
<td><strong>2.15 (1-3)</strong></td>
</tr>
</tbody>
</table>

PPNB- Periprostatic nerve block, VAS-Visual analogue scale