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Area of Expertise: Urology

Title: The effect of age on pain perception among patients undergoing systematic ultrasonography guided transrectal prostate biopsy.

Short title: Transrectal prostate biopsy and pain.

Abstract

Purpose: To investigate the effect of age on the pain levels caused by placing the transrectal probe and biopsy needle into the prostate tissue in transrectal ultrasound-guided prostate biopsy (TRUS-PB).

Materials and methods: The study included 308 patients. These patients into groups based on age: Group 1 had 103 patients aged 65 or younger, Group 2 had 100 patients aged 66-70, and Group 3 had 105 patients over 70. 11 ml 2% lidocaine gel was administered intrarectally to the patients included in the study as anesthesia. Thirty minutes after the biopsy procedure, we measured each patient's pain using the VAS score, which ranged from 0 (no pain) to 10 (worst pain). Patients were asked for pain level during the insertion of the rectal probe and the maneuvers (VAS-p) and the pain level during the insertion of the needle through the prostate to take a biopsy (VAS-b).

Results: VAS-p score was lower in Group.2 than in the other age groups. When the groups were evaluated in terms of VAS-b, no significant difference was observed between the 3 groups. Across all patients, the pain felt during probe insertion was greater than the pain felt during biopsy and this was statistically significant ($p<0.001$). When prostate volume was compared with pain score, each unit increase in prostate volume increased the probability of pain in VAS-p by 1.014 times.

Conclusion: Pain sensation in patients undergoing biopsy is mainly felt during probe insertion and that this pain sensation increases with increasing prostate size.

Keywords: Anesthesia, pain score, prostate biopsy, transrectal ultrasound.

Makale başlığı: Sistematik ultrasonografi eşliğinde transrektal prostat biyopsisi yapılan hastalarda yaşın ağrı algısı üzerine etkisi.

Kısa başlık: Transrektal prostat biyopsisi ve ağrı.

Öz

Amaç: Transrektal ultrason eşliğinde prostat biyopsisinde (TRUS-PB) transrektal prob ve biyopsi iğnesinin prostat dokusuna yerleştirilmesi sonucu oluşan ağrı düzeylerine yaşın etkisini araştırmak.

Gereç ve yöntem: Çalışmaya 308 hasta dahil edildi. Bu hastalar yaşlarına göre gruplara ayrıldı: Grup 1'de 65 yaş ve altı 103 hasta, Grup 2'de 66-70 yaş arası 100 hasta ve Grup 3'te 70 yaş üstü 105 hasta vardı. Çalışmaya dahil edilen hastalara anestezi olarak 11 ml %2'lik lidokain jel intrarektal olarak uygulandı. Biyopsi işleminden 30 dakika sonra her hastanın ağrısını, 0 (ağrı yok) ile 10 (en şiddetli ağrı) arasında değişen VAS skorunu kullanarak ölçtük. Hastalara rektal prob yerleştirilmesi ve manevralar sırasındaki ağrı düzeyi (VAS-p) ve biyopsi almak için iğnenin prostattan içeri sokulması sırasındaki ağrı düzeyi (VAS-b) soruldu.

Bulgular: VAS-p skoru Grup 2'de diğer yaş gruplarına göre daha düşüktü. Gruplar VAS-b açısından değerlendirildiğinde 3 grup arasında anlamlı fark görülmedi. Tüm hastalarda probun yerleştirilmesi sırasında hissedilen ağrı biyopsi sırasında hissedilen ağrıdan daha fazlaydı ve bu istatistiksel olarak anlamlıydı ($p<0,001$). Prostat hacmi ağrı skoru ile karşılaştırıldığında, prostat hacmindeki her birim artış VAS-p'de ağrı olasılığını 1.014 kat artırıyordu.

Sonuç: Biyopsi yapılan hastalarda ağrı duyusunun çoğunlukla prob yerleştirilmesi sırasında hissedildiği ve bu ağrı duyusunun prostat büyüklüğü arttıkça arttığı görülmektedir.

Anahtar kelimeler: Ağrı skoru, anestezi, prostat biyopsisi, transrektal ultrason.

Introduction

Prostate cancer (PCa), which may even be classified as a geriatric illness, is second only to skin cancer in prevalence [1]. Prostate biopsy is the only method used for histopathological diagnosis, regardless of the biopsy method used. However, there is an ongoing debate regarding who should undergo a biopsy and what type is appropriate. According to European Association of Urology (EAU) guidelines, a multiparametric prostate magnetic resonance imaging (mpMRI) scan should be conducted on all biopsy candidates, and targeted fusion biopsy and additional systematic biopsy are recommended for patients with suspicious lesions on mpMRI [2]. Although prostate biopsy is typically recommended for patients with a life expectancy of 10-15 years, due to

the increase in life expectancy and higher PSA values with age, there is a growing elderly population in need of prostate biopsies.

The EAU guidelines suggest transperineal biopsy as the first option due to its low risk of infection [2]. However, ultrasonography-guided transrectal prostate biopsy (TRUS-PB) is the most commonly used method, as it can be performed under local anesthesia in an outpatient setting [3]. This is advantageous for elderly individuals at risk of general or spinal anesthesia.

Pain management is crucial when performing biopsies since pain can affect the accuracy of the biopsy sample collection and may result in premature termination of the biopsy procedure. The two primary causes of pain during transrectal ultrasound-guided prostate biopsy (TRUS-PB) are the insertion of an ultrasound probe into the rectum and a puncture of the biopsy needle into the prostate tissue [4, 5]. The most conventional local anesthetic methods for TRUS-PB are intrarectal local anesthesia (IRLA), ultrasound-guided peri-prostatic nerve block (PNB), pelvic plexus nerve block (PPNB), and intraprostatic local anesthesia (IPLA). Lidocaine, available in gel, spray, or injectable form, is commonly used anesthetic agent. Studies have demonstrated that PNB, which involves the injection of lidocaine bilaterally along the apex to the base, is a superior option compared to IRLA [6-8]. However, IRLA, compared to PNB, is a noninvasive method and is also widely used to reduce pain during a prostate biopsy [9].

Numerous studies have indicated that younger patients undergoing a biopsy may experience more pain due to higher anal sphincter tone [5, 10]. Additionally, studies have found that acute pain decreases with age, while chronic pain increases with age [11]. These findings suggest that age can be a significant factor in the experience of pain during biopsy procedures.

This study aimed to investigate the effect of age on pain levels created by the transrectal probe and the biopsy needle insertion into the prostate tissue, in which 11 ml 2% lidocaine gel was used as an IRLA before TRUS-PB.

Materials and methods

The study was conducted by the Declaration of Helsinki and received approval from the local ethics committee (approval no. 2023/1446, dated June 11, 2023). Informed consent was obtained from all patients prior to the procedure.

Although this study is retrospective, we followed all patients prospectively. We recorded detailed data of all patients on electronic media from November 2020 to maintain a higher standard of care in our clinic.

Our study involved 308 patients who underwent TRUS-PB between November 2020 - March 2023. Our biopsy protocol included patients with a PSA level above 4 ng/ml, suspicious digital rectal examination (DRE), mpMRI PI-RADS score higher than 2, any mpMRI PI-RADS score with suspicious DRE or PSA >4 ng/ml, patients with previous suspicious pathology results, or who needed staging for prostate carcinoma. All patients were given prophylactic antibiotics, and an enema was applied on the morning of the biopsy. A pre-biopsy urine culture was obtained from all patients. Patients on anticoagulation therapy were stopped from taking anticoagulation drugs and switched to low molecular weight heparin five days before the biopsy.

Study inclusion criteria were the patients who were given 11 ml 2% lidocaine gel intrarectally as a local anesthesia. The study did not include patients who have undergone previous prostate biopsies or any prostate surgery, those with less than eight core biopsies, chronic prostatitis, large hemorrhoids, and severe anal strictures impeding the insertion of a rectal probe, lidocaine or povidone-iodine allergies, active use of analgesic medications, urethral catheterization, and those who are incapable of indicating their pain level on the pain scale. Consequently, the study includes a remaining cohort of 308 patients. We divided these patients into groups based on age: Group 1 had 103 patients aged 65 or younger, Group 2 had 100 patients aged 66-70, and Group 3 had 105 patients over 70.

The same urology doctor (CB) performed 10-12 core systematic TRUS-PB procedures using a 7.5-MHz biplane probe (ProSound SSD-5500, Aloka, Tokyo, Japan) in the left lateral decubital position. A single-use automatic biopsy gun with an 18 gauge-24 cm needle and 11 ml of 2% lidocaine gel provided local anesthesia to the patient in the same outpatient room. The rectal probe's maximum diameter is 60 mm, increasing to 65 mm when the biopsy attachment is added.

The local anesthesia procedure begins with the perineal cleaning with a gauze soaked in povidone-iodine. Then, 11 ml of 2% lidocaine gel was applied intrarectally, followed by a digital rectal examination to distribute the gel on the prostate equally. After allowing 5 minutes for the anesthesia to take effect, pre-biopsy rectal cleaning was done by using sterile gauze soaked in 40 ml of povidone-iodine and 11 ml of 2% lidocaine gel. The gauze was manually inserted into the rectum and placed over the prostate for 2 minutes. The biopsy procedure started 10 minutes after the initial lidocaine gel application.

Thirty minutes after the biopsy procedure, we measured each patient's pain using the VAS score, which ranged from 0 (no pain) to 10 (worst pain). Patients were asked for pain level during the insertion of the rectal probe and the maneuvers (VAS-p) and the

pain level during the insertion of the needle through the prostate to take a biopsy (VAS-b).

Statistical analysis

Statistical analyses were performed using IBM SPSS 22.0 (Armonk, NY: IBM Corp.). The normal distribution of data was analyzed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive data were expressed as mean \pm standard deviation (SD) or median (25th-75th percentile) depending on the data distribution. Normally distributed variables were compared using the Independent Sample t-test. Quantitative variables that were not normally distributed and independent groups with ordinal data were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-square test. A value of $p < 0.05$ was considered significant.

Results

The mean age was 67.5 (± 6.95) years, the mean BMI was 26.6 (19.6-46.7) kg/m², the mean serum PSA level was 7.1 (0.2-575) ng/dL, and the mean prostate volume was 59.5 (10-220) mm³. When the biopsy pathology results were compared, Group 3 had a higher incidence of PCa than the other groups (Table 1). However, the pathology results had no impact on VAS-p or VAS-b.

A statistically significant difference was observed between the groups in terms of VAS-p. Pain was observed in 83.5% of patients in Group 1, 70% in Group 2 and 81.99% in Group 3. VAS-p score was lower in Group 2 than in the other age groups ($p = 0.038$). No significant difference was observed between Group 1 and Group 3. When the groups were evaluated in terms of VAS-b, no significant difference was observed between the 3 groups ($p > 0.005$).

Pain during probe insertion developed in 74.5% of those who had no pain during biopsy, while pain during probe insertion developed in 90.9% of those who had pain during biopsy. The likelihood of pain during probe insertion was significantly higher in patients with pain during biopsy than in those without pain during biopsy ($p = 0.002$).

Across all patients, the pain felt during probe insertion was greater than the pain felt during biopsy, and this was statistically significant ($p < 0.001$) (Figure 1).

When prostate volume was compared with pain score, each unit increase in prostate volume increased the probability of pain in VAS-p by 1.014 times ($p < 0.005$).

Discussion

Despite ongoing criticism, TRUS-PB remains the most widely used procedure for prostate cancer diagnosis. Since it is an invasive procedure, it is not without risks and

can lead to complications, including sepsis. Additionally, the pain experienced during the biopsy procedure often discourages patients from undergoing it. For this reason, various forms of local anesthesia have been introduced to alleviate the pain and discomfort associated with prostate biopsy [12, 13]. Although advances have been made in the procedure over the years, pain and discomfort remain the most common side effects. Our study aimed to determine whether pain arises primarily during probe insertion or biopsy.

Desgrandchamps et al. [14] investigated the effect of 2% lidocaine gel on pain during the procedure and concluded that rectal administration of lidocaine had no effect on tolerance to prostate biopsy. Likewise, Peyromaure et al. [15] reported that only 51 of 275 patients (18.6%) did not feel any pain or discomfort during the biopsy procedure, while Aus et al. [16] reported that only 24 of 343 patients (7%) did not feel any discomfort. Pain developed during probe insertion in 25.5% of the patients included in our study and was consistent with the existing literature. Unlike the existing studies, we evaluated biopsy and probe pain separately and 90.9% of the patients who had pain during biopsy felt pain during probe insertion. Therefore, it was concluded that the main reason for the patients to feel pain was the probe insertion procedure.

In a study comparing anesthesia types by Kravchick et al. [17], in which the pain felt during probe insertion was evaluated, it was found that the lowest pain scores were observed in the perianal injection and DMSO/lidocaine groups, and that there was no correlation between the pain felt during probe insertion and biopsy. When we looked at the data we obtained, it was observed that the main reason why the patients felt pain during the biopsy was the pain felt at the probe entrance, and it was observed that as the pain score increased during the probe procedure, the pain score increased during the biopsy procedure.

Among the techniques to alleviate pain during TRUS-guided prostate biopsy, periprostatic nerve placement (PPNB) is the most effective method PPNB has been found to significantly reduce pain during biopsy [9, 18]. In addition, studies have reported that patients who underwent periprostatic anesthesia felt more pain during probe insertion than during the biopsy procedure [7]. 2% intrathecal lidocaine gel was administered as anesthesia to our patients before the biopsy procedure and 80% of the patients in all three patient groups felt pain during the procedure.

In the study in which the age of the patients and the pain felt during the biopsy procedure were evaluated, it was found that younger patients felt more pain due to high sphincter tone, while older patients felt less pain due to pain tolerance [5, 11]. When the data of our current study were examined, it was observed that the pain sensation was

mostly in patients under 65 years of age, and they felt this pain especially during probe entry.

The strengths of our study are the separate evaluation of pain during probe insertion and biopsy procedure and its classification according to age groups. The study has several limitations, including its retrospective design and single-center setting, as well as the relatively small sample size. Another limitation is the use of VAS scoring, which is a subjective measurement tool. In addition to pain perception, which changes from patient to patient, sociocultural factors may also impact the results of this subjective assessment, potentially influencing the study's findings.

It has been concluded that pain sensation in patients undergoing biopsy is mainly felt during probe insertion and that this pain sensation increases with increasing prostate size. It can be concluded that younger and older patients are also more sensitive to pain. Larger prospective multicenter studies are needed to reach clearer conclusions.

Conflicts of interest: No conflict of interest was declared by the authors.

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Informed consent: All human subjects provided written informed consent with guarantees of confidentiality

Ethics committee approval: Permission was obtained from Karabük University Non-Interventional Clinical Research Ethics Committee (approval number: 2023/1446, date:06/11/2023)

Authors contributions

S.B. conception, interpretation of data, manuscript writing and editing. C.B.: analysis and interpretation of data, editing of manuscript.

Table 1. Main characteristics of groups. Group 1 patients aged 65 and under. Group 2 patients aged between 66-70 years old. Group 3 patients aged 71 and over

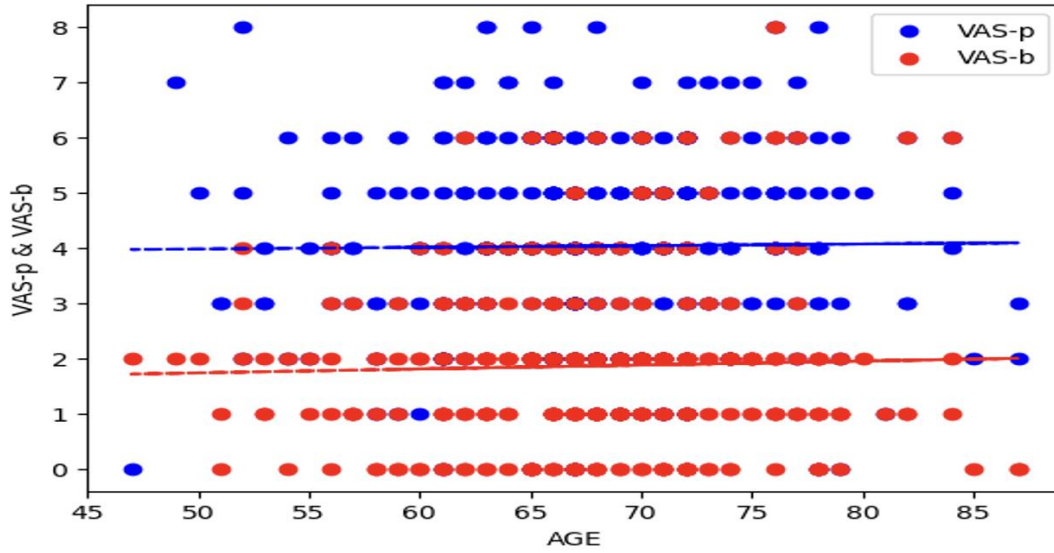
| Parameters | Overall | Group 1 | Group 2 | Group 3 | p- value |
|----------------------------|------------------|------------------|------------------|------------------|----------|
| Number of patients (%) | 308 | 103 (33.4%) | 100 (32.5%) | 105 (34.1%) | |
| Age mean (min-max) | 67.5 (47-87) | 62 (47-65) | 67 (66-70) | 74 (71-87) | <0.001* |
| PSA mean (min-max) | 7.1 (0.2-575) | 6.2 (0.2-151) | 6.9 (1-575) | 8.6 (2.4-456) | <0.001* |
| PV mean (min-max) | 59.5 (10-220) | 55 (10-220) | 66.5 (25-168) | 60 (20-211) | 0.008* |
| BMI mean (min-max) | 26.6 (19.6-46.7) | 27.7 (21.5-39.7) | 26.7 (20.3-42.0) | 25.5 (19.6-46.7) | 0.075* |
| No. of cores | 12 (8-12) | 12 (8-12) | 12 (8-12) | 12 (8-12) | 0.054* |
| Anormal DRE n, % | 160 (51.9%) | 43 (41.7%) | 54 (54%) | 63 (60%) | 0.027*** |
| Pathology results | | | | | |
| PIN n, % | 13 (4.2%) | 3 (2.9%) | 6 (6%) | 4 (3.8%) | 0.025** |
| ASAP n, % | 26 (8.4) | 7 (6.8) | 11 (11%) | 8 (7.6%) | |
| BPH n, % | 131 (42.5) | 52 (50.5%) | 47 (47%) | 32 (30.5%) | |
| PCa n, % | 138 (44.8) | 41 (39.8%) | 36 (36%) | 61 (58.1%) | |
| DM n, % | 111 (%36) | 41 (39.8%) | 35 (35%) | 35 (33.3%) | 0.602** |
| Biopsy time mean (min-max) | 9 (7-11) | 9 (7-11) | 9 (7-11) | 8 (7-11) | 0.309* |
| VAS- p mean (min-max) | 4 (0-8) | 4 (0-8) | 4 (0-8) | 4 (0-8) | 0.372* |
| VAS- b mean (min-max) | 2 (0-8) | 2 (0-6) | 1 (0-6) | 2 (0-8) | 0.882* |

*Kruskall Wallis test **Chi-square test

PSA: prostate specific antigen, PV: prostate volume, BMI: body mass index,

DRI: digital rectal xamination, PIN: prostatic intraepithelial neoplasia,

ASAP: atypical small acinar proliferation, PCa: prostate carcinoma, BPH: benign prostate hyperplasia DM: diabetes mellitus, VAS-p: visual analog scale for rectal probe, VAS-b: visual analog scale during biopsy needle puncture



VAS-p: Visual Analogue Scale of Probe

VAS-b: Visual Analogue Scale of Biopsy

Figure 1. Scatter plot of VAS-p and VAS-b according to age

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