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Can the Degree of Pain During Transrectal Ultrasound- Guided Prostate Biopsy be Predicted Before Biopsy?

Transrektal Ultrason Kılavuzluğunda Prostat Biyopsisi Sırasındaki Ağrı Derecesi Biyopsi Öncesinde Tahmin Edilebilir mi?

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Abstract

Objective: To evaluate whether the assessment of anxiety and pain perception before a biopsy procedure may predict patients' perceived pain scale scores during transrectal ultrasound-guided prostate biopsy.

Materials and Methods: Patients who were administered the Mini-Mental State Examination 24 h before the biopsy were evaluated based on electrically and mechanically induced pain thresholds. Patients were assessed with Generalized Anxiety Disorder (GAD)-7 scale scores in the hour before biopsy. The pain experienced by patients during rectal probing and biopsy was assessed using Visual Analog Scale (VAS) scores.

Results: The mean age and median PSA level of the patients were 65.52 ± 7.85 years and 9.73 (1.4-155) ng/dL, respectively. The median VAS scores during rectal probing and biopsy were 3 (0-10) and 4 (0-10) respectively. VAS scores calculated during procedures were moderately-to-strongly correlated with the index finger of mechanically induced pain pressure threshold (PPT) ($r=-0.606$, $p=0.001$ and $r=-0.760$, $p=0.001$). Multiple regression analyses revealed that severity of the intraprocedural pain was correlated with age, GAD-7, and PPT index finger scores ($p=0.005$, $p=0.001$, $p=0.001$, respectively). A correlation was noted between the refusal of repeat prostate biopsy and higher pain scores ($p<0.001$).

Conclusion: A moderate-to-strong correlation was found between pain scores evaluated after rectal probing and during prostate biopsy with PPT index finger pain and GAD-7 scores. Therefore, psychological support and/or additional anesthetic options should be considered in younger patients with high GAD-7 and PPT index finger scores before application of prostate biopsy to decrease the refusal rates of repeat biopsy.

Keywords: prostate cancer, transrectal prostate biopsy, pain, anxiety

Özet

Amaç: Biyopsi işlemi öncesinde anksiyete ve ağrı algısının değerlendirilmesinin, transrektal ultrason eşliğinde prostat biyopsisi sırasında hastaların algıladıkları ağrı ölçeği skorlarını öngörüp öngöremeyeceğini değerlendirmek.

Gereçler ve Yöntemler: Biyopsiden 24 saat önce Mini-Mental Durum Muayenesi uygulanan hastalar, elektriksel ve mekanik olarak indüklenen ağrı eşiklerine göre değerlendirildi. Hastalar biyopsiden 1 saat önce Yaygın Anksiyete Bozukluğu (YAB)-7 ölçek skorları ile değerlendirildi. Hastaların rektal prob yerleştirilmesi ve biyopsi sırasındaki ağrı deneyimi Görsel Analog Skala (VAS) skorları kullanılarak değerlendirildi.

Bulgular: Hastaların ortalama yaşı ve medyan PSA düzeyi sırasıyla 65.52 ± 7.85 yıl ve 9.73 (1.4-155) ng/dL idi. Rektal prob yerleştirilmesi ve biyopsi sırasındaki medyan VAS skorları sırasıyla 3 (0-10) ve 4 (0-10) idi. İşlemler sırasında hesaplanan VAS skorları mekanik olarak indüklenen ağrı basınç eşiğinin (PPT) işaret parmağı ile orta-kuvvetli derecede korelasyon gösterdi ($r=-0.606$, $p=0.001$ ve $r=-0.760$, $p=0.001$). Çoklu regresyon analizleri, prosedür içi ağrının şiddetinin yaş, GAD-7 ve PPT işaret parmağı skorları ile ilişkili olduğunu ortaya koymuştur (sırasıyla $p=0.005$, $p=0.001$, $p=0.001$). Prostat biyopsisinin tekrarlanmasının reddedilmesi ile daha yüksek ağrı skorları arasında bir korelasyon kaydedilmiştir ($p<0.001$).

Sonuç: Rektal prob yerleştirilmesi ve prostat biyopsisi sırasında değerlendirilen ağrı skorları ile PPT işaret parmağı ağrısı ve GAD-7 skorları arasında orta ila güçlü bir korelasyon bulunmuştur. Bu nedenle, GAD-7 ve PPT işaret parmağı skorları yüksek olan genç hastalarda, tekrar biyopsiyi reddetme oranlarını azaltmak için prostat biyopsisi uygulanmadan önce psikolojik destek ve/veya ek anestezi seçenekleri düşünülmelidir.

Anahtar kelimeler: prostat kanseri, transrektal prostat biyopsisi, ağrı, anksiyete

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Introduction

Prostate cancer (PCa) is one of the most common diseases among men [1]. Over one million transrectal ultrasound-guided prostate biopsies (TRUS-Bx) which are among the gold standard diagnostic procedures for PCa have been performed annually [2]. Although TRUS-Bx is an invasive procedure, it can be performed safely, even under outpatient conditions. Patients often feel pain during the procedure, and such methods as intrarectal application of local anesthetics and periprostatic nerve blockade are implemented before TRUS-Bx to reduce intraprocedural pain [3]. Despite the use of various methods of anesthesia, approximately 16% of patients experience moderate to severe pain during the procedure and 18% of them state that they will not accept application of such a procedure again [4].

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and notes that "pain is always a subjective feeling" [5]. So, pain is a subjective unpleasant experience and therefore has an emotional impact [6]. Pain can only be assessed self-reportedly because it is the unique cognitive process of previous pain experiences of an individual concerning duration, and intensity of pain, social parameters, emotional stress, and memory. The sensory components of pain are felt when the impulses are trensferred to the lateral thalamus, somatosensory cortex, and finally to posterior insular cortex [7]. The pain threshold is defined as the minimal level of pain that an individual can recognize. To induce painful stimuli, commonly, four different types namely pressure, electrical, thermal, and laser-induced pain assessment techniques are used. However, pain scores can only be assessed subjectively, and individuals rate the pain according to their own previous experiences [8].

Local anesthesia whose effectiveness in reducing intraprocedural pain has been shown in placebo-controlled studies is commonly applied to the periprostatic region during prostate biopsy [9-11]. However, despite perception of pain is reduced after application of anesthesia, patients still feel pain during biopsy [12]. Predicting patient's discomfort during the procedure with anxiety, pain assessment before TRUS-Bx might be useful in reducing the intraprocedural pain of the patient. Thus, decreasing patient's discomfort can reduce the rate of refusals for a repeat biopsy.

In this study, we investigated the relationship between emotional status and pain assessments in patients scheduled for TRUS-Bx and the pain they felt during the biopsy procedure.

Materials and Methods

A total of 259 patients who were admitted to Bolu Abant İzzet Baysal University, Faculty of Medicine Department of Urology were included in the study. This prospective study was performed according to the principles of World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects and with permission obtained from the local ethics committee (date: 12.14.2017, and protocol #: 2017/188). This study was conducted between February 1, 2019, and February 1, 2020. Patients scheduled for biopsy because of suspicious prostatic lesions palpated on digital rectal examination and/or PSA value ≥4 ng/dL were evaluated for inclusion in the study. Written informed consent was obtained from all patients for participation in the study.

Patients who had a history of a surgical operation or pathology involving the anal/rectal region, prostate biopsy, prostatitis, urinary tract infection, chronic pelvic pain syndrome, and diabetes mellitus, individuals who had used analgesisc within three days prior to the procedure or cases with Mini-Mental State Examination (MMSE) score <24 points were excluded from the study [13].

Outcome Measurements

Demographic data of the patients were collected prior to clinical assessments. Electrically induced pain (EIP) and mechanically induced pain (MIP) assessments were performed 24 h before TRUS-Bx. Biopsy-related anxiety levels were assessed with a generalized anxiety disorder (GAD)-7 scale an hour before the TRUS-Bx. The pain experience of patients during rectal probing and prostate biopsy was assessed with a visual analog scale (VAS) scores.

Electrically Induced Pain

The EIP assessment was performed by transcutaneous electrical nerve stimulation (TENS) with Myomed 632 (Enraf-Nonius, Rotterdam, Netherlands) on the index finger of the dominant hand. The passive electrode was placed on the dorsal side of the hand, and the active electrode was placed on the distal phalanx of the index finger. The current was set to a 200-µs duration, starting from a 0-mA 100-Hz rectangular wave and increasing at the rate of 0.1 mA/s until the perception threshold (a level at which the patient begins to feel the current) the pain threshold (a level at which the current became a painful stimulus) were reached [14,15].

Mechanically Induced Pain

The pain pressure threshold (PPT) was used to assess MIP with an analog algometer (Baseline; FE, White Plains, NY, USA) with a 1-cm2 rubber tip. The algometer was placed perpendicularly over the distal phalanx of the index finger, and the pressure was progressively increased by 0.5 kg/s until the patient verbally reported pain under the tip of the algometer. The measurements were repeated three times, and the average score was recorded [16].

Generalized Anxiety Disorder-7 Scale

Patients were asked if they experienced anxiety-related issues over the past two weeks by answering seven items on a 4-point scale. The total score of GAD-7 ranged from 0 to 21, based on which the anxiety levels were categorized as follows: 0–4: mild anxiety, 5–9: moderate anxiety, 10–14: high anxiety, and 15–21: severe anxiety. A score of ≥10 indicated a diagnosis of GAD [17,18].

Visual Analog Scale

The patients were asked to mark the severity of their pain during rectal probing and prostate biopsy on a 10-cm long horizontal line from 0 (no pain) to 10 (the most severe pain I felt in my life). Moreover, the patients were asked to rate the discomfort of biopsy experience between 0 (no discomfort) and 10 (the most severe discomfort ever experienced) [19,20].

Rectal Biopsy Procedure

Prophylactic oral ciprofloxacin 500 mg was prescribed for patients scheduled for TRUS-Bx according to our hospital infectious control committee recommendations to be used at the

Table 1. Demographics and scores of patients

	Mean± SD	Median (min-max)	N (%)
Age (y)	65.52 ± 7.85		
PSA (ng/dL)		9.73 (1.4-155)	
Prostate volume (cc)		69.0 (20-195)	
BMI (kg/m^2)	28.16 ± 4.02		
Pathological results			
BPH			73 (58.5)
Prostatitis			21 (16.9)
Cancer			30 (24.1)
ISUP 1			17 (13.6)
ISUP 2			4 (3.2)
ISUP 3			3 (2.4)
ISUP 4 and 5			6 (4.8)
VAS score			
Probing		3 (0-10)	
Biopsy		4 (0-10)	
GAD-7 scale score		10 (2-21)	
MIP (PPT) (N)		8.15 (2.0-17.8)	
EIP (TENS) (mA)			
Feel treshold		8.45 (2.5-23.0)	
Pain treshold		13.6 (4.7-44.0)	

PSA: prostate specific antigen; y: year; cc: cubic centimeter; BPH: benign prostatic hyperplasia; ISUP: international society of urological pathology; VAS: visual analog scale; GAD: generalized anxiety disorder; MIP (PPT): mechanical induced pain (pain pressure treshold); N: newton; EIP (TENS): electrical induced pain (transcutaneous electrical nerve stimulation); mA: miliAmper; SD: standart deviation; min-max: (minumum- maximum); n (%): number (per cent). Continuous variables with normal distribution were expressed with mean± SD, without normal distribution expressed with median (min-max), and categorical variables were expressed with n (%).

day before the procedure. Enema was used the evening before the procedure and the morning of the procedure for intestinal cleansing.

The TRUS-Bx procedure was performed with Siemens Sonoline G20 EC9-4 transducer and a 4–9-MHz probe by the same urologist experienced in TRUS-Bx procedures. Prostate volume was measured during the biopsy using the ellipsoid formula (0.52×width×depth×height). The procedure was performed with patients in the left lateral decubitus position with their knees firmly bent towards the abdomen. Before the biopsy, 1 mL of lidocaine was applied on each side between the prostate and the seminal vesicle, and 5 mL of lidocaine was used for peri-prostatic nerve block. The biopsy procedure was performed with 5-min intervals [12]. After discharge, patients were asked whether they will agree for another biopsy, if necessary, and request them to respond with a definite "yes or no".

Statistical Analysis

The Shapiro–Wilk test was used to check for the normal distribution of continuous variables. Continuous variables with normal distribution were expressed with mean± standard deviation (SD), without normal distribution with median (minumum-maximum) values and categorical variables with numbers and percentages (%). Spearman's rank-order correlation test was used for analyzing the correlation between VAS and induced pain levels. The multiple regression analysis was used to identify predictors of experienced pain levels. All statistical analyses were performed using the SPSS for Windows, version 20.0 (IBM, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. The power analysis of the data shows that with an effect size of 0.464 and a type I error probability of 0.05 to reach 80% power, 122 patients were required.

Results

Two-hundred and fifty-nine patients were evaluated, of those, 128 patients who accepted and met the inclusion criteria were included in this study. Four patients who refused to participate in post-biopsy assessments were excluded from the study. Finally, data of 124 patients were included for analysis. The flowchart of the study design is shown in **Figure 1**.

The mean age and body mass index (BMI) of the patients were 65.52 ± 7.88 years, and 28.16 ± 4.02 kg/m^2, respectively. The median prostate volume and PSA level were 69 (20–195) cm^3 and 9.73 (1.4–155) ng /dL. After the histopathological examination of the biopsy specimens, patients received the diagnoses of benign

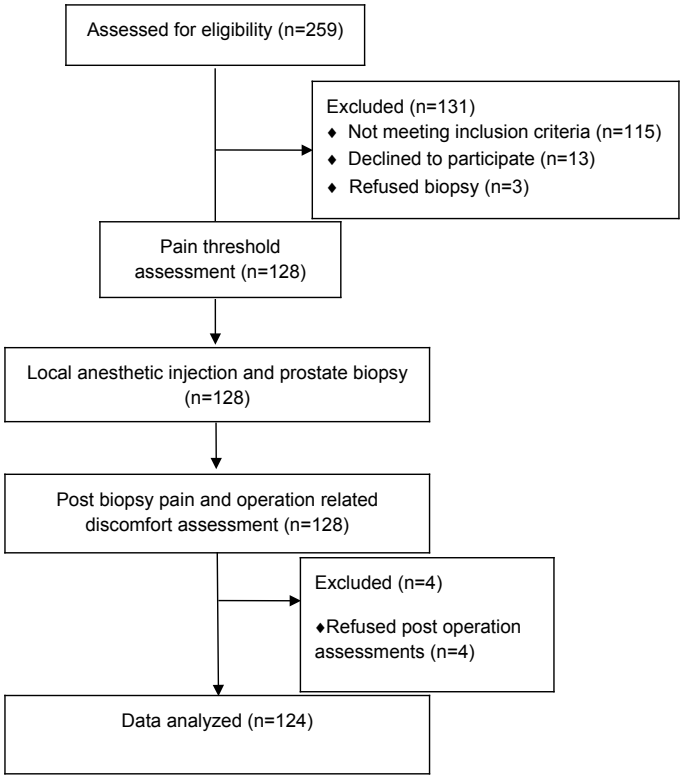

Figure 1. Flowchart of the study design

prostatic hypertrophy (n=73: 58.5%), prostate cancer (n=30: 24.1%), and chronic prostatitis (n=21:16.9%).

The median VAS scores of the patients after insertion of the rectal probe (3: 0-10) and during biopsy (4: 0-10) were recorded. There was a statistically significant correlation (r=0.74, p= 0.001) between increase in VAS scores during biopsy and rectal probing (p=0.012). The median GAD-7 scale score of patients was 10 (2-21). Twenty-one (16.9%), 42 (33.9%), 27 (21.7%), and 34 (27.5%) patients showed mild, moderate, high, and severe anxiety levels based on assessments made using GAD-7 scale scores, respectively. The median MIP, EIP scores in the first feeling of pain were 8.15 (2.0-17.8), 8.45 (2.5-23.0), and 13.6 (4.7-44.0), respectively. Baseline demographic data and scores of patients are summarized in **Table 1.**

After rectal biopsy, 26 (21%) of the patients stated that they would not accept another biopsy due to pain. There was a significant correlation between refusal of repeat biopsies and VAS scores during rectal probing and prostate biopsy (r=0.301, p<0.001 and r=0.285, p<0.001, respectively).

Spearman's rank-order correlation was used to determine the relationship between VAS scores recorded during rectal probing and prostate biopsy and TENS feel threshold, TENS pain threshold, and index finger PPT. There were no significant correlations between VAS scores and TENS feel (r=-0.092, p=0.309 and r=0.058, p=0.519, respectively) and TENS pain threshold scores (r=-0.101, p=0.266 and r=0.049, p=0.591, respectively) during rectal probing and prostate biopsy. There was a strong, statistically significant negative correlation existed between VAS scores of rectal probing and prostate biopsy and PPT index finger scores (r=-0.606, p<0.001 and r=-0.760, p<0.001, respectively).

Table 2. Spearman's correlation coefficient between visual analog scale scores and the results of electrically and mechanically induced pain assessment

	VAS			
	Probing		Biopsy	
	r	p	r	p
TENS feel threshold (mA)	-0.092	0.309	0.058	0.519
TENS pain threshold (mA)	-0.101	0.266	0.049	0.591
PPT (N)	-0.606	**0.001**	-0.760	**0.001**

VAS: visual analog scale; TENS: transcutaneous electrical nerve stimulation; PPT: pain pressure threshold; mA: miliAmper; N: Newton. Statistically significant values stated with bold

Table 3. Multiple regression analysis for variables predicting intraprocedural pain intensity according to Visual Analog Scale score

	B	OR (95% CI)	P
PPT (N)	-0.505	0.82 (0.74-0.92)	**0.001**
GAD-7 score	0.116	1.12 (0.91-1.32)	**0.001**
Age (y)	0.090	0.93 (0.85-1.02)	**0.005**
BMI (kg/m^2)	0.019		0.671
Prostate volume (cc)	-0.007		0.106
Pathological results	0.002		0.324

OR: odds ratio; CI: confidence interval; PPT: pressure pain threshold; N: Newton; GAD: generalized anxiety disorder; y: year; BMI: body mass index; cc: cubic centimeter. Statistically significant values stated with bold.

Spearman correlation coefficient estimated between visual analog scale scores and the results of electrically and mechanically induced pain assessment shown in **Table 2.**

The multiple regression analysis was performed to predict levels of pain intensity during procedure. Index finger PPT and GAD-7 scores significantly predicted pain intensity, F (3,120) = 58.572, p < 0.001, R2 = 0.584. Index finger PPT scores, GAD-7 scores and, age variables in combination significantly predicted intraprocedural pain intensity according to VAS scores (OR (95% CI): 0.82 (0.74-0.92) p=0.001, 1.12 (0.91-1.32) p=0.001, 0.93 (0.85-1.02) p=0.005; and, respectively) but BMI, prostate volume and pathological results did not. The results of multiple regression analysis of variables predicting intraprocedural pain intensity are shown in **Table 3.**

Discussion

Painful stimuli cause emotional responses and especially projects to the limbic system [21]. Electrically or mechanically induced pain models are frequently used for generating painful stimuli [22]. Electrically induced pain is a sharp, quick, and well-located pain sensation that is similar to biopsy pain. Mechanically induced pain is a dull, throbbing, and hard to locate pain sensation that is similar to the pain felt during insertion of a rectal probe. Algometers were used with the higher reliability for pain measurement although the perception and subjective analysis of pain is multifactorial with its physiological and psychological aspects [23]. Thus, it remains unclear which patients need anesthesia or whether adjustment

of analgesic doses should be individualized. To the best of our knowledge, this is the first study in which pain threshold values of individuals who underwent TRUS-Bx were measured, assessed, and the severity of intraprocedural pain was correlated with preoperative pain perception levels.

In our study, VAS scores exceeded 5 points during the biopsy in 35.5% of patients receiving local analgesia. Also, a moderate-to-strong correlation was found between pain scores and anxiety levels of patients. In some cases, biopsies need to be repeated at regular intervals after the first prostate biopsy performed for diagnostic purposes. However, very severe intraprocedural pain experienced by patients leads to refusal of repeat biopsies [4]. In the present study, 21% of the patients reported that they would not accept a similar procedure again. We speculate that if a patient's pain threshold can be evaluated before the procedure and appropriate treatment can be applied to lower their physiological or psychological perception of the pain they experienced then the refusal rates of repeat biopsies may be minimized.

According to several studies, quantitative assessment of a patient's basal pain perception and pain perception threshold before surgery or invasive procedures has a clinical value only when it can predict the intensity level of pain and required analgesic dosage [24-26]. In order to obtain a reliable result from quantitative assessment methods, in this study assessment of MIP was performed by the physician using the index finger of his/her dominant hand. Although there are multiple appropriate regions for evaluating the relationship between PPT and intraprocedural pain including firstly index finger, followed by the first web space of hand, and trapezius, which does not yield consistantly reliable results as the index finger [27] that might be due to a high number of myofascial-related sensitive areas on the trapezius muscle affecting the precision of measurements [12,28]. Individual variations of adipose tissue thickness of the first web space of hand might have impaired the accuracy of measurements which explains the relatively weak correlation existing between PPT values obtained, and the level of perceived pain. Whereas the index finger is one of the least affected regions by lipidosis caused by weight gain. For these possible reasons, in the present study the index finger was found to be a reliable region for pain assessment which showed a strong correlation with reported pain intensity levels during the biopsy.

We found that the patient's age, index finger PPT score, and GAD-7 scores were effective predictive factors for rating perceived pain during TRUS-Bx. Studies have investigated pain intensities during the prostate biopsy procedure with experimental pain models, but most of them have focused on the somatosensory aspect of pain [28-30]. We found a significant correlation between index finger PPT measurements and the patient's anxiety level. Age as a predictive factor negatively correlated with perceived pain scores, which might be due to a decrease in pain perception with aging [31]. Also, a reduction in the anal tone with old age may have made the rectal probing easier, causing less procedural pain during the biopsy [32].

We have also some potential limitations. First, our study included small number of patients. Secondly, although all procedures were performed by the same urologist, we could not record the duration of the whole procedure. The last and the most important limitation in our study was that we did not analyze the pelvic floor muscle tone during rectal probing and biopsy which has a very potential role for the evaluation of the anal tone and perceived pain during procedure.

Conclusion

In this study, patients with low PPT levels felt more pain during TRUS-Bx. The rate of patient's acceptance of another similar procedure decreased with the increased perception of intraprocedural pain. Furthermore, patients with increased anxiety levels had lower PPT levels and higher VAS scores. To reduce the refusal rate of TRUS-Bx because of the severely perceived pain levels, using additional alternative methods can be useful for patients who are found to have high anxiety levels and low pain thresholds. Assessment methods for mechanically and electrically induced pain can be easily applied, besides they are less time-consuming, and more comfortable for the patients compared to digital examination of rectal sensitivity. Using a pre-biopsy pain threshold scale to determine anesthetic dosage and anxiety level screening requiring the support of a psychiatrist might be effective in reducing the severity of pain perceived by the patient.

Ethics Committee Approval: This prospective study was performed according to the Helsinki Declaration and with permission from the local ethics committee (Date: 12.14.2017-Number: 2017/188).
Informed Consent: An informed consent was obtained from the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.S., U.U.; Design – E.S., E.K.; Supervision – U.U., R.K.; Resources – E.S., R.K., U.U.; Materials – U.U., R.K.; Data Collection and/or Processing – U.U., R.K.; Analysis and/or Interpretation – U.U., R.K., E.S., E.K.; Literature Search – H.A.Y., A.G.; Writing Manuscript – E.S., U.U., R.K; Critical Review – E.S., R.K., A.G., E.K., H.AY., U.U.
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