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Tolerance of prostate biopsy with use of local anesthesia and benzodiazepines: a randomized, prospective study

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Introduction: Prostate biopsy is an uncomfortable procedure, and attempts are therefore being constantly made to try and decrease biopsy-related pain.
Materials and methods: A randomized, prospective study including 160 procedures was designed. Inclusion criteria were: first biopsy, PSA < 15 ng/mL, and age under 75 years. Patients were randomized into 4 groups. Group A was the control group, while group B received intracapsular anesthesia (8 mL of 2% lidocaine), group C 5 mg of oral clorazepate dipotassium one hour before biopsy, and group D both local anesthesia and clorazepate. Each patient completed a questionnaire including three 10-point visual analog scales for pain immediately after the procedure and 30 minutes later.
Results: Mean pain scores were 5.17 (group A), 1.72 (group B), 2.43 (group C), and 0.88 (group D) in the first questionnaire, and 1.71, 0.25, 0.75 and 0.35 respectively in the second questionnaire. Statistically significant differences were found in the ANOVA test. Group comparisons showed the following:
1. A vs B: statistically significant differences in both questionnaires (p = 0.006 and 0.011).
2. A vs C: a significant difference was found in the first questionnaire (0.051), but not in the second (0.012).
3. A vs D: significant differences in both questionnaires (0.001 and 0.010).
No statistically significant differences were seen in both questionnaires (0.825 and 0.685) when benzodiazepines where added to local anesthesia (B vs D).
Conclusion: Use of benzodiazepines as a single method to decrease biopsy-related pain is not warranted

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Tolerancia a la biopsia prostática con el uso de anestesia local y benzodiacepinas: estudio prospectivo aleatorizado

Palabras clave:
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R E S U M E N

Introducción: La biopsia prostática es un procedimiento molesto, lo que condiciona que constantemente intentemos disminuir el dolor durante su realización.
Material y métodos: Diseñamos un estudio prospectivo aleatorizado en el que incluimos 160 procedimientos. Criterios de inclusión: primera biopsia, antígeno prostático específico (PSA) < 15 ng/ml, edad menor de 75 años. Los pacientes fueron aleatorizados en 4 grupos. El primero (A) quedó como control, el B recibió anestesia intracapsular (8 ml de lidocaína 2%), el C 5 mg de clorazepato dipotásico vía oral una hora antes y en el D se aplicaron las dos medidas (anestesia local y clorazepato). Se entregó un cuestionario con tres medidas de dolor (valorándolo de 0 a 10) tras el procedimento y otro 30 minutos después.
Resultados: Las medias del dolor fueron 5,17 (A), 1,72 (B), 2,43 (C) y 0,88 (D) en el primer cuestionario. En el segundo fueron 1,71, 0,25, 0,75 y 0,35, respectivamente. La comparación de medias realizada mediante el test de ANOVA pone de manifiesto diferencias significativas. Al comparar los grupos entre sí encontramos:
1. A frente a B: diferencia significativa en ambos cuestionarios (p 0,006 y 0,011).
2. A frente a C: no significación en el primer cuestionario (0,051) y sí en el segundo (0,012).
3. A frente a D: diferencia en ambos cuestionarios (0,001 y 0,010).
El uso de benzodiacepinas añadidas a la anestesia local (B frente a D) no mostró diferencias estadísticas en ambos cuestionarios (0,825 y 0,685).
Conclusión: Consideramos que el uso de benzodiacepinas no está justificado como método único de control del dolor para la realización de la biopsia prostática.

Introduction

Prostate cancer is currently the third leading cause of death from cancer in Spanish men, and is the tumor most commonly diagnosed in males[1].

Although many studies have attempted to identify valid markers for diagnosis of prostate cancer, pathological confirmation of diagnosis is still required. Prostate tissue samples are usually taken through an ultrasound-guided transrectal biopsy performed by an urologist.

There has been a constant increase in the number of prostate biopsies performed at urology departments since prostate-specific antigen (PSA) was introduced as a tumor marker, particularly in recent years because of the trend to request biopsy at lower PSA levels[2].

In addition, the traditional sextant biopsy scheme of Hodge appears to be inadequate for diagnosis and characterization of prostate tumors, and there is a current trend to calculate the number of samples to be taken based on prostate volume and patient age[3]. Anyway, even if the biopsy scheme is not planned this way, most centers take 10, 12, or even more cores because an increased cancer detection rate has been shown with such sampling schemes[4].

Ultrasound-guided transrectal biopsy is usually an outpatient procedure with a low complication rate. However, the increased number of prostatic punctures makes this test an uncomfortable and often poorly tolerated procedure. We therefore considered the possibility of using some analgesic technique that allows for using these extended schemes without increasing patient discomfort or complexity of the biopsy.

An ideal analgesic procedure would be one that achieves optimal pain control, is easy to perform, and does not increase the number of complications. European guidelines advise use of local prostatic anesthesia before biopsy because this is the procedure shown to be most effective for pain control, but do not specify the type of local anesthetic or how it should be administered[5].

The need to undergo a prostate biopsy causes some anxiety in patients because of both biopsy itself and the possibility that cancer is diagnosed, which contributes to increase discomfort during the test.

Objective

A prospective study was undertaken to assess the value of local prostate anesthesia for pain control, and also of administration of anxiolytics before ultrasound-guided transrectal biopsy is performed.

Materials and methods

A prospective, randomized, simple blind study was designed. To be enrolled into the study, patients had to be scheduled to undergo their first ultrasound-guided transrectal prostate biopsy, be younger than 75 years, and have PSA levels < 15 ng/mL.

Inclusion criteria were concomitant anorectal disease, chronic pelvic pain of other etiology, and current treatment with benzodiazepines.

Preparation for biopsy was the same in all patients and consisted of intravenous administration of metamizol magnesium 2 g 30 minutes before biopsy, a 250 mL cleansing enema administered two hours before biopsy, and antibiotic treatment with oral ciprofloxacin 500 mg every 12 hours for 4 days, starting the night before the procedure. A gel vial containing lidocaine hydrochloride (Cathejell®) was used as intrarectal lubricant.

Patients were allocated to 4 groups by block randomization. Group A was used as control and only received the abovementioned preparation. Group B received local prostate anesthesia consisting of 4 mL of 2% lidocaine administered by intracapsular injection on each prostate side, at the level of entry of the neurovascular bundle, using a transrectal ultrasound-guided 22 G Chiba needle (0.7 x 203 mm). Group C patients received clorazepate dipotassium 5 mg (Tranxilium®) orally one hour before biopsy. Group D received local prostate anesthesia and oral benzodiazepine.

Biopsy was performed in all groups using transrectal ultrasound guidance (Aloka SSD-1400 ultrasound system with 5 MHz rectal transducer) and a spring device with a 18 G puncture needle which takes 1.5 cm-long tissue samples, following a systematic 12-core sampling scheme (fig. 1).

At the end of biopsy, a questionnaire with three visual analog pain scales was provided and explained to patients, who completed them immediately. They were asked to answer another identical questionnaire 30 minutes after biopsy. These scales measure pain from 0 (no pain) to 10 (the worst pain ever experienced) (Fig. 2).

Patient age ranged from 58 and 75 years, with a mean age of 63.6 years (standard deviation [SD]: 5.8) in group A, 65.4 (SD: 6.3) years in group B, 64.3 years (SD: 7.2) in group C, and 63.5 years (SD: 6.7) in group D.

Mean PSA level in all 4 groups was 7.2 ng/mL (SD: 3.4), 6.9 ng/mL (SD: 3.2), 7.8 ng/mL (SD: 3.7), and 9.3 ng/mL (SD: 3.8) respectively (Table 1).

All patients were discharged after biopsy, and were subsequently followed up at outpatient clinics.

The Spanish version of SPSS 15.0 statistical software was used for data analysis. An ANOVA test was used to assess differences and a Student's t test was used for means comparison, and the p value was calculated using Bonferroni correction.

Results

One hundred and sixty patients were enrolled into the study from July 2007 to December 2008. Block randomization was performed in the order of study entry to form 4 groups of 40 patients each.

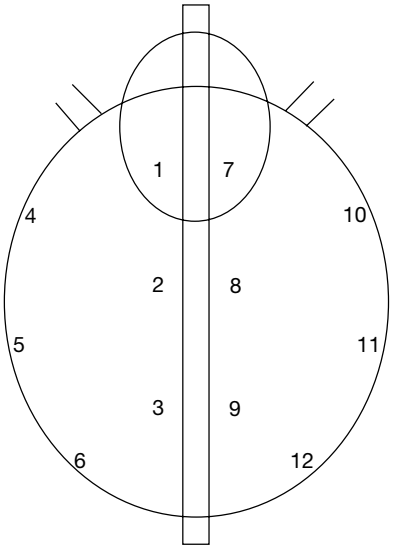

Figure 1 – Biopsy scheme.

All patients adequately completed both questionnaires and returned for the next visit.

Differences in mean age and PSA levels between the groups were not statistically significant.

No between-group differences were either seen in complications derived from biopsy. Eleven patients required care at the emergency room within 72 hours of biopsy (2 for acute urinary retention, 5 for rectal bleeding, 3 for hematuria, and 1 for sepsis). only one of them required hospital admission for intravenous antibiotic treatment of sepsis.

Pain assessment was performed by calculating for each patient the mean score in the three scales. Mean scores for pain perceived just after biopsy were 5.17 (SD: 2.48) in group A, 1.72 (SD: 1.27) in group B, 2.43 (SD: 1.76) in group C, and 0.88 (SD: 1.18) in group D. Lower mean scores were found in the questionnaire administered 30 minutes after biopsy: 1.71 (SD: 1.61), 0.25 (SD: 0.68), 0.75 (SD: 0.79), and 0.35 (SD: 0.79) for groups A, B, C, and D respectively (Table 2).

Data comparison using an ANOVA test showed statistically significant differences between the 4 groups in pain assessment in both questionnaires. Groups were compared to each other using a Student's t test, applying the Bonferroni correction. A value of $p < 0.0125$ was therefore required to consider a difference as statistically significant.

A statistically significant difference was found in pain perception between the control group (A) and the group given local anesthesia (B) both in the immediate assessment and 30 minutes after biopsy ($p = 0.006$ and $p = 0.011$ respectively). Statistically significant differences were also seen in both questionnaires ($p = 0.001$ and $p = 0.010$ in the first and second questionnaires respectively) between the control group and the group given local anesthetic and oral benzodiazepine (D). Differences between control group patients and patients who received benzodiazepine

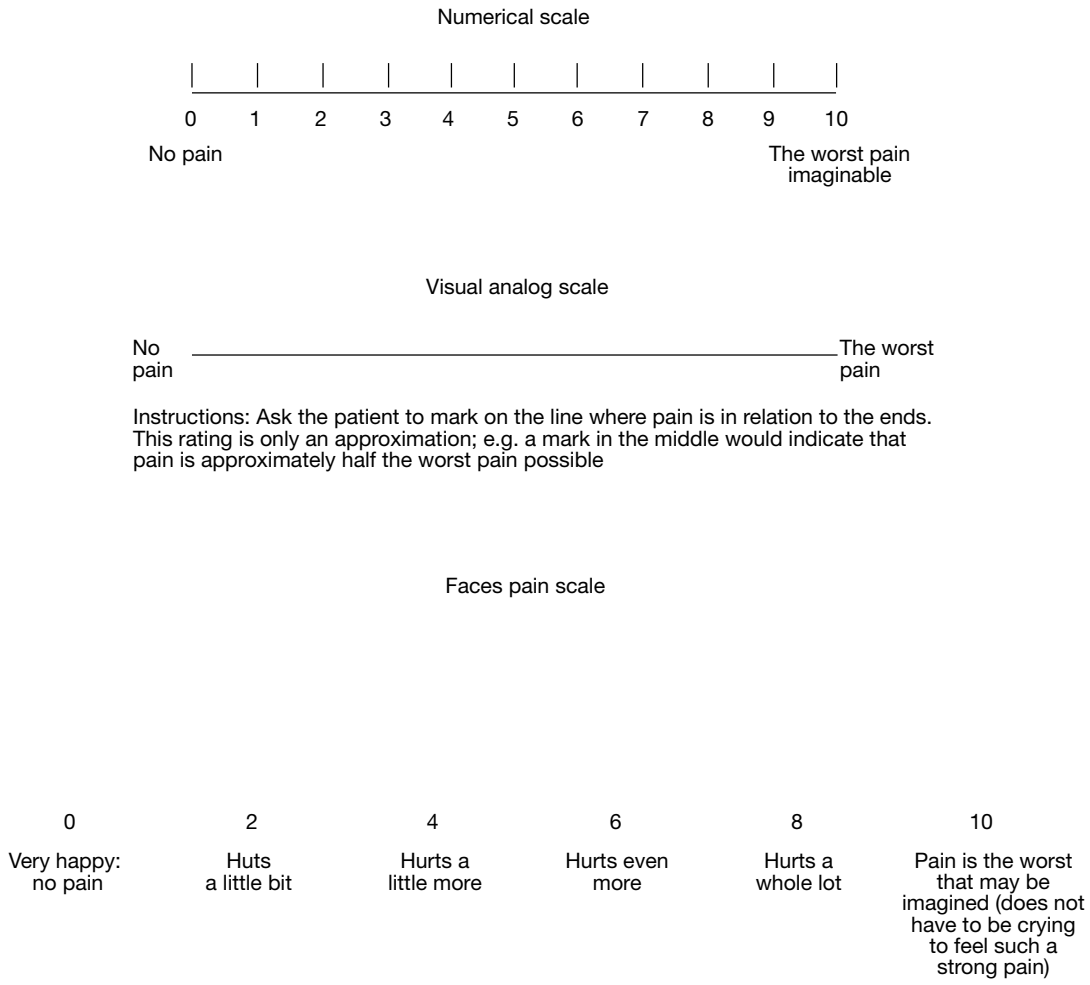

Figure 2 – Visual pain scales.

Table 1 – Age and prostate-specific antigen levels of patients

	Age (mean and SD)	PSA (mean and SD)
Group A	63.6 years (± 5.8)	7.2 ng/mL (± 3.4)
Group B	65.4 years (± 6.3)	6.9 ng/mL (± 3.2)
Group C	64.3 years (± 7.3)	7.8 ng/mL (± 3.7)
Group D	63.5 years (± 6.7)	9.3 ng/mL (± 3.8)

Table 2 – Results of pain questionnaires. P value obtained by comparison to the control group (A)

	First questionnaire		Second questionnaire	
	Mean (SD)	p	Mean (SD)	p
Group A	5.17 (2.48)	-	1.71 (1.61)	-
Group B	1.72 (1.27)	0.006	0.25 (0.68)	0.011
Group C	2.43 (1.76)	0.051	0.75 (0.79)	0.012
Group D	0.88 (1.18)	0.001	0.35 (0.79)	0.010

alone (C) were not significant just after biopsy (p = 0.051), but were significant in the second questionnaire (p = 0.012) (Table 2). No statistically significant differences were found in any of the questionnaires (p = 0.825 and p = 0.685 respectively) between the groups administered anesthesia (B) and anesthesia plus benzodiazepine (D).

Discussion

Ultrasound-guided transrectal prostate biopsy is the procedure of choice for diagnosing prostate cancer. The high number of patients performed PSA measurements and the current trend to request biopsy with lower PSA levels has led to a substantial increase in the number of patients who undergo biopsy. Because of this, we should constantly think about how diagnostic yield of biopsy may be improved and maximum comfort may be offered to the patient.

The traditional sextant biopsy scheme has become obsolete. Multiple studies have shown that the new schemes, in which more samples are taken (12, 18, or

even 12 cores), have an improved diagnostic yield[6,7]. The Vienna nomogram, for example, optimizes biopsy yield by calculating a number of samples ranging from 6 and 18 cores based on patient age and prostate volume[3]. An increased number of prostate punctures increases pain, which causes biopsy not to be as well tolerated as it was some decades ago. In addition, it not uncommon that patients with an initial negative result have to undergo another biopsy, and many of them may be reluctant to the test because they remember it as a painful experience[8]. This is why the need has arisen in recent years to decrease the pain associated to prostate biopsy.

At our department, we use a systematic 12-core scheme in the first biopsy, and increase the number of samples in the second and third biopsies (to 18 and at least 24 samples respectively). Because of this, one of the inclusion criteria for our study was that the biopsy was the first to be undergone by the patient, so that pain was always assessed on 12 prostate punctures. Also for group homogeneity, only patients with PSA levels less than 15 ng/mL were enrolled, because patients exceeding this cut-off point are subject to seminal vesicle biopsy. Patients with chronic pelvic pain or anorectal disease were excluded, so that pain experienced could only be attributed to the biopsy. Patients on prior benzodiazepine treatment were also excluded because one of the study arms was to receive a drug of the benzodiazepine class.

Both an intravenous analgesic (metamizole magnesium) and an intrarectal lubricant gel containing lidocaine were used as preparation in all our patients, including those in the control group. Use of intravenous analgesics as the only method to prevent pain currently appears to be inadequate, as their efficacy is lower than that shown in randomized studies by other more recent procedures[9]. The same applies to use of intrarectal lidocaine gel[10]. Some authors think that this helps relieve pain associated to insertion of the ultrasound transducer into the rectum[11], but some prospective, randomized studies found no differences when lidocaine gel was compared to a rectal lubricant with no anesthetic[12,13]. We used a lidocaine gel in all patients because our study was intended to assess pain control achieved during prostate punctures, rather than during transducer insertion or ultrasonography itself.

In recent years, there has been a trend in a great number of hospitals to try and achieve pain control by injecting local anesthetics. This is the method currently recommended by the European guidelines[5].

The original technique, initially described by Nash, consists of prostatic nerve block by injecting a local anesthetic into the periprostatic tissue under transrectal ultrasound guidance[14]. This method has been modified by many authors changing both the type of anesthetic used and its injection site. In any of its variants, this method has been shown to be superior to topical and intravenous anesthetics in many studies[15]. It has also been shown to provide a better pain control as compared to other more complex anesthesia procedures, such as caudal block or use of inhaled anesthetic agents, with the added advantages of being faster and involving a lower risk of complications[16,17].

We decided to use lidocaine in our study because of its faster action, even at the expense of losing the longer duration of anesthesia provided by other drugs. Since pain induced by biopsy is attributed to the prostate puncture, we thought it more desirable that the drug used had a fast onset of action, as we considered more important not to prolong test duration, rather than a longer or shorter anesthetic action. As regards injection technique, intracapsular administration was selected because it is a method that is easy to learn, simple, and effective.

Some authors advocate use of lidocaine for periprostatic block, while others use bupivacaine. There are also some studies reporting combined use of two anesthetics (lidocaine plus bupivacaine)[18]. Many studies are available comparing different anesthetic injection sites. Some authors perform bilateral injections in the prostato-seminal angle[19], while others have also compared the efficacy of apical versus basal injections[20-22]. Still other authors prefer intracapsular anesthetic injection[23]. In any case, there are many studies designed to assess the best blocking technique and reporting highly variable results. Most studies do show the superiority of prostatic block over other modalities of analgesia or placebo for pain control (Table 3).

Analysis of our results showed statistically significant differences in pain assessment between the control group and the group receiving local anesthesia, thus supporting the results reported by other authors. Significant differences were also found between the control group and the group given both local anesthesia and a benzodiazepine. Since these differences could be attributed to any of the two agents used, the group administered local anesthesia alone was compared to the one receiving both local anesthesia and the benzodiazepine, and no significant difference was found between both groups. It was therefore assumed that the difference found between the group given anesthesia plus an anxiolytic drug and the control group should be attributed to the local anesthetic. Lower pain scores were seen in the group given the benzodiazepine alone, as compared to the control group, in both the first and second questionnaires, but the difference was only significant in the second questionnaire. Thus, benzodiazepine use does not appear to decrease pain during biopsy. Use of anxiolytics before transrectal biopsy for analgesic purposes should thus be dismissed, since our results appear to suggest that patients feel the greatest discomfort at the time of prostate punctures, which is when we want to decrease pain perception. However, we do not rule out prior use of benzodiazepines to decrease anxiety potentially associated to biopsy performance.

The need to undergo a test for the first time, performance of transrectal ultrasound, and the possibility of cancer diagnosis are three factors causing anticipatory anxiety in patients scheduled for biopsy[24]. This anxiety state before invasive diagnostic procedures or outpatient minor surgery has been widely studied in other specialties (anesthesia, orthopedic surgery, ophthalmology, gynecology,...), and the most adequate treatment to control it has been assessed in most cases[25]. Use of benzodiazepines as premedication is commonly accepted in such cases because they are the

Table 3 – Studies on prostatic local anesthesia

Author (reference)	Study	Group 1	Group 2	Group 3	n	Statistical significance
Rabets JC et al[19]	Prospective, randomized	Bupivacaine, bilateral prostato-semina angle	Bupivacaine/ lidocaine (1:1), bilateral prostato-seminal angle	Control	75	Yes (bupivacaine alone)
Lee HY et al[23]	Prospective, randomize, double-blind	Intraprostatic lidocaine, periprostatic physiological saline	Periprostatic idocaine, intraprostatic lphysiological saline	Intra- and periprostatic lidocaine	152	Yes (combination)
Akan H et al[20]	Prospective, randomized	Lidocaine, bilateral basal	Lidocaine, single apical injection	-	117	No
Lee-Elliot CE et al[17]	Prospective, randomized	Lidocaine, periprostatic	Lidocaine/ bupivacaine (1:1), periprostatic	-	300	Yes (combination)
Nguyen CT et al[21]	Prospective, randomize, simple-blind	Lidocaine, bilateral apical	Lidocaine, bilateral basal	-	143	Yes (apical)
Philip J et al[22]	Prospective, randomize, simple-blind	Lidocaine, bilateral apical	Lidocaine, bilateral basal	-	143	No

anxiolytics indicated for treating anxiety symptoms not reaching a psychiatric dimension that may occur in daily psychopathology. Various prospective studies controlled with placebo or with other drugs as premedication have been conducted and have reported that benzodiazepines achieved a better reduction of anxiety[26]. There is also a study conducted in patients scheduled to undergo tooth surgery which assessed whether patients in whom preoperative anxiety has been more effectively controlled had less postoperative pain. Its results, however, did not demonstrate this hypothesis[27]. The purpose of our study was to assess whether prior benzodiazepine use would counteract the influence of anxiety on pain perception and assessment by our patients. We also thought that the muscle-relaxant effect of benzodiazepines could perhaps contribute to decrease the discomfort associated to insertion of the transducer into the rectum and such decrease could be reflected in overall pain assessment. Clorazepate dipotassium (Tranxilium®) was selected because it is a bendodiazepine already tested in anxiety states related to surgical procedures with good results[28.29]. It is also a drug with a very good oral bioavailability that reaches peak plasma levels in a short time (one hour). It may therefore be easily administered at the hospital upon patient arrival.

Not all patients have the same sensitivity to pain. Age distribution in our 4 study groups was homogeneous. We did not therefore consider analysis of results by age ranges, although some authors have found age differences in pain perception, with younger patients showing the worst tolerance to biopsy[30]. Multiple studies have also been conducted in an attempt to find which risk factors may identify patients who will tolerate worse biopsy-related pain, as these will theoretically be the patients most benefitting from use of anesthetic procedures[31,32]. Based on the results of our study, we think that this prior assessment of patients is unnecessary, because the anesthetic technique used does not excessively increase examination time or causes greater morbidity, and may therefore be widely used.

Few biopsy complications were recorded in our patients, the most common of which was rectal bleeding. A single patient experienced a major complication (sepsis) that required hospital admission for treatment. Safety of the periprostatic block technique was already reported in other studies conducted to assess the incidence of rectal bleeding after biopsy[33], or in studies to assess pain control which also include morbidity data[34,35].

Conclusion

Based on the results of this study, intracapsular lidocaine injection should be considered as a valid and highly effective procedure to control pain associated to ultrasound-guided transrectal prostate biopsy. Such procedure does not increase the technical complexity of biopsy nor appears to increase its morbidity, and may therefore be widely used as it allows for taking a greater number of samples. Prior administration of anxiolytics will only be aimed at decreasing the anticipatory anxiety state associated to performance of the test, but should not be considered effective as the only pain control method.

REFERENCES

1. Instituto de Salud Carlos III. Centro Nacional de Epidemiología. Datos epidemiología ambiental y cáncer; 2006.
2. Schröder FH, Van der Cruijsen-Koeter I, de Koning HJ, Vis AN, Hoedemaeker RF, Kranse R. Prostate cancer detection at low prostate specific antigen. J Urol. 2000;163(3):806-12.
3. Djavan B. Prostate biopsies and the Vienna nomograms. Eur Urol. 2006 Suppl 5:500-10.
4. Presti JC. Prostate biopsy: current status and limitations. Rev Urol. 2007;9(3):93-8.
5. Van Knobloch R, Weber J, Varga Z, Feiber H, Heidenreich A, Hoffman R. Bilateral fine-needle admininteredlocal anaesthètic nerve block for pain control during TRus-guided multi-core prostate biopsy: a prospective randomined trial, Eur Urol. 2002;41(5):508-14.
6. Stamatiou K, Alevizos A, Karanasiou V, Mariolis A, Mihas C, Papathanasiou M, et al. Impact of additional sampling in the TRUS-guided biopsy for the diagnosis of prostate cancer. Urol Int. 2007;78(4):313-7.
7. Guichard G, Larré S, Gallina A, Lazar A, Faucon H, Chemama S, et al. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1,000 consecutive patients. Eur Urol. 2007; 52(2):430-5.
8. Irani J, Fournier F, Bon D, Gremmo E, Dore B, Aubert J. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. Br J Urol. 1997;79(4):608-10.
9. Öbeck C, Özkan B, Tunc B, Can G, Yalcin V, Solok V. Comparison of 3 different methods of anesthesia befote transrectal prostate biopsy: a prospective randomized trial. J Urol. 2004;172(2):502-5.
10. Rodríguez A, Kyriakou G, Leray E, Lobel B, Guillé F. Prospective study comparing two methods of anaesthesia for prostate biopsies: apex periprostatic nerve block versus intrarectal lidocaine gel: review of the literature. Eur Urol. 2003;44:195-200.
11. Yun TJ, Lee HJ, Kim SH, Lee SE, Cho JY, Seong CK. Does the intrarectal instillation of lidocaine gel before periprostatic neurovascular bundle block during transrectal ultrasound guided prostate biopsias improve analgesic efficacy? A prospective, randomized trial. J Urol. 2007;178(1):103-6.
12. Adamakis I, Mitropoulos D, Haritopoulos K, Alamanis C, Stravodimos K, Giannopoulos A. Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocaine cream. World J Urol. 2004;22(4):281-4.
13. Desgrandchamps F, Meria P, Irani J, Desgrippes A, Teilllac P, Le Duc A. The rectal administration of lidocaine gel and tolerante of transrectal ultrasonography-guided biopsy of the prostate: a prospective randomized placebo-controlled study. BJU Int. 1999;83:1007-9.
14. Nash PA, Bruce JE, Indudhara R, Shinohara K. Transrectal ultrasound guided prostatic nerve blockade eases systematic needle biopsy of the prostate. J Urol. 1996;155(2):607-9.
15. Seymour H, Perry MJ, Lee-Elliot C, Dundas D, Patel U. Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. BJU Int. 2001;88(6):540-4.
16. Horinaga M, Nakashima J, Nakanoma T. Efficacy compared between caudal block and periprostatic local anestesia for transrectal ultrasound-guided prostate needle biospy. Urology. 2006;68(2):348-51.
17. Massod J, Shah N, Lane T. Nitrous oxide (entonox) inhalation and tolerance of transrectal ultrasound guided prostate biopsy: a double-blind randomized controlled study. J Urol. 2002;168(1):116-20.
18. Lee-Elliott CE, Dundas D, Patel U. Randomized trial of lidocaine vs lidocaine/bupivacaine periprostatic injection on longitudinal pain scores after prostate biopsy. J Urol. 2004;171(1):247-50.
19. Rabets JC, Jones JS, Patel AR, Zippe CD. Bupivacaine provides rapid, effective periprostatic anaesthesia for transrectal prostate biopsy. BJU Int. 2004;93(9):1216-7.
20. Akan H, Yildiz Ö, Dalva I, Yücesoy C. Comparision of two periprostatic nerve blockade techniques for transrectal ultrasound-guided prostate biopsy: bilateral basal injection and single apical injection. Urology. 2009;73(1):23-6.
21. Nguyen CT, Jones JS. Comparison of traditional basal and apical periprostatic block: impact on injection pain and biopsy pain. BJU Int. 2006;99(3):575-8.
22. Philip J, McCabe JE, Roy SD, Samsudin A, Campbell M, Javle P. Site of local anaesthesia in transrectal ultrasonography-guided 12-core prostate biopsy: does it make a difference? BJU Int. 2006;97(2):263-5.
23. Lee HY, Lee HJ, Byun SS, Lee SE, Hong SK, Kim SH. Effect of intraprostatic local anesthesia during transrectal ultrasound guided prostate biopsy: comparison of 3 methods in a randomized, double-blind, placebo controlled trial. J Urol. 2007;178(2):469-72.
24. Collins GN, Lloyd SN, Hehir M, McKelvie GB. Multiple transrectal ultrasound-guided prostatic biopsies--true morbidity and patient acceptance. Br J Urol. 1993;71(4): 460-3.
25. VanVlymen JM, Rego S, White PF. Benzodiazepine premedication: can it improve outcome in patients undergoing breast biopsy procedures? Anesthesiology. 1999;90(3):740-7.
26. Kretz FJ, Gonzales I, Peidersky P. Oral premedication with clorazepate dipotassium. Comparision with oral premedication with flunitrazepam and intramuscular premedication with promethazine, pethidine and atropine in adults. Anaesthesist. 1993;42(1):15-22.
27. Tolksdorf W, Siefert S, Schmitt W. The influence of premedication with dipotassium chlorazepate on preoperative stress and postoperative pain. Anaesthesist. 1990;39(1):1-5.
28. Meybohm P, Hanss R, Bein B, Schaper C, Buttqereit B, Scholz J, et al. Comparision of premedication regimes. A randomized controlled trial. Anaesthesist. 2007;56(9):890-2, 894-6.
29. Mielke L, Breinbauer B, Schubert M, Kling M, Entholzner E, Hargasser S, et al. Comparision of the effectiveness of orally administered clorazepate dipotassium and nordiazepam on preoperative anxiety. Anaesthesiol Reanim. 1995;20(6):144-8.
30. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol. 2001;166(3):856-60.
31. Soyupek S, Bozlu M, Armagan A, Özorak A, Perk H. Does experimental pain assessment before biopsy predict for pain during transrectal ultrasound-guided prostate biopsy? Urology. 2007;70(4):681-4.
32. Bastide C, Lechevallier E, Eghazarian C, Ortega JC, Coulange C. Tolerance of pain during transrectal ultrasound-guided biopsy of the prostate: risk factors. Prostate Cancer Prostatic Dis. 2003;6:239-41.
33. Khurshid RG, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day

morbidity after a six-, eight- and 12-core biopsy protocol. BJU Int. 2004;94:1014-20.
34. Addla SK, Adeyoju AA, Wemyss-Holden GD, Neilson D. Local anaesthetic for transrectal ultrasound-guided prostate biopsy: a prospective, randomized, double blind, placebo-controlled study. Eur Urol. 2003;43(5):441-3.
35. Obek C, Onal B, Ozkan B, Onder A, Yalçin V, Solok V. Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. J Urol. 2002;168(2):558-61.