ORIGINAL ARTICLE

Assessment and clinical factors associated with pain in patients undergoing transrectal prostate biopsy☆


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KEYWORDS
Prostate cancer; Diagnosis; Analog pain scale; Transrectal prostate biopsy

Abstract

Objectives: To quantify the degree of pain experienced by patients who undergo ultrasound-guided transrectal prostate biopsy in standard clinical practice and assess the clinical factors associated with increased pain.

Material and methods: Analysis of a multicenter series of patients with prostate biopsy was done according to standard clinical practice. The biopsy was performed transrectally with a protocol of local anesthesia on the posterolateral nerve bundle. The pain was assessed at 20 min into the procedure using the visual analog scale (0–10). The degree of pain was analyzed, and the association was studied using a univariate/multivariate analysis of selected clinical variables and the degree of pain.

Results: A total of 1188 patients with a median age of 64 years were analyzed. Thirty percent of the biopsies were diagnosed with a tumor. The median pain score was 2, with 65% of the patients reporting a pain score ≤2. The multivariate analysis showed that the prostate volume (RR, 1.34; 95% CI 1.01–1.77; p < 0.04), having a previous biopsy (RR, 2.25; 95% CI 1.44–3.52; p < 0.01), age (RR, 0.63; 95% CI 0.47–0.85; p < 0.01) and palpation (RR, 1.95; 95% CI 1.28–2.96; p < 0.01) were factors independently associated with greater pain during the procedure.

Conclusions: Transrectal biopsy with local anesthesia is a relatively painless technique. Factors such as age, a previous biopsy, pain on being touched and prostate volume were associated with the presence of greater pain during the procedure.

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PALABRAS CLAVE
Cáncer de próstata; Diagnóstico; Escala analógica del dolor; Biopsia prostática transrectal

Evaluación del dolor y factores asociados en pacientes sometidos a biopsia de próstata

Resumen

Objetivos: Cuantificar el grado de dolor que sufren los pacientes sometidos a biopsia transrectal de próstata secuestrada en la práctica clínica habitual, y evaluar qué factores clínicos se encuentran asociados a un mayor dolor.

Material y métodos: Análisis de una serie multicéntrica de pacientes con biopsia de próstata según la práctica clínica habitual. La biopsia se realizó vía transrectal con un protocolo de anestesia local sobre el paquete nervioso posterolateral. Se evaluó el dolor a los 20 min del procedimiento a través de la escala visual analógica (0–10). Se analiza el grado de dolor soportado y se estudia la asociación de forma univariante de variables clínicas seleccionadas y el grado de dolor.

Resultados: Se analizaron un total de 1.188 pacientes de 64 años de mediana de edad. Un 30% de las biopsias fueron diagnósticas de tumor. La mediana de dolor fue de 2, con un 65% de pacientes con dolor <2. El análisis multivariante muestra que el volumen prostático (RR: 1,34, IC 95%: 1,01–1,77; p = 0,04), el hecho de tener una biopsia previa (RR: 2,25, IC 95%: 1,44–3,52; p < 0,01), la edad (RR:0,63, IC 95%: 0,47–0,85; p < 0,01) y un tacto doloroso (RR: 1,95, IC 95%: 1,28–2,96; p < 0,01), son factores asociados de forma independiente con mayor dolor durante el procedimiento.

Conclusiones: La biopsia transrectal con anestesia local es una técnica poco dolorosa. Factores como la edad, una biopsia previa, un tacto doloroso y el volumen prostático se asocian con la presencia de un mayor dolor durante el procedimiento.

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Introduction

Prostate cancer (PC) is the second most common tumor in men in Europe,1 and for its diagnosis, prostate biopsy is the standard procedure.2 Currently, prostate biopsy is not only part of the diagnosis, but it is also an important tool in the management of the patients within the framework of active surveillance.3

Prostate biopsy has had a great evolution with the introduction of transrectal ultrasound to guide it, leaving behind digital rectal examination-guided biopsy, with the possibility of transrectal and perineal approach,4,5 and with the introduction of periprostatic local anesthesia.6

However, it remains a procedure that when patients are communicated the need for its realization causes fear and rejection. It has been suggested that it may be due to the psychological stress that the fear of cancer, the route of anal penetration, and the anticipated pain raise.7 Thus, there are studies that estimate that more than a third of patients think that the procedure will be painful, reducing to 6% after the completion of the biopsy.8

There are many studies that evaluate the potential complications of prostate biopsy associated with it,9,10 but few studies that prospectively and in a large population series assess the degree of pain endured by patients in the procedure.5,11,12

There is a need to inform patients before performing the biopsy of the degree of pain that is supported, as well as letting them know which factors can be found associated with it. Therefore, our goal is to quantify the degree of pain suffered by patients undergoing transrectal ultrasound-guided prostate biopsy (TRUS) in routine clinical practice and evaluate which clinical factors are associated with greater pain.

Material and methods

Population and study design

Retrospective analysis of a prospective series of patients who undergo a prostate biopsy for a period of 2 years (2012–2013) at the Oncology Institute of Valencia, Valencia, and the Reina Sofia University Hospital in Cordoba.

The indication for biopsy was performed according to several clinical contexts: opportunistic screening, routine clinical practice, follow-up of patients on active surveillance. The procedure was carried out by 11 urologists.

All patients signed an informed consent.

Exclusion criteria: failure to register relevant clinical variables.

Study variables

Demographic (age, date of biopsy) and clinical variables (PSA, digital rectal examination, IPSS questionnaire of symptoms and quality of life), and other data related to the prostate biopsy such as volume, biopsy pain, biopsy number, number of cylinders, and biopsy result.

Biopsy technique

All patients underwent antibiotic prophylaxis with a fluoroquinolone in short dose regimen (during the previous day, the day of the biopsy, and the day after).
The patient is placed in left lateral decubitus in fetal position. CATHEJELL® lubricant gel (lidocaine and chlorhexidine) is introduced 5 min prior to the completion of the DRE.

After performing the digital rectal examination, the biopsy was performed:

After entering the ultrasound scanner, local anesthetic consisting of 2% mepivacaine 5 ml on either side of the prostate was carried out, in the transition between the seminal vesicle and the prostate with the formation of the well-known "Mount Everest", which is where the nerve bundle runs.

Once anesthetized, the prostate size was calculated using the formula: \((\text{transverse } \times \text{anteroposterior diameter } \times \text{crown-rump } \times 0.52)\). Biopsies were taken, according to recommendations already published by authors in this group,\(^{14}\) with a minimum of 10 cylinders, 12 cylinders being the standardized number for the first biopsies and that figure increasing depending on whether it was a repeat biopsy, prostate volume, and ultrasound suspicious areas.

### Pain assessment

20 min after the completion of the biopsy, the degree of pain experienced during the same was assessed according to the visual analog scale (VAS) from 0 to 10 (where 0 corresponds to no pain and 10 maximum pain).

### Statistical analysis

A descriptive analysis of the study variables was conducted expressing them in median and interquartile range, and absolute number and percentage depending on whether they were quantitative or qualitative.

Then, the association between the different variables and the degree of pain was evaluated, according to the techniques of Student’s-“t” for independent data in dichotomous and ANOVA test in polychotomous. When performing multivariate, correlation was made according to Finner.

The correlation between pain and different quantitative variables was studied according to the statistical criterion of Pearson correlation.

To analyze the factors independently associated with the presence of greater pain during the biopsy, quantitative variables were categorized according to their median distribution (volume, age, no. of biopsy), considering them qualitative, except for the number of cylinders which was considered quantitative.

The target pain dependent variable was categorized according to its median and by standardization with other scales, using as a cut-off point the degree of mild pain (VAS 2).

All contrasts were bilateral and were considered significant when \(p < 0.05\).

The SPSS 16.0 program and Winpepi were used to perform the analyses.

### Results

Of all patients included, 10 (0.8%) were excluded for lack of data. A total of 1188 patients were analyzed, ranging in age between 41 and 91. A total of 355 PCs (30%) were diagnosed with 17.7% with Gleason ≥8. The descriptive data of the series are presented in Table 1.

The median of pain was 2, with 65% of patients who considered mild or less the pain experienced during testing, with less than 10% of patients experiencing a severe to moderate pain (VAS > 4). Fig. 1 shows the distribution of population in the VAS.

Table 2 shows the pain differences according to the qualitative variables of painful touch, biopsy result, and number of biopsy. Of the quantitative variables, univariate correlation is observed but weak of the number of cylinders and the tumor volume with the degree of pain (\(p > 0.05\)), presenting a tendency to inverse correlation with respect to age, without this being significant (\(p = 0.057\)).

![Graphic of distribution of pain](image)

**Figure 1** Chart of histograms of pain distribution according to the visual analog scale.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (percentile 25–75)(/n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 (59–69)</td>
</tr>
<tr>
<td>No. biopsy</td>
<td>1 (1–2)</td>
</tr>
<tr>
<td>PSA</td>
<td>5 (3.7–7.5)</td>
</tr>
<tr>
<td>No. cylinders</td>
<td>12 (10–14)</td>
</tr>
<tr>
<td>Volume (cc)</td>
<td>41.6 (30.9–59.0)</td>
</tr>
<tr>
<td>IPSS</td>
<td>9 (5–16)</td>
</tr>
<tr>
<td>QL</td>
<td>3 (2–3)</td>
</tr>
<tr>
<td>Tumor biopsy (yes)</td>
<td>355 (30)</td>
</tr>
<tr>
<td>Painful rectal examination (yes)</td>
<td>120 (12.6)</td>
</tr>
<tr>
<td>Pathological rectal examination (yes)</td>
<td>229 (19.3)</td>
</tr>
</tbody>
</table>

Table 2  Association of different variables with the degree of pain.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Numerical scale of pain in biopsy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful rectal examination</td>
<td>Yes</td>
<td>2.72 (1.88)</td>
</tr>
<tr>
<td>Tumor biopsy</td>
<td>Yes</td>
<td>2.03 (1.69)</td>
</tr>
<tr>
<td>1st biopsy</td>
<td>Yes</td>
<td>1.94 (1.70)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>2.05 (1.67)</td>
</tr>
</tbody>
</table>

Values expressed as mean and standard deviation. Significance through Student’s ‘t’-test.

Figure 2  Chart of error bars showing pain distribution depending on age. Significance through Student’s ‘t’ test for independent data.

No correlation between the degree of symptomatic involvement of the IPSS and pain in the prostate biopsy (p > 0.05) was found; no correlation was found either among patients according to mild, moderate, or severe symptoms or with the quality of life.

Fig. 2 shows the decrease in pain according to categorized ages.

Multivariate logistic regression analysis was adjusted according to the urologist who performed the biopsy, due to differences in pain according to this variable.

The above-mentioned analysis shows that the prostate volume (RR: 1.34, 95% CI: 1.01–1.77; p = 0.04), the fact of having a previous biopsy (RR: 2.25, 95% CI: 1.44–3.52; p < 0.01), age (RR: 0.63, 95% CI: 0.47–0.85; p < 0.01), and a painful touch (RR: 1.95, 95% CI: 1.28–2.96; p < 0.01) are factors independently associated with greater pain during the procedure (Table 3).

Discussion

TRUS under local anesthesia is an essential outpatient procedure in all patients for histological confirmation of PC.

The results of pain during the biopsy resemble those of other examinations in other specialties, such as colonoscopy or laser hemorrhoidectomy, where most patients have mild or no pain.

The use of VAS 0-10 has been used by various authors for measuring pain. In our series, this assessment reveals that the majority of patients experience pain lower than 2 on the numerical scale, which corresponds to mild or almost non-existing. This result is similar to other series explored, such as Rodríguez-Patrón et al. and Clements et al., differing regarding the series of Zisman et al., Rosario et al., in a multicenter study of similar number of patients, assessed the degree of pain at different times, also using local anesthesia on the posterolateral nervous bundle, and found that 85% of patients reported no pain or only mild during the biopsy.

We need to keep in mind that our study only measured pain on the biopsy day and no further. However, days after the biopsy, there are often no other complications such as infection, hemospermia, hematuria, rectal bleeding, etc., assessment of these complications not being the object of this study.

Regarding the use of anesthesia and the type, local anesthesia in the posterolateral prostate plexus is the standard technique, as this neurovascular bundle is the main nerve supply to the prostate, the rest remaining in the upper lateral and anterior area of the prostate in a very low percentage.

The meta-analysis of Hergan et al. was the first to provide evidence with high recommendation grade for the use of this type of anesthesia. The superiority of this method over local anesthetics, gel type, has also been confirmed, as shown by the results of the meta-analysis by Ting et al. (difference in pain scale −1.53, 95% CI [−0.53 to −2.67]), and regarding diclofenac suppositories.

Table 3  Logistic regression of factors associated with the presence of a pain greater than mild (VAS > 2) on biopsy, adjusted by the urologist who performed the biopsy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>p</th>
<th>95% CI (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume &gt;40 vs &lt;40</td>
<td>1.34</td>
<td>0.042</td>
<td>1.01–1.77</td>
</tr>
<tr>
<td>Age &gt;65 vs &lt;65</td>
<td>0.63</td>
<td>0.002</td>
<td>0.47–0.85</td>
</tr>
<tr>
<td>Number of cylinders</td>
<td>0.96</td>
<td>0.454</td>
<td>0.88–1.05</td>
</tr>
<tr>
<td>Repeat biopsies vs 1st biopsy</td>
<td>2.25</td>
<td>0.000</td>
<td>1.44–3.52</td>
</tr>
<tr>
<td>Painful rectal examination</td>
<td>1.95</td>
<td>0.002</td>
<td>1.28–2.96</td>
</tr>
</tbody>
</table>

Hosmer–Lemeshow test: 13.56. GL = 8; p = 0.09.
However, combinations of anesthetic gels or diclofenac suppository with local anesthesia of the plexus seem to further reduce pain without increasing complications, but increasing time needing an hour for the suppository to have its effect.23–25

It is important to know what factors can make prostate biopsy more painful, regardless of the type of analgesia used. However, there are few relevant studies with this objective.26

One of the most important factors described in other series is age.13,27 Our results agree with those published, noting that older patients experienced less pain than younger ones.

The number of cylinders taken is not associated with the degree of pain, as described Naughton et al. and Bastide et al.,28,29 although in our series most patients have at least 12 biopsied cylinders. In contrast, Kaver et al.30 reported a cumulative pain for each cylinder biopsied when they analyzed the degree of pain after each cylinder.

So far there was no evidence to support that factors such as prostate volume, having a previous biopsy, or the presence of pain in the rectal examination was associated with the degree of pain in the biopsy.13,26 In our study, these variables have shown to have an independent association to the degree of pain experienced in the biopsy.

Regarding the association of prostate volume with the pain of the biopsy, this is observed regardless of the number of cylinders to be taken in relation to prostate size.

Having a previous biopsy in our study should be interpreted with caution, as nothing compares to the pain experienced by the same subject in the first biopsy, but it compares to that suffered by other patients undergoing a first biopsy. This fact was analyzed by Djavan et al.,13 showing no significantly greater pain in the repeat biopsy.

Certainly, these results are conditioned by the fact that in both centers those patients who had pain in the first biopsy, when they were recommended a repeat biopsy may request that the procedure is conducted under sedation or even under general anesthesia. These patients are not included in the study due to lack of evaluation of postoperative pain.

No differences were found on the pain experienced as to whether the patient had symptoms of the lower urinary tract or not, or as to the greater or lower severity of their symptoms.

The knowledge of these results may help us to provide detailed information to patients who recommend a prostate biopsy on predictions of pain that they will experience.

According to our results, young patients (with special attention to active surveillance protocols) with a painful rectal examination should be considered as potential candidates for biopsies with combined anesthetic techniques, or under sedation.2

Our study has several limitations: the patients whose biopsies or repeat biopsies were performed under general anesthesia due to impossibility of performance caused by pain were not taken into account, this corresponds to 1% according to some series.3 So in a small number of patients who presented a vaginal picture, or need for further perineal compression due to rectal bleeding, we had to delay the time of the assessment. The clinical significance of changes in pain is discrete according to the associated factors (limitation of most of the studies in this field), and late pain experienced by patients is not taken into account. Nevertheless, we believe that our study is, to date, the most contemporary series that assesses pain in patients undergoing TRUS in clinical practice, from patients selected by screening.

Future studies establishing comparative groups with other techniques such as transperineal one, and evaluating the pain by biopsy sites may even provide further information for a better understanding of this diagnostic test.

Conclusions

This study provides very useful information to report to patients about pain intensity produced by applying the technique, stating that TRUS under local anesthesia on the posterolateral nerve bundle is a painless technique in most cases, and that certain factors such as age, the existence of previous biopsy, painful rectal examination, and prostate volume are associated with increased intensity of pain during the procedure.

Conflict of interest

The authors declare that there is no conflict of interest.

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