

## **Analgesia for Prostate Biopsy: Efficacy of Diclofenac Patch versus Diclofenac Suppository as Compared to Placebo during Prostate Biopsy**

**Kishore Thekke Adiyat<sup>1\*</sup>, Prashanth Kanagarajah<sup>2</sup>, Antony PG<sup>1</sup>, Suresh Bhat<sup>1</sup>**

<sup>1</sup>West Fort Hospital Punnamm Road Thrissur, Kerala, India

<sup>2</sup>Madras Medical College E.V.R. Periyar Salai Chennai, Tamilnadu, India

### **Abstract**

**Background and Aims:** Trans-rectal ultrasound guided prostate biopsy (TRUS) remains the gold standard to diagnose patients with prostate cancer. The purpose of this study is to prospectively evaluate the efficacy of diclofenac suppository versus diclofenac patch as compared to placebo, on pain reduction during prostate biopsy.

**Methods:** A prospective, randomized, single-blind, placebo controlled study was performed in 73 patients requiring transrectal ultrasound guided prostate biopsy (TRUS). Patients were randomly allocated to receive 100 mg diclofenac suppository or 100 mg diclofenac patch or matching placebo 1 hour prior to the procedure. They were asked to indicate on a 10 cm visual analogue scale the degree of discomfort during probe insertion, needle penetration and four hours post biopsy. Statistical analysis was done using one way ANOVA. The data was analyzed using SPSS version 10.0.

**Results:** Patients given diclofenac suppository and diclofenac patch had statistically significant lower four hour pain scores than those who were given placebo. There was no statistically significant difference in the pain scores between the three groups during probe insertion and needle penetration. The three groups were similar in regards to age, prostate volume, biopsy number, prostate specific antigen levels, histological diagnosis and complication rate.

**Conclusions:** Diclofenac in the form of a patch or suppository does not confer a superior intraprocedural analgesic effect compared to the placebo, but it reduces post procedural pain to a significant extent. We do not recommend its use as a single agent analgesic for prostate biopsy and it should be used as an adjunctive analgesic for reducing post procedural pain.

**Keywords:** Prostate Biopsy, Prostate Cancer, Trans-Rectal Ultrasound Guided Biopsy, Local Analgesia, Local Anesthesia

### **Introduction**

Elevated prostate specific antigen (PSA) and abnormal digital rectal examination raise clinical suspicion of prostatic neoplasia (1, 2). Transrectal ultrasound-guided prostate biopsy (TRUS) is an essential diagnostic tool for patients with clinical suspicion of prostate cancer. Though widely accepted as an uncomfortable experience for the patient, with the help of analgesia or anaesthesia biopsies are

considered a safe outpatient procedure (3). Crundwell et al found that 24% of patients undergoing TRUS thought that the procedure was moderate to severely

*\*Correspondence:*  
Kishore Thekke Adiyat, MD  
West Fort Hospital Punnamm Road Thrissur, Kerala, India.  
E-mail: kishoreta@yahoo.com  
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painful with pain scores greater than 5 on a visual analogue scale of 0 to 10 (4). Irani et al found that 19% of men, when questioned after biopsy, would refuse the procedure again without anaesthesia or analgesia (5). The acceptability of this procedure is critical as re-biopsy can increase the diagnostic yield of carcinoma of the prostate by up to 30%, and hence more men require to be re-biopsied (6). Diclofenac in all forms has potent systemic anti-inflammatory and analgesic properties. Diclofenac is absorbed rapidly and it attains peak concentration in less than 40 minutes (7). Therefore, we performed a randomized, single blinded, placebo controlled clinical trial to compare the efficacy of diclofenac suppository and diclofenac patch with that of a placebo. The analgesic effect of diclofenac suppository while performing TRUS has been studied previously by Haq et al and Ragavan et al although the conclusions derived were contradictory (8, 9).

## Materials and Methods

At the time of designing the study we practiced prostate biopsy without any analgesia, so a placebo group was considered ethical. Seventy three patients presented to our institution over a period of one year to have TRUS biopsy. The study was clearly explained to the patients and upon receipt of their consent; patients were prospectively enrolled into the study.

All patients referred for TRUS to our hospital during a 12-month period from September 2005 to August 2006 were considered eligible for the study. All patients had an indication for biopsy (elevated prostate specific antigen [PSA] or abnormal digital rectal examination). The only exclusion criterion was a known contraindication to the use of non-steroidal anti-inflammatory medications. Patients were informed that they were participating in a single-blind, placebo controlled study. The 73 patients who agreed to participate in the study were randomized into three

groups, of which 24 patients received Diclofenac patch, 25 patients received Diclofenac suppository and 24 patients received placebo. Block randomization technique was employed to randomize patients into the 3 groups. Each block was defined by 3 patients, with one patient each falling into the placebo, diclofenac suppository and diclofenac patch groups. Three physicians were assigned the individual tasks of administering analgesia to all patients, performing the biopsy, and lastly to assess pain scores and complications after the procedure in order to eliminate bias. Data analysis was performed by a qualified statistician.

Patients randomized to the analgesia group received diclofenac suppository 100 mg or diclofenac patch 100 mg placed over the inner thigh 1 hour prior to the procedure. Patients randomized to the placebo group received an identical placebo patch made of a plastic foil or suppository made of frozen butter 1 hour prior to the procedure. All patients received 500mg of ciprofloxacin as antibiotic prophylaxis prior to the procedure. Patients were placed in the lateral decubitus position. TRUS was performed using a 7.5 MHz transrectal probe. An average of 6 prostate biopsies was taken using a spring loaded biopsy gun needle with an 18 gauge, 25 cm needle.

Immediately after the procedure, patients were asked to show on a 10 cm linear visual analogue scale the degree of discomfort experienced during insertion of the probe and during the passage of needle. A questionnaire providing patient details and biopsies performed was completed simultaneously. Patients were kept under observation for four hours and a pain score was again recorded. On post-op day five, patients were contacted to discuss the biopsy results and were also questioned about the presence of late complications: infection, gross hematuria, rectal irritation and gastrointestinal discomfort. Information provided by individual patients was recorded for analysis.

**Table 1.** Data characteristics of the three groups

Group	Placebo	Suppository	Patch
Mean Age	69.2	66.8	68.1
Mean Serum PSA	40.36	44.68	39.92
Mean prostate gland size	40.08	32.48	33.88
Mean pain score during probe insertion	2.32	2.12 (p=0.626)	2.13 (p=0.588)
Mean pain score during needle penetration	3.80	3.72 (p=0.229)	3.45 (p=0.277)
Mean four hour post-procedural pain score	1.60	0.64 (p=0.001)	0.96 (p=0.0159)

PSA, Prostate specific antigen.

### Statistics:

The data was analyzed using SPSS version 10.0. The differences in pain scales, age, PSA and gland size between the three groups were analyzed using one-way ANOVA. A two sided p-value of less than or equal to 0.05 was considered to be significant.

## Results

The three groups did not differ significantly in age (P=0.614, Confidence interval (CI) 95%), gland size (P=0.862) and PSA levels (P=0.880). There was significant reduction in the 4 hour mean pain scores in suppository (P=0.001) and patch (P=0.0159) groups as compared to placebo. But there was no significant difference in 4 hour mean pain scores when comparisons were made between suppository and patch groups. There was no significant difference in the mean pain scores during needle penetration in suppository (P=0.229) and patch (P=0.277) in comparison with placebo. (Table 1) Similarly, we could not demonstrate any statistical significance in the mean pain scores during probe insertion between the suppository (P=0.626), patch (P=0.588) and placebo groups. Three patients in each of the groups had postoperative urinary tract infection; no other significant complications were noted.

## Discussion

Pain associated with prostate biopsy is attributable to insertion of the ultrasound probe and needle puncture

into the prostate. The nerve supply of the prostate is autonomic and originates from the inferior hypogastric plexus adjacent to the seminal vesicles. The nerves pass along the plane between the rectum and prostatic capsule. The pain associated with prostate biopsy is thought to be contributed by direct contact of the biopsy needle with these nerves within the stroma and the prostatic capsule, which are richly innervated (10). Pain following the procedure may be associated with the production of potent local mediators, such as cytokines, prostaglandins and leukotrienes, leading to local pain, edema and the recruitment of immune competent cells (11). Diclofenac acts locally and systemically as an anti-inflammatory and it decreases the effects of local mediators involved in the pain response. In our study using diclofenac patch and suppository we could not demonstrate any superior analgesia in comparison with placebo while insertion of probe and penetration of needle. There was also no increased incidence of complications in the treatment group compared to those previously published in literature (12).

Contrary to the results obtained by our study, Haq et al found that the administration of diclofenac suppositories 1 hour prior to biopsy decreased the discomfort associated with the procedure, improving patient tolerance without a significant increase in morbidity (8). Ragavan et al found that combination of diclofenac suppository and lidocaine perineural blockade provides good additional pain relief during and after biopsy without any increased risk

of complications (9). The same authors found that administration of diclofenac suppository alone reduced the evening pain score but had less effect on pain during needle passage. While administration of perineural blockade (PNB) alone decreased the pain during needle passage, it had minimum impact on evening pain score. Moinzadeh et al studied the use of Rofecoxib, a selective cyclooxygenase-2 inhibitor, given orally 1 to 2 hours before the procedure as a form of pre-biopsy medication (12). They found the same overall mean pain level between the placebo and Rofecoxib groups, and concluded that it had no role in this setting.

Of the various methods of analgesia, PNB has gained much popularity. Nash et al initially suggested bilateral injections at the junction of the base of the prostate and seminal vesicles (13). Their positive findings were subsequently confirmed by various studies as highly effective (14-16). On the contrary, Wu et al in his study reported that PNB was not efficacious (17). Concerns about the potential of increased infection, fibrosis, and intravascular injection have been raised by some authors (18). In addition, patients who undergo transurethral prostate resection may have distorted anatomy, which could decrease the effectiveness of local anesthetic administration. The seminal vesicle biopsies remain painful despite adequate prostatic anesthesia (18).

Lidocaine gel over the years has been used for many outpatient urological procedures, such as cystoscopy. Therefore, it was considered to be a form of local anesthesia during TRUS due to its easy mode of application. Desgrandchamps et al did not observe evidence of any superiority of this gel because of similar pain score data in the placebo group (19). On the other hand, Isaac et al recommended the administration of 2% lidocaine gel led to a significant difference in the median pain score compared with the placebo jelly (20). Therefore, although this is the simplest and least

invasive method of local anaesthesia for prostate biopsy, however, its efficacy for pain control remains controversial.

## Conclusions

Diclofenac sodium as a suppository or a patch when administered alone does not render a significant analgesic effect during the biopsy. We do not recommend its use as a single agent analgesic for prostate biopsy. Diclofenac sodium should be used as an adjunct analgesic for reducing post procedural pain. At present there is strong evidence in the current literature that anesthesia and/or analgesia improves patient tolerance and comfort. Therefore, it would be prudent to include analgesia in prostate biopsy protocol.

## Conflict of Interest

None declared.

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