

# The efficiency of a sedative or analgesic supplement to periprostatic nerve blockage for pain control during transrectal ultrasound-guided prostate biopsy – a prospective, randomized, controlled, double blind study

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## Abstract

**Introduction:** The aim was to examine the effect of a sedative or analgesic supplement to periprostatic nerve blockage (PNB) on pain reduction during probe insertion and needle penetration in patients undergoing transrectal ultrasound (TRUS)-guided prostate biopsy. We also investigated the effects of this procedure on the positive response rate in re-biopsy.

**Material and methods:** One hundred TRUS-guided prostate biopsy patients due to prostate-specific antigen (PSA) levels higher than 2.5 ng/ml and/or abnormal rectal examination findings were evaluated. Group 1 (PNB) was given periprostatic lidocaine injection before the procedure. Group 2 (analgesic) was given tramadol and PNB. Group 3 (sedative) was given midazolam and PNB. Group 4 (control) was not given any anaesthesia or analgesics. Pain scores were assessed during probe insertion and needle penetration by a visual analogue scale.

**Results:** During probe insertion, the mean pain score of the sedative group was lower than that of the control, analgesic and PNB groups ( $p < 0.001$ ,  $p = 0.009$ , and  $p < 0.001$ , respectively). During needle penetration, the mean pain score of the control group was higher than that of the other groups ( $p < 0.001$ ). The rate of positive response to re-biopsy was found to be 56% in the control group and between 92% and 100% in the other three groups ( $p < 0.001$ ).

**Conclusion:** According to our results, it can be concluded that midazolam, given supplementary to PNB, contributes as an effective and safe alternative for pain control during both probe insertion and penetration of the biopsy needle into the prostate capsule; however, tramadol supplement does not provide any additional contributions.

**Key words:** analgesia, anaesthesia, biopsy, prostate.

## Introduction

Transrectal ultrasound-guided biopsy (TRUS-Bx) has become a standard method for early diagnosis of prostate cancer [1]. Previously, the process was supposed to be painless or cause a feeling of slight discomfort; thus, it was performed without any analgesia or anaesthesia [1-3]. In subsequent studies 65% or 90% of men were reported to have pain increasing from mild discomfort to severe pain [4]. Furthermore, approximately 20% of patients reported that they would not consent to undergo a re-biopsy

without any analgesia or anaesthesia [4-6]. Additionally, urologists have reported frequent anxiety in anticipation of prostate biopsy. Patients with maximum anxiety have been found to be vulnerable to high levels of pain [7]. Although numerous studies have revealed the efficacy of periprostatic nerve blockade (PNB) for prostate biopsy in achieving pain reduction, there have been only a limited number of effect and control-related studies on anal discomfort due to probe insertion [8-10].

Consequently, we performed a randomized, prospective, controlled, double blind study to investigate whether a sedative or an analgesic supplement to PNB would reduce the sensation of discomfort associated with probe insertion, whether prostate needle penetration-associated pain would be controlled more effectively, and how the patients requiring a re-biopsy would be affected.

### Material and methods

Our study population comprised 100 patients who were admitted to our clinic between February 2008 and June 2009. Patients with prostate-specific antigen (PSA) above the level of 2.5 ng/ml and/or with abnormal digital rectal examination (DRE) findings were included in the study. Patients who underwent a previous TRUS-Bx; had active rectal problems such as haemorrhoids, anal fissure or stricture; had neurological pathologies; were allergic to one of the drugs used in the study; had hemorrhagic diathesis; or had a disease requiring the treatment of chronic pain were excluded from the study. Patients in the study group were assessed by a consultant anaesthetist for suitability for sedation and were divided into 4 groups using computer-generated random numbers. All patients and the physician performing the final evaluation were unaware of which method of pain management procedure was used. Local ethical committee permission and written patient information and consent forms were collected before the initiation of the study.

Group 1 (PNB group,  $n = 25$ ) patients received periprostatic injection of 10 ml lidocaine 10 min before the procedure; Group 2 (analgesic group,  $n = 25$ ) patients received per os tramadol hydrochloride in a dose of 50 mg 45 min and periprostatic injection of 10 ml lidocaine 10 min before the procedure; Group 3 (sedative group,  $n = 25$ ) patients received intramuscular injection of 0.05 mg/kg midazolam 30 min and periprostatic injection of 10 ml lidocaine 10 min before the procedure; Group 4 (control group,  $n = 25$ ) was composed of patients receiving periprostatic administration of 10 ml 0.9% serum physiologic. Lubricant was used in the process of probe insertion in all patients.

The medication was stopped for patients using anticoagulants or aspirin a week before the process. 500 mg of oral ciprofloxacin as a prophylaxis was initiated a night before and on the morning of the biopsy and continued for 3 days. Patients were assigned to receive fleet enema for bowel preparation on the morning of the process. All patients had DRE before the biopsy. First they were placed in a left lateral decubitus position, then prostate glands were examined in sagittal and transverse planes using a biplanar 7.5 MHz transrectal ultrasonography probe (Aloka Co, Tokyo, Japan). In the meantime morphological assessment of the prostate was performed and the volume of the prostate was determined automatically with ultrasonography equipment. PNB was achieved by the bilateral injection of 10 ml of 2% lidocaine via a 22-gauge 20 cm Chiba needle at the apex and the junction between the prostate and seminal vesicles. The injection site was confirmed by TRUS monitoring when the prostate and seminal vesicles were monitored diverging from the rectal wall. For biopsy an 18-gauge 25 cm Tru-cut biopsy needle was used (Marflow AG, 8134 Adliswil, and Zurich, Switzerland). A total of 10-core biopsies were taken: 3 cores from each peripheral zone and 2 from each far lateral zone. Moreover, additional biopsy cores were taken from sonographically hypoechoic or suspected sites in the DRE.

After the process, the patients were given a questionnaire to rate their pain between scores 0 and 10 using a visual analogue scale (VAS). They were asked to assess the level of pain during probe insertion and needle passage into the prostate gland. Furthermore, all patients were asked whether they would accept a second biopsy if necessary. Ten days later patients were asked to fill in a form about side effects such as haematuria, rectal bleeding, vasovagal reaction, urinary infection and retention.

Statistical data analysis was performed using SPSS 11.5 for Windows Statistical Software Package. Continuous variables were analysed for almost normal distribution using the Shapiro-Wilk test. Statistical results were presented as follows: mean  $\pm$  standard deviation for age; PSA, prostate volume, PSA density, number of biopsies and VAS levels as median (minimum-maximum). Nominal variables were presented as the number of subjects and percentages (%). The importance of age-related differences between groups was assessed using one-way analysis of variance. The presence of statistical differences with respect to PSA, prostate volume, PSA density, number of biopsies and VAS levels between groups was analysed using the Kruskal-Wallis test. Nominal variables were assessed via Pearson's chi-square or Fisher's exact

probability test. The results were considered significant for  $p < 0.05$ .

## Results

No statistically significant difference was found with respect to mean age between groups, PSA level, prostate volume, PSA density, abnormal DRE findings and mean number of biopsy cores taken (Table I).

There was a significant difference between the groups regarding pain during probe insertion ( $p = 0.016$ ,  $\chi^2 = 10.280$ ). Group 3 had significantly lower mean pain scores than Groups 1, 2 and 4 (Table II). Conversely, Group 1 and Group 2 were not statistically different from the control group (Group 4) regarding pain during probe insertion (Group 1 ~ Group 4,  $p = 0.476$  and Group 2 ~ Group 4,  $p = 0.846$ ).

There was a significant difference between groups regarding pain while inserting the needle into the prostate gland ( $p < 0.001$ ,  $\chi^2 = 34.139$ ). In this respect, mean pain score for Group 4 was significantly higher than for Groups 1, 2 and 3 (Table III). Statistically, Groups 1, 2 and 3 had lower pain levels than Group 4 ( $p < 0.001$ ). Furthermore, Group 3 had a lower pain level than Group 1 ( $p = 0.039$ ). On the other hand, there was no difference between Groups 3 and 2 ( $p = 0.125$ ) and Groups 2 and 1 ( $p = 0.568$ ) with respect to pain during the needle passage into the prostate gland.

When assessed with respect to the rate of positive replies to the question "Would you agree to another prostate biopsy if it was considered necessary?", the rate of positive answers was higher among patients in Groups 1, 2 and 3 than that of the control group (Table IV). No significant difference was found between Group 1 and Groups 2-3 ( $p = 1.00$  and  $p = 1.00$ , respectively) and between Group 2 and Group 3 ( $p = 0.490$ ).

When biopsy-related side effects were compared in our study, the groups were found to be similar (Table V). Conversely, light sedation observed in the sedative group required hospital stay for no patients. No drug-related cardiac or respiratory side effects were observed among patients.

## Discussion

In the present study we found that midazolam supplement to PNB during TRUS-Bx reduced anal discomfort in the course of probe insertion more than application of only PNB or tramadol supplement to PNB. Moreover, we found that sensation of pain was apparently lessening during needle passage into the prostate gland via PNB. Additional medication of midazolam had significant contributions in contrast to ineffective tramadol addition.

Two major factors are responsible for pain during prostate biopsy: anal discomfort due to the ultrasound probe and the development of pain due to the needle penetrating the prostatic capsule and originating from the autonomic nerve fibres innervating the prostatic capsule or the stroma [7, 11, 12]. Also, there may be a relationship between pain and strong mediators such as cytokines, prostaglandins and leukotrienes after TRUS-Bx [12]. Numerous authors have believed that transrectal probe insertion is an important component of pain during prostate biopsy and nerve blockade will not reduce pain [13, 14]. To prevent pain during insertion of the ultrasound probe, the use of topical local anaesthetics, non-steroid anti-inflammatory or centrally acting analgesics and sedative anaesthetics was investigated before the process [8, 15, 16]. In a recent study by Raber *et al.* administration of lidocaine and prilocaine gel was reported to decrease pain and anal discomfort during probe insertion [17]. However, the effect of this procedure in reduction of pain development during needle insertion has been controversial [17-19]. Pain during probe insertion has not been investigated in studies performed with midazolam [20, 21]. When assessed regarding pain sensation during probe insertion, the sedative group achieved statistically more effective pain control during probe insertion in our study. We consider that the sedative, anxiolytic and myorelaxing properties of midazolam have been effectual. Contrary to our expectations, we were unable to observe a statistical difference, although pain sensation during probe insertion in the analgesic group was lower than the mean pain scores of the PNB and

**Table I.** Patients' demographic and clinical characteristics

Parameter	Group 1 (n = 25)	Group 2 (n = 25)	Group 3 (n = 25)	Group 4 (n = 25)	p
Age [years]	65.0 ±7.6	66.6 ±8.1	64.6 ±7.9	66.1 ±5.7	0.762
PSA [ng/ml]	9.9 (3.4-41.3)	8.5 (2.5-150.0)	9.3 (3.7-63.0)	9.4 (3.5-84.0)	0.608
Prostate volume [ml]	42.7 (20-100)	40.0 (20-72)	38.6 (20-86.8)	50.0 (18.3-120)	0.179
PSA density	0.24 (0.01-1.76)	0.22 (0.06-3.07)	0.23 (0.11-1.91)	0.17 (0.07-1.76)	0.699
Abnormal DRE	4 (16.0%)	3 (12.0%)	4 (16.0%)	3 (12.0%)	0.954
Biopsy cores (n)	11 (9-12)	11 (10-12)	12 (9-12)	10 (9-12)	0.122

**Table II.** Pain during probe insertion, comparison with group 3

Group	Median Pain Score	p
1 (n = 25)	4 (2-7)	< 0.001
2 (n = 25)	3 (0-8)	0.009
3 (n = 25)	2 (0-5)	
4 (n = 25)	4 (2-6)	< 0.001

**Table III.** Pain during needle passage into the prostate gland

Group	Median Pain Score	p
1 (n = 25)	2 (0-6)	< 0.001
2 (n = 25)	1 (0-6)	< 0.001
3 (n = 25)	1 (0-5)	< 0.001
4 (n = 25)	6 (3-8)	

**Table IV.** Acceptance of a re-biopsy. Comparison between control and other groups

Group	Yes, N (%)	No, N (%)	p
1 (n = 25)	24 (96)	1 (4)	< 0.001
2 (n = 25)	23 (92)	2 (8)	0.004
3 (n = 25)	25 (100)	0 (0)	< 0.001
4 (n = 25)	14 (56)	11 (44)	
Total	87 (87)	14 (14)	

control groups. We believe that the prevalent anxiety observed in patients during surgical intervention has contributed to levels of pain or discomfort emerging in the sphincter region during probe insertion and tramadol is not sufficiently active since it does not exhibit an anxiolytic effect.

Various methods and drugs have been used for pain control during needle passage into the prostate gland [7, 8, 15, 16, 22]. The effectiveness of transrectal periprostatic lidocaine injection has been reported in various studies [8, 22]. The PNB group provided statistically better pain control than the control group during needle passage through the prostate gland in our study. Nash *et al.* formerly described PNB as an effective and reliable method [20]. Our results have confirmed the description of

Nash *et al.* We also observed in our study that the combination of midazolam + PNB statistically reduced pain during needle passage into the prostate compared to the control and PNB groups. These results are parallel to the results obtained by Peters *et al.* and Turgut *et al.*, who used midazolam in their studies [20, 21]. On the other hand, our results revealed that PNB + tramadol administration lessened pain statistically significantly more than the control group during needle passage into the prostate gland; however, the difference with respect to mean pain score was not statistically significant in general, although the mean pain score was observed to be lower in comparison with the PNB group. According to us, this insignificant result was not possibly due to an insufficient analgesic effect of tramadol, but because of a very effective local anaesthetic effect of PNB. The reports have been conflicting on tramadol use for controlling the pain emerging during needle passage into the prostate gland. Bozlu *et al.* reported that tramadol application had no analgesic benefit during biopsy. Hirsh *et al.* found that tramadol provided effective and reliable analgesia in their study where they compared rectal administration of lidocaine ointment before the process with the combination of lidocaine ointment and per oral tramadol [19, 23]. Consequently, we also believe that lidocaine gel and ointment + tramadol combination can be more effective with respect to avoidance of the invasive effect of injection during PNB.

In a study, patients requiring re-biopsy were reported to be reluctant to undergo a second intervention due to disagreeable memories of the first trial [24]. The proportion of patients accepting re-biopsy suggestions was observed to be significantly higher than the control group in all groups. Pain during probe insertion in PNB was not statistically different from that of the control group. However, a lot of patients in the PNB group responded positively for re-biopsy, suggesting that the main pain deterrent was the pain during needle penetration. We observed that the sedative group accepted re-biopsy statistically more than the control group. We consider that midazolam + PNB

**Table V.** Comparison of biopsy-related complications between groups

Group	Haematuria n/%	Rectal bleeding n/%	Urinary retention n/%	Urinary infection n/%	Vasovagal reaction n/%
1 (n = 25)	8/32%	6/24%	1/4%	3/12%	1/4%
2 (n = 25)	10/40%	5/20%	3/12%	5/20%	3/12%
3 (n = 25)	9/36%	7/28%	2/8%	4/16%	2/8%
4 (n = 25)	6/24%	6/24%	1/4%	5/20%	1/4%
Total	33	24	7	19	7

provided very active pain control as well as the anterograde amnesic effect of midazolam, providing a positive contribution.

The morbidity and complications of TRUS-Bx are well known [5, 25]. Sepsis is the most serious potential complication and the application of prophylactic antibiotic treatment reduces the risk successfully [26]. More common but minor complications are also well documented and the patient can be informed about the possible complications. Haematuria has taken the first rank among the most frequently observed side effects, with a rate of 33% in our study. This complication has been reported at between 12.5% and 58.4% in various studies [5, 27-29]. In addition, we did not observe any cardiological or respiratory side effects during the administration of local anaesthetics and sedation. We consider that midazolam administered premedication dose and local anaesthetics are within the confidence interval. The follow-up of vital findings should be routinely performed by a physician in the group [20, 21]. Other limitations of midazolam use were restriction of motor activities of patients, such as driving, and the necessity of a companion [20, 21].

In conclusion, according to our data we can state that PNB is an effective and reliable method in controlling pain during passage of the biopsy needle into the prostate capsule. Supplementary midazolam provides an additional contribution as an effective, safe and reliable alternative means of pain control during both probe insertion and penetration of the biopsy needle into the prostate capsule. However, we found that unlike midazolam, supplementary tramadol does not provide an extra contribution. On the other hand, discomfort experienced during probe insertion is an important problem caused by the biopsy procedure. Nevertheless, we can assert that pain during penetration of the biopsy needle into the prostate capsule is the actual deterrent factor when re-biopsy is necessary.

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