Evaluation of the efficacy of a combination of diltiazem and periprostatic nerve block in pain control during transrectal ultrasonography-guided biopsy of the prostate

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ABSTRACT

INTRODUCTION The choice of analgesia during prostate biopsy remains controversial. The pain has dual origin: from the insertion of the probe as well as the biopsy itself. Periprostatic nerve block (PPNB) is currently the gold standard modality for decreasing pain of prostate biopsy but it does not alleviate the pain of probe insertion. A randomised controlled trial was performed to test the efficacy and safety of the combination of topical application of diltiazem gel and PPNB for pain control during transrectal ultrasonography guided prostate biopsy.

METHODS A total of 73 patients who were to undergo their first prostate biopsy were randomised to receive either 2ml of 2% topical diltiazem gel or a placebo 15 minutes before the biopsy. All the patients then had a PPNB using 1% lignocaine. A ten-point visual analogue scale was used to record the pain immediately after the insertion of the probe and during the 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 patients who received topical diltiazem than in the placebo group ($p < 0.0001$). There was no significant difference between the pain scores during the biopsy itself between the two groups.

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

KEYWORDS

Prostate – Biopsy – Diltiazem – Pain

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Prostate biopsy is one of the commonly performed procedures for the diagnosis of prostate carcinoma. It is usually performed as an office procedure under ultrasonography guidance using a transrectal 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 ultrasonography (TRUS)-guided biopsy of the prostate. It has been evaluated extensively and has been found to be very effective.^{6,7}

Pain during TRUS biopsy of the prostate has dual origin: the pain of insertion of the ultrasonography probe into the rectum, which is due to the stretching of the anal sphincter, as well as the pain of the insertion of the biopsy needle in the prostate.^{2,8} It has been found that the pain due to the insertion of the probe is higher than the pain of the biopsy itself.^{9,10}

PPNB effectively reduces the pain due to the insertion of the 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, drugs should be added that have an effect on the anal sphincter. Diltiazem is a drug that has been used in the treatment of anal fissures. It acts by relaxing the anal sphincter.¹² Hypothetically, if diltiazem is combined with PPNB, pain due to both aforementioned reasons can be alleviated. The aim of this study was to evaluate the efficacy of the 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 from January 2012 to June 2012. Ethical clearance was obtained from the ethical committee of Calcutta National Medical

Table 1 Patient characteristics, and mean time for nerve block and biopsy

	Non-medicated gel + PPNB (Group 1)	Diltiazem gel + PPNB (Group 2)	<i>p</i> -value
Number of patients	35	38	
Mean age (years)	70.00 (52–86)	70.26 (51–90)	0.93
Mean volume of prostate (cc)	85.05 (40–124)	79.57 (40–127)	0.40
Mean PSA (ng/ml)	22.45 (6–35)	19.23 (6–34)	0.12
Mean time taken for PPNB (secs)	222.0 (160–278)	213.7 (160–279)	0.33
Mean time taken for biopsy (secs)	403.6 (287–496)	389.6 (291–500)	0.35

PPNB = periprostatic nerve block; PSA = prostate specific antigen

Table 2 Pain scores during the biopsy

	Non-medicated gel + PPNB (Group 1)	Diltiazem gel + PPNB (Group 2)	<i>p</i> -value
Mean VAS pain score during probe insertion	4.22 (2–6)	2.60 (1–5)	<0.0001
Mean VAS pain score during biopsy	2.15 (1–3)	2.02 (1–3)	0.48

PPNB = periprostatic nerve block; VAS = visual analogue scale

Figure 1 Visual analogue scale (VAS) pain scores in the two groups at the time of insertion of rectal probe

College and the trial was registered with the Indian clinical trials registry (CTRI/2012/09/003027). Patients who were to have their first prostatic biopsy owing to clinical or biochemical suspicion of carcinoma prostate were included in the trial. The exclusion criteria included history of active anal disease, anal fissures, haemorrhoids, rectal ulcers, chronic pelvic pain syndrome, active urinary tract infections, coagulopathies, neuropathies, uncontrolled diabetes, ingestion of aspirin or clopidogrel or any other antiplatelet drugs, recent use of narcotics and analgesics, antihypertensive medications, known allergy to diltiazem or lignocaine, low systolic blood pressure (<100mmHg) and severe renal, cardiac or hepatic illness. Written informed consent was taken from all the patients in the study.

Preprocedural preparation was done by administration of oral ciprofloxacin, twice daily, from the day before the biopsy and this was continued for another four days. Patients were also administered an enema in the morning of the day of the biopsy. They were randomised with the help of a

computer program into two groups. Group 1 received 2ml of a non-medicated lubricating gel perirectally and intrarectally (placebo) while Group 2 received 2ml of 2% diltiazem gel perirectally and intrarectally. These gels were applied 15 minutes before the biopsy procedure by a single person (SM). The patients were blinded regarding the type of medication applied.

The biopsies were performed in the left lateral decubitus position by a single operator (TJ), who was blinded towards the gels applied peri and intrarectally. The biopsies were performed using a 7.5MHz handheld probe of the HD7 ultrasonography system (Philips, Amsterdam, Netherlands).

First, a digital rectal examination was performed followed by TRUS of the prostate. PPNB was administered using a 16cm long 22G spinal needle. The procedure was started on the right side with the identification of the junction between the prostate and the seminal vesicle, and 5ml of 1% lignocaine was instilled in this area. A similar procedure was performed on the left side. The biopsy was started five minutes after the PPNB. A 26cm long, spring-loaded 18G biopsy gun was used. Twelve core biopsies were taken in all the cases, which included six parasagittal and six lateral biopsies with one core each from the apex, central zone and base of the prostate.

Pain scoring was done at the time of insertion of the ultrasonography probe and at the time of the biopsy. The standard ten-point visual analogue scale was used for determination of pain with a score of 0 meaning no pain while a score of 10 represented 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 complications.

The statistical analysis was performed using Student's *t*-test for independent variables. The *p*-value was considered statistically significant if it was <0.05. The data were analysed using SPSS® version 19.0 (SPSS, Chicago, IL, US).

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 prostate-specific antigen (PSA) values were similar in both groups, as was the time taken for PPNB and during biopsy (Table 1).

The mean pain scores during insertion of the probe into the rectum were significantly lower in the patients who received diltiazem than in those receiving non-medicated gel (2.6 vs 4.22, $p < 0.0001$). Figure 1 shows the distribution of pain scores during the time of insertion of the probe in both groups. Pain scores were grouped as 1–3 (mild), 4–6 (moderate) and 7–9 (severe). There were no patients with a pain score of 0 (no pain) or 10 (severe unbearable pain) in either group. The mean pain scores during the time of biopsy were similar in both groups (Table 2).

No significant immediate complications following the procedure were noted in either group. Sixteen patients (eight in each group) noted mild complications on follow-up. These included haematuria ($n=12$), haemospermia ($n=8$), haematochezia ($n=11$) and dysuria ($n=9$). All these were self-limiting and did not require hospital admission.

Discussion

TRUS 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. Although it is a technically simple and safe procedure, it is associated with significant pain, therefore 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 and oral cyclooxygenase-2 inhibitors such as rofecoxib. Sedation with nitrous oxide, nitrous oxide mixed with oxygen, midazolam and propofol has 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 and Obek.^{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. On the one hand, there is pain owing to the insertion of the transducer probe into the rectum but there is also pain owing to the insertion of the biopsy needle in the substance of the prostate. Much of the apprehension of patients who are to have a biopsy is related to the anal route of this manoeuvre; it has been reported that the introduction of the probe in the rectum is in fact the most painful part of the procedure.¹⁰ Unfortunately, PPNB is ineffective in reducing the pain of probe insertion.^{2,8,9}

The pain of probe insertion is due to stretching of the anal sphincter and can be reduced to some extent by drugs that relax the anal sphincter such as nitroglycerin. Nitroglycerin 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.¹⁰ McCabe *et al* described their experience with the use of nitroglycerin gel along with PPNB.² They noted a significant reduction in pain scores during TRUS biopsy. One major issue in both of these studies was the high incidence of headaches, which may not be acceptable to the patients or the urologist.^{2,10} A drug that relaxes the anal sphincter without the risk of significant complications can therefore prove to be an ideal adjuvant to PPNB.

Diltiazem is a calcium channel blocker. It has been used in the treatment of anal fissures and acts by relaxing the sphincter by a calcium-mediated mechanism.¹² It has a large therapeutic index and is not associated with complications like headaches or a sudden drop in blood pressure.^{2,18} We have previously evaluated the efficacy and safety of a combination of diltiazem gel along with lignocaine gel for prostate biopsy, and have compared it with nitroglycerin gel: diltiazem gel reduced the pain of prostatic biopsy and was safe compared with nitroglycerin.¹⁹ Owing to its safety profile and clinical efficacy, we used diltiazem in the present study along with PPNB, which is presently the recommended form of analgesia for prostate biopsy. To our knowledge, this study is the only one in the literature that evaluates the efficacy of a combination of diltiazem and PPNB in reducing the pain of prostatic biopsy.

We evaluated pain scores at each step of the prostatic biopsy instead of just assessment at the end of the procedure. This was done in order to avoid 'recall bias', which has been a common problem in previous studies.²⁰ Our results indicate that diltiazem reduces the pain of probe insertion. The mean pain scores of the group of patients receiving diltiazem were significantly lower than those of the group not receiving it (2.6 vs 4.22, $p < 0.0001$). However, addition of diltiazem did not have any effect on the pain during the biopsy itself as the mean pain scores in both the groups were similar (2.15 vs 2.02, $p=0.48$).

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

Conclusions

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

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