ORIGINAL ARTICLE

Factors associated with pain sensation in patients with ultrasound-guided prostate biopsy

Factores asociados a la sensación de dolor en pacientes con biopsia de próstata guiada por ecografía

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Abstract

Introduction:

TRUS-guided prostate biopsy is a current method used to obtain the histopathological material necessary to make a definitive diagnosis of prostate cancer.

Objective:

To investigate patient-related variables affecting the level of pain felt during prostate biopsy to determine what can be done to minimize pain.

Methods:

The study included 241 patients scheduled for prostate biopsy. Four patients who did not meet the criteria were excluded. Local anesthesia was administered intrarectally 10 minutes before the biopsy to 237 patients, and a conventional 12-core biopsy was performed. The level of pain felt by all patients during the biopsy was measured using the Visual Analog Scale (VAS) score. Pain scores were compared by forming groups according to the selected parameters

Results:

The study included 241 patients scheduled for prostate biopsy. Four patients who did not meet the criteria were excluded. Local anesthesia was administered intrarectally 10 minutes before the biopsy to 237 patients, and a conventional 12-core biopsy was performed. The level of pain felt by all patients during the biopsy was measured using the Visual Analog Scale (VAS) score. Pain scores were compared by forming groups according to the selected parameters.

Conclusions:

Some patient parameters may affect the level of pain felt during TRUS-guided prostate biopsy.

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Pain level; prostate biopsy; positive tumor pathology; alpha-blocker; 5-alpha reductase inhibitor; perineural invasion.

Palabras clave:

Nivel de dolor; biopsia de próstata; patología tumoral positiva; alfa-bloqueante; inhibidor de la 5-alfa reductasa; invasión peri neural.

Conflict of interest:
The authors report no conflict of interest

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Resumen

Introducción:

La biopsia de próstata guiada por ecografía transrectal (TRUS) es un método utilizado para obtener el material histopatológico necesario para realizar un diagnóstico definitivo de cáncer de próstata.

Objetivo:

Investigar las variables relacionadas con el paciente que afectan al nivel de dolor sentido durante la biopsia de próstata para para tratar de minimizar el dolor durante el procedimiento.

Métodos:

El estudio incluyó a 241 pacientes programados para biopsia de próstata. Se excluyeron cuatro pacientes que no cumplieron los criterios. Se administró anestesia local por vía intrarrectal 10 minutos antes de la biopsia a 237 pacientes y se realizó una biopsia convencional de 12 núcleos. El nivel de dolor sentido por todos los pacientes durante la biopsia se midió mediante la puntuación de la Escala Visual Analógica (EVA). Se compararon las puntuaciones de dolor formando grupos según los parámetros seleccionados

Resultados:

De los casos presentados, el 80% fueron varones, con edad de presentación a los 65 años y tiempo de duración desde el diagnostico hasta el deceso de 6.5 meses. Los signos clínicos relevantes fueron la demencia rápidamente progresiva y las mioclonias. Se realizo exámenes de laboratorio, imágenes (Resonancia Cerebral) y dosaje de proteína 14.3.3 para apoyo a la sospecha clínica.

Conclusiones:

Algunos parámetros del paciente pueden afectar al nivel de dolor sentido durante la biopsia de próstata guiada por TRUS

Remark

1) Why was this study conducted?

To find ways to make the patient feel less pain by investigating the factors affecting the level of pain felt during TRUS-guided prostate biopsy, which is uncomfortable but necessary for the patient.

2) What were the most relevant results of the study?

Patients who use 5 Alpha reductase inhibitors for at least three months before biopsy feel less pain during trus guide biopsy. Our study is the first to find such a result in the literature. Patients with suspicion of the tumor during DRE have more pain during the biopsy.

3) What do these results contribute?

Starting a 5-alpha reductase inhibitor in patients planning to undergo a trus guide biopsy may help them feel less pain. İf a tumor is detected during DRE, it may be beneficial to use more effective anesthesia methods when performing a trus guıde biopsy.

Introduction

Prostate cancer is one of the most common malignancies in men. According to the 2020 cancer data from the USA, it ranks first among newly diagnosed cancers and second in terms of cancer-related deaths among men [1]. The use of tumor markers has led to an increase in the pre-diagnosis of prostate cancer. It is estimated that around a million prostate biopsies are performed in the USA every year [2]. The prostate gland is an organ accessible via the transrectal route. Clinical suspicion, elevated serum Prostate-specific antigen (PSA) levels (>4 ng/dL), and abnormal findings in digital rectal examination (nodule, hardness) are indications that lead to prostate biopsies [3]. Prostate biopsy is a necessity for the definitive diagnosis of prostate cancer. Unfortunately, a prostate biopsy is a painful and discomforting procedure. Although targeted biopsy methods are taking the place of 10-12 quadrant prostate biopsies performed under Transrectal Ultrasound (TRUS) guidance, the validity of this method remains [4]. Unwanted effects in prostate biopsies performed under TRUS guidance include pain and discomfort felt by the patient. The intense innervation of the autonomous fibers in the prostate capsule and stroma is the fundamental reason for the pain felt during the biopsy. To make this procedure acceptable, selecting the appropriate anesthesia method by predicting the potential pain level becomes crucial. Many studies have examined which method is more effective. Nowadays, sedation, periprostatic nerve blockage, and intrarectal lidocaine gel application reduce the negative sensations experienced during the biopsy and make the procedure more acceptable [5-9]. Studies have shown that the more effective method for pain control is periprostatic nerve blockage, and it is superior to intrarectal lidocaine jelly application alone [9-11]. Even if the same anesthesia method is used, the level of pain experienced by patients and their tolerance to pain vary.

Some patients can tolerate this procedure comfortably, even without any anesthesia, while others experience significant pain and require intensive analgesic support. Therefore, it is thought that patient-specific variables can influence the perceived pain level. Bruyère et al.[11], in a study involving 70 patients, also compared lithotomy and lateral decubitus positions and found that patients reported less pain in the lithotomy position. In studies conducted in this field, various parameters such as age, prostate volume, anxiety, body mass index, number of cores taken, anorectal compliance, and even patient position have been investigated about VAS scores [12-16].

This study aims to identify the factors related to the patient that affect the level of pain felt during prostate biopsies performed under TRUS guidance. Predicting the pain level felt during biopsy under TRUS guidance would be beneficial in facilitating the decision-making process regarding the choice of anesthesia method. In our study, we also investigated the relationship between pain level during biopsy and the presence of suspicious findings in digital rectal examination (DRE), the diagnosis of cancer and perineural invasion in pathology results, and the use of agents in benign prostatic hyperplasia (BPH).

Materials and Methods

Study population

The study was initiated after the ethics committee approved the study protocol (Approval no: 2018/2174). The Helsinki Declaration conducted our study. All enrolled patients were informed about the study and provided written consent. Between September 2018 and April 2023, a total of 239 primary patients aged 48 to 86 with suspected findings in digital rectal examination (DRE) and a decision to perform a prostate biopsy under transrectal ultrasound (TRUS) guidance due to elevated PSA levels were included in the study. Two patients were excluded from the study at baseline, one because of hemorrhoids and the other because of a previous prostate biopsy. Of the remaining 239 patients, 2 had communication problems during pain measurement. Therefore, it was decided to exclude the data of these two patients, and the study was completed with 237 patients. Patients with anal region diseases such as anal fissures, hemorrhoids, and prostatodynia were not included due to the possibility of additional

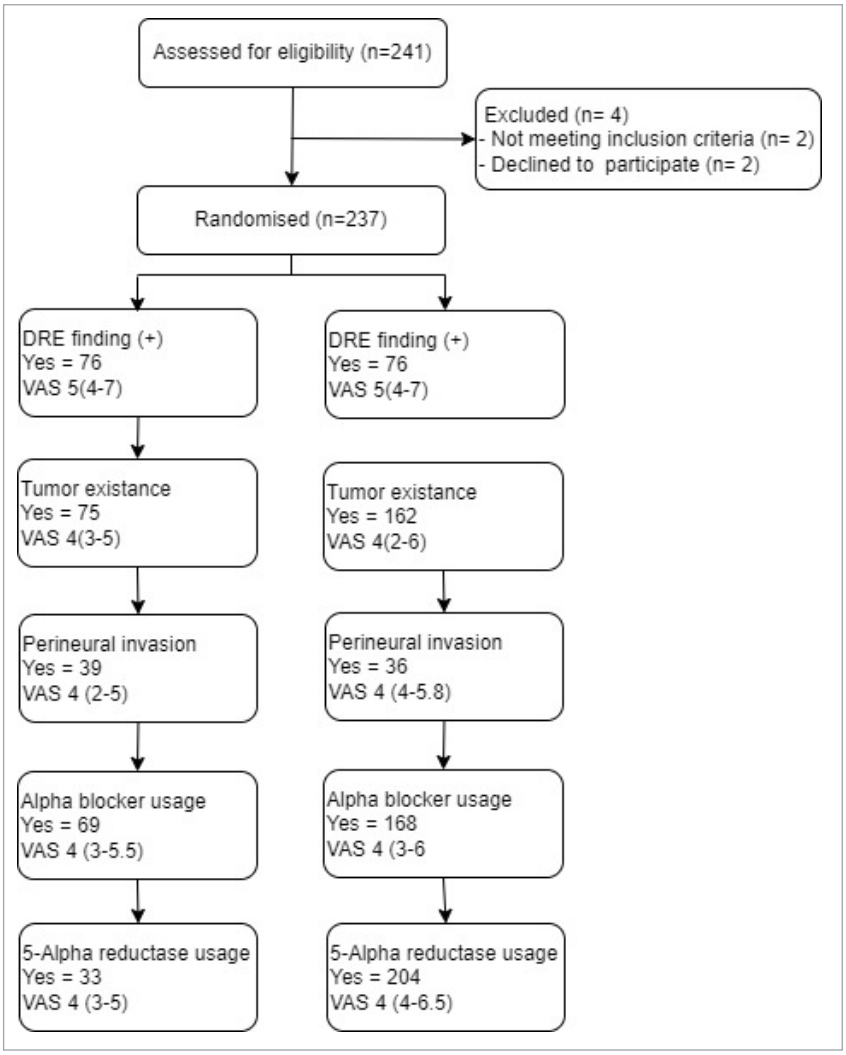

Figure 1. Recruitment of patients included in the study. Consort Flow Chart

pain and incorrect pain measurement. Patients' age, body mass index (BMI), prostate volume, serum PSA levels, findings in digital rectal examination (DRE), pathological examination of biopsy samples for prostate cancer and perineural invasion, and the prior use of alpha-blockers and 5-alpha reductase inhibitors (dutasteride) were recorded for analysis.

Before the TRUS-guided prostate biopsy procedure, all patients underwent urine culture, hemogram, and coagulation tests, and their medication use was recorded. One day before the biopsy, prophylactic antibiotic treatment with 500 mg ciprofloxacin 2x1 was initiated for all patients. Bowel preparation was performed for all patients the evening before the biopsy procedure. Prostate volumes were measured transversally to ensure the unaffected measurement of pain scores.

Study design

Our study is designed to be prospective. The G-Power 3.1 program was used to determine the study's sample size. According to the group averages in the reference studies, when the effect size is 0.37, the α-error rate is 5%, and the power of the study is 80%, a total of 235 patients were planned to be included (Extra patients were included because there might be a few patients who might be excluded from the study) (Figure 1).

Anesthesia and biopsy technique

Ten minutes before the biopsy, 10 mL of 2% lidocaine gel (Cathejell: 2% Lidocaine Hydrochloride, 5% Chlorhexidine Dichloride) was applied transrectally. The biopsy procedure was performed by a doctor from our clinic using a Mindray Digital Ultrasonic Diagnostic Imaging System device and a 6.5 MHz rectal probe with an automatic gun loaded with an 18-gauge biopsy needle in the lateral decubitus position. Conventional 12-core biopsies were obtained from all patients. No complications requiring hospitalization occurred in any patient. A nurse measured pain immediately after the procedure using a verbal numerical rating scale (VAS) ranging from 0 to 10. The presence and absence of the examined parameters were compared by analyzing VAS scores for intergroup differences.

Statistical analysis

Descriptive statistics for evaluation results were provided: number and percentage for categorical variables and mean, standard deviation, minimum, maximum, and median for numerical variables. The Mann-Whitney U test was used to compare VAS scores based on the presence or absence of various parameters. The statistical alpha significance level was accepted as $p < 0.05$. Statistical analysis was performed using SPSS 23.0 software for Windows (IBM, Armonk, NY).

Results

The average age of the participating patients was 66 ± 7.8 years, BMI was 26.9 ± 4.0 kg/m², PSA was 33.7 ± 197.5 ng/dL, and prostate volume was 54.8 ± 39.3 mL. The prostate cancer detection rate was 31.6% (Table 1). The average VAS score for patients was 4.3 ± 1.9. Of the patients, 51% used alpha-blockers or 5-alpha reductase inhibitors (5-ARIs). The usage rates were 29.1% for alpha-blockers alone, 13.9% for 5-ARIs alone, and 8% for the combined use of these two drugs (Table 1). Patients were grouped based on the presence of pathological findings in DRE, the diagnosis of prostate cancer in pathology results, and the presence of perineural invasion, and their VAS scores were compared. The median VAS score was 5 (4-7) for those with DRE findings and 4 (2-5) for those without DRE findings. The mean VAS score in the patient group with suspected tumor during DRE was higher than in the group without suspected tumor on examination. The difference between the two groups was statistically significant. ($p < 0.001$). Pain was significantly higher in patients with DRE findings ($p < 0.001$). For patients diagnosed with prostate cancer and those with benign results in the biopsy, their VAS scores were 4 (3-5) and 4 (2-6), respectively. Although the mean VAS scores differed between the groups of patients with tumor presence due to the microscopic examination of the biopsy material and those with benign pathology reports, the difference was not statistically significant ($p= 0.937$).

Similarly, VAS scores were calculated as 4 (2-5) and 4 (4-5.8) for patients with and without perineural invasion, respectively. When patient groups with perineural invasion were compared with patient groups without perineural invasion in patients diagnosed with prostate cancer, the difference was not statistically significant ($p=0.160$). No intergroup differences were

Table 1. Evaluation of demographic and clinical variables of the patients (n= 237).

Variables	n (%)	Mean (SD)
Age (Years)		66.0 (7.8)
BMI (kg/m2)		26.9 (4.0)
Serum PSA level (ng/dL)		33.7 (197.5)
Prostate volume (cc)		54.8 (39.3)
Positive DRE finding	76 (32.1)	
Tumor existance	75 (31.6)	
Positive perineural invasion in patients with Pca	39 (52.0)	
Alpha blocker usage	69 (29.1)	
5-alpha reductase usage	33 (13.9)	
Combined treatment usage	19 (8.0)	

BMI: Body mass index, PSA: Prostate-specific antigen, DRE: Digital rectal examination, Pca: Prostate cancer

Table 2. Comparing the VAS score in the different variable groups

Variables	*VAS Score, median (IQR)	P value
DRE finding		
Yes	5 (4-7)	<0.001
No	4 (2-5)	
Tumor existance		
Yes	4 (3-5)	0.937
No	4 (2-6)	
Perineural invasion		
Yes	4 (2-5)	
No	4 (4-5.8)	0.160
Alpha blocker usage		
Yes	4 (3-5.5)	0.926
No	4 (3-6)	
5-alpha reductase usage		
Yes	4 (3-5)	0.034
No	4 (4-6.5)	
Combined treatment usage		
Yes	4 (4-7)	0.304
No	4 (3-6)	

VAS: Visual Analogue Scale, DRE: Digital Rectal Examination.

observed in comparisons based on pathological parameters (Table 2). The VAS scores were calculated as 4 (3-5.5) for patients using alpha-blockers and 4 (3-6) for those not using alpha-blockers, with no significant difference in perceived pain (p= 0.937). The difference between the pain levels felt during a biopsy in the patient groups consisting of patients who used alpha blockers due to BPH and patients who did not use alpha blockers was not statistically significant (p = 0.926). The VAS scores for patients using and not using 5-ARIs were 4 (3-5) and 4 (4-6.5), respectively. When the VAS scores felt during prostate biopsy were compared between patients using 5-ARI and those not using 5-ARI, the difference was statistically significant (p = 0.034). Patients undergoing biopsy and using 5-ARIs had significantly lower perceived pain. The VAS scores for patients using and not using combined treatment were 4 (4-7) and 4 (3-6), respectively. When the VAS scores felt during prostate biopsy were compared between patients who received combined treatment (5-ARI + alpha-blockers) and those who did not, the difference was not statistically significant (p = 0.304). (Table 2).

Discussion

Studies show that patient-related factors can affect the perceived level of pain [12-16]. To make a painful procedure such as a prostate biopsy as bearable as possible, it may be important to know the characteristics of the patient. In our study, we investigated the relationship between the level of pain felt during biopsy and the presence of suspicious findings for tumors on digital rectal examination (DRE), the presence of tumors in the pathology report, the presence or absence of perineural invasion in patients with tumor in pathology, and whether the patient was taking medications for benign prostatic hyperplasia (BPH).

In a study by Yun et al.[12], involving 71 patients, two groups were created with small and large prostates, similar in age and PSA levels. When they compared the VAS scores measured during and 20 minutes after the procedure, they concluded that larger prostates caused more pain. In a study by Sönmez et al.[13], involving 319 patients, they compared VAS scores between groups with prostate volumes above and below 50cc and found a positive correlation between prostate volume and perceived pain level. Similarly, in a study by Gomez et al.[14], involving 1,188 patients, it was reported that patients with prostate volumes more significant than 40 mL felt more pain than those with volumes smaller than 40 mL. In addition, Gomez et al.[14], reported in this study that there was no relationship between the detection of prostate cancer during biopsy and perceived pain. This finding is consistent with our results. Luan et al. [15], conducted a study with 568 patients and found no differences in age and PSA levels between groups. Still, they noted significantly lower pain and higher satisfaction levels in patients with smaller

prostate volumes compared to those with larger volumes. In contrast, a study by Avcı et al.[16], involving 123 patients reported that prostate volume did not affect perceived pain level. In this study, it was reported that there was no significant difference between the two groups when the pain scores of patients with positive DRE findings during biopsy were compared with the pain scores of patients without DRE findings. This result is opposite to our study. As far as we know, no study predicts that findings such as nodules during DRE would cause higher pain levels during the biopsy procedure. In our study, patients with pathological findings in DRE felt significantly more pain, possibly due to the local inflammatory effect of tumor tissue or prostatic nodules, which are palpable and have relatively high volume.

On the other hand, Ozah et al.[17], created two groups by administering anesthesia with 1% xylocaine apical infiltration before TRUS and intrarectal 2% xylocaine gel. In the group where apical infiltration was performed, the pain level in patients with prostates smaller than 50 mL was higher than that of patients with 50 mL or larger prostates. In the group that received intrarectal xylocaine, no difference was found between the two groups.

Factors affecting pain level during biopsy were investigated by Bolat et al. [18], in a study with 198 patients, where it was found that patients with lower body mass index (BMI) experienced more pain. Saraçoğlu et al,[19], showed that the patient's anxiety level was associated with pain during the biopsy. To reduce anxiety and, thereby, perceived pain, Chang et al.[20], had patients listen to music during the biopsy, reporting reduced pain and discomfort. However, due to the lack of standardization in music interventions, a meta-analysis by He et al. [,21], concluded that while music appeared to be effective in reducing anxiety and pain, definite conclusions couldn't be drawn.

The effect of patient position on pain during biopsy was investigated by Kilciler et al.[22], in a study involving 340 patients comparing lithotomy and lateral decubitus positions, finding that the lithotomy position resulted in higher pain levels. Lodeta et al.[23], similarly examined pain levels in prostate biopsies performed in lithotomy and lateral decubitus positions in a study with 148 patients, dividing them into three groups: lateral decubitus without anesthesia, lithotomy without anesthesia, and lithotomy with intrarectal lidocaine, concluding that patients in the lateral decubitus position experienced less pain.

Digital rectal examination (DRE) is generally a minimally uncomfortable and well-tolerated examination form, and studies have reported that patients experience minimal discomfort during the procedure [24].

Rempega et al.[25], in a study involving 143 patients, demonstrated a correlation between Gleason score and pain perceived during biopsy. Still, the relationship between prostate tumor burden and pain felt during biopsy is not known. Our study investigated the relationship between tumor presence and perineural invasion and VAS score but not the Gleason score. However, as far as we know, the issues we are investigating have not been explored before. Agents used in the medical treatment of benign prostatic hyperplasia (BPH) are widely used in the patient population undergoing prostate biopsy. In our patients, this rate was found to be 51%. Alpha-blockers are commonly used treatments for improving symptoms of prostatitis and prostatodynia,[26]. The effect of alpha-blockers on pain during prostate biopsy is not known. In a study by Şefik et al.[27], patients were started on alpha-blocker therapy one week before the biopsy, and their biopsy pain scores were recorded and compared with the VAS scores of those not receiving alpha-blockers. The average VAS scores for the groups using and not using alpha-blockers were 2.7 ± 2.3 and 4.2 ± 2.2, respectively, and a statistically significant decrease in pain scores was observed (p= 0.001). In our study, we found that the use of alpha-blocker drugs was not associated with pain during prostate biopsy (p= 0.926). The patient group in Şefik et al.'s study started alpha-blocker treatment before biopsy, while our patients consisted of those who had been on treatment for longer.

5-alpha reductase inhibitors (5-ARIs) are also drugs that have been investigated for their effectiveness in chronic pelvic pain syndrome and chronic prostatitis, similar to alpha-blockers,[28]. Despite the lack of effectiveness in chronic pelvic pain and prostatitis, an experimental study showed a decrease in thermal and visceral pain sensitivity. In our research, we found a significant reduction in VAS scores during prostate biopsy in patients using 5-ARIs (p= 0.034). However, we did not observe this difference in patients using alpha-blockers and 5-ARIs (p= 0.304). This might be related to the duration of combined treatment. New studies could explore the relationship between treatment duration and VAS scores during biopsy.

The weaknesses of our study are that pain perception may vary according to the individual, and stress factors may affect the pain level. Every patient referred for a prostate biopsy thinks that he will be diagnosed with prostate cancer, which affects mood, and the level of pain felt. Further research with larger sample sizes is needed in this previously uninvestigated area.

Conclusion

Not all patients experience the same level of discomfort from TRUS-guided prostate biopsy, which is mandatory for the definitive diagnosis of prostate cancer. Patients with positive DRE findings may feel more pain during biopsy, while patients receiving 5-ARI therapy may feel less pain. For TRUS-guided prostate biopsy, some patient data may be helpful in deciding the method of anesthesia to be used.

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