

Meperidine relieves pain during transrectal ultrasound-guided prostate biopsy

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ABSTRACT

الأهداف: لمقارنة فعالية وسلامة الحقن العضلي الميبيريدين مع محيط البروستاتة إحصار العصب (PNB) خلال خزعة البروستاتا تسترشد الموجات فوق الصوتية عبر المستقيم.

الطريقة: أجريت هذه الدراسة في الفترة من يوليو 2010م إلى يونيو 2012م في مستشفى التابع الأول للجامعة فوجيان الطبية، فوتشو، فوجيان، الصين. هذه الدراسة العشوائية والمزدوجة التعمية المضبوطة اشتملت 186 مريضاً. هؤلاء المرضى تم تعيينهم بشكل عشوائياً إلى 3 مجموعات علاجية: PNB عن طريق حقنة لمدة 10 دقائق عبر خزعة البروستاتا، الحقن العضلي الميبيريدين أعطيت قبل 30 دقيقة من الخزعة، ومجموعة الشاهد (لكل منهما، n=62). في وقت إدراج الموجات فوق الصوتية، خلال الخزعة وبعد 30 دقيقة من الخزعة فمستويات الألم لتدرج المرضى هي 10 نقاط من مقياس النظير البصري (VAS).

النتائج: لم يكن هناك فروق إحصائية في المظاهر السريرية للمجموعات 3. فالمرضى الذين أعطوا الميبيريدين كان لديهم المعدل الأدنى من درجة VAS خلال إدراج المسبار. خلال خزعة البروستاتا، لم يكن هناك اختلاف كبير في درجات VAS بين مرضى PNB ومجموعات الميبيريدين، وكلاهما كان أقل بكثير من مجموعة الشاهد. سجلت درجات VAS 30 دقيقة بعد الخزعة وكانت مشابهة للمجموعات 3.

الخاتمة: الحقن العضلي الميبيريدين هو مسكن آمن وفعال لاستخدامه خلال خزعة البروستاتا عبر المستقيم الموجهة بالأمواج فوق الصوتية، وهو يخفف الألم بشكل أفضل من PNB خلال إدراج المسبار.

Objective: To compare the efficacy and safety of intramuscular meperidine injection with periprostatic nerve block (PNB) during transrectal ultrasound-guided prostate biopsy.

Methods: This study was carried out from July 2010 to June 2012 at the First Affiliated Hospital of

Fujian Medical University, Fuzhou, Fujian, China. This controlled, double-blinded, randomized study included 186 patients. These patients were randomly assigned to 3 treatment groups: PNB by injection 10 minutes prior to the prostate biopsy; intramuscular meperidine injection administered 30 minutes before the biopsy, and a control group (n = 62, each). At the time of ultrasound probe insertion, during biopsy, and 30 minutes after biopsy, patients graded their level of pain on a 10-point visual analog scale (VAS).

Results: There was no statistical difference in clinical features of the 3 groups. The patients administered meperidine had the minimum mean VAS score during probe insertion. During the prostate biopsy, there was no significant difference in VAS scores between patients in the PNB and meperidine groups, and both were significantly lower than that of the control group. The VAS scores recorded 30 minutes after biopsy were similar among the 3 groups.

Conclusion: Intramuscular meperidine injection is a safe and effective analgesic for use during transrectal ultrasound-guided prostate biopsy, and provides better analgesia than PNB during the probe insertion.

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Transrectal ultrasound (TRUS)-guided needle biopsy of the prostate is the standard procedure for diagnosing prostate cancer.¹ Although prostate biopsy is commonly performed as an office procedure with no anesthesia, many patients experience mild discomfort to severe pain.^{2,3} Various methods of controlling pain during prostate biopsy have been described. The most widely used is periprostatic nerve block (PNB) with lidocaine, which is simple, safe, easy to perform, and highly effective.^{1,3,4} However, PNB alone has little effect on pain during probe insertion or the initial rectal wall puncture.⁴⁻⁷ In order to reduce the pain of the probe insertion and the initial rectal wall puncture, a systemic analgesic may be required. Meperidine is a synthetic opioid commonly used for providing relief of moderate to severe acute pain.⁸ Some authors recently reported the use of meperidine to provide analgesia during TRUS-guided prostate biopsies.^{9,10} We hypothesized that intramuscular meperidine might provide better analgesia than PNB during TRUS-guided prostate biopsy during probe insertion or the initial rectal wall puncture to improve patients' satisfaction. We compared the 2 analgesic modalities in a controlled, double-blinded, randomized study to determine the easier and more appropriate method for use in patients undergoing TRUS-guided prostate needle biopsy.

Methods. Patients. This study was carried out at the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, People's Republic of China. During a 2-year period from July 2010 to June 2012 at our institution, 354 consecutive patients suspected of having prostate cancer underwent TRUS-guided prostate

biopsy. The indications for biopsy were abnormal digital rectal examination, elevated prostate-specific antigen (PSA) level (>4.0 ng/mL), or both. The age, weight, PSA level, prostate volume, family history of prostate cancer, and abnormal digital rectal examination were recorded. A detailed medical history including demographic data and clinical status were documented.

Enrollment and randomization. A PubMed search was performed using keywords "prostate biopsy," "pain," "meperidine" to find prior related research. The Ethics Committee of the First Affiliated Hospital of Fujian Medical University (No. 2009077) approved this trial. Patients provided informed consent in writing one day before biopsy after careful explanation of the procedure and goals of the study by the surgeon. The study was carried out according to principles of the Helsinki Declaration. All of the patients were randomly divided into 3 groups, according to computer-generated random numbers. Sequentially numbered sealed envelopes with information disclosing the type of treatment to be applied were used to decide the treatment of the patient. The first patient was enrolled in July 2010, and the study was terminated in June 2012. Included in the study were 186 patients, and 168 patients were excluded. Patients were excluded if they had chronic prostatitis/pelvic pain syndrome, coagulation disorders, concomitant use of analgesics, previous allergy to lidocaine, a history of prostate biopsy, presence of urinary tract infection, or any anal pathology that could exacerbate pain such as anal stricture, anal fissure, or hemorrhoidal disease. The 186 patients were randomly assigned to 3 groups (Figure 1), and all patients were blinded to the treatment group assignment. All patients also received intramuscular

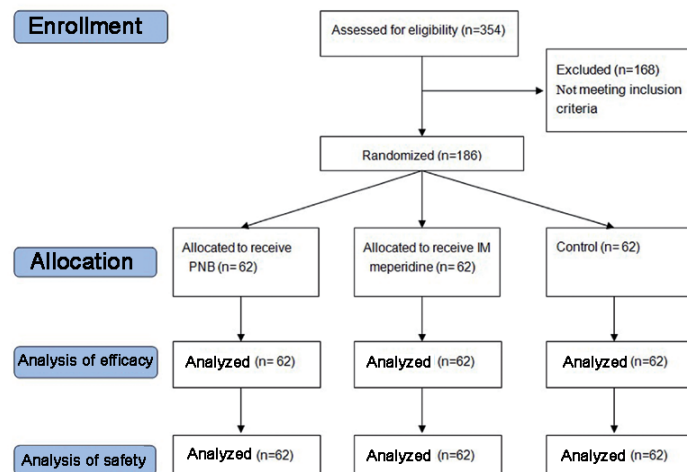


Figure 1 - Consolidated standard of reporting trials flow diagram of study participants. PNB - periprostatic nerve block, IM - intramuscular

injection, 30 minutes prior to the prostate biopsy. The meperidine treatment group received an intramuscular injection of one mg/kg meperidine hydrochloride, and other groups received an intramuscular injection of one ml normal saline. In all groups, 20 mL of lubricating hydrophilic gel was applied intrarectally before the prostate biopsy. The main ingredient of the lubricating hydrophilic gel was polyethylene glycol.

Periprostatic nerve block was performed by infiltrating 5 mL of 2% lidocaine to the neurovascular bundle on each side (total of 10 mL) of the prostate, guided by ultrasound using an 18-cm 22-gauge spinal needle. The injection site was localized to the angle between the prostate and the seminal vesicles. Prostate biopsy was performed 10 minutes after nerve blockade.

Biopsy procedure. Patients were instructed to take levofloxacin 500 mg/day for 5 days, starting the evening before the procedure, and to self-administer a cleaning enema in the evening before the procedure. An 18-gauge and 20-cm biopsy needle loaded in a spring-action automatic biopsy device was used. All patients underwent a 12-core biopsy protocol, including 6 parasagittally- and 6 laterally-targeted cores covering the base, mid zones, and apex. The patients were placed in the left lateral decubitus position with knees, and hips flexed. The procedure was performed using an ultrasound machine with a 7.5-MHz TRUS probe (TechnosMPX DU 8, Esaote, Italy). Before the biopsy, the total volume of the prostate was measured (for all treatment groups) with standardized three-dimensional measurements computed by the ultrasound machine. Each procedure was performed in the same way, to ensure that the groups were as homogeneous as possible.

Pain and complication assessment. All patients were hospitalized in a one-day surgery center and

observed for 2 hours after the procedure. An assistant nurse, blinded to the patients' group allocation, asked the patients to complete a questionnaire after the procedure. Pain assessments were carried out using a linear, 10-point visual analog pain scale (VAS) with 0 indicating no pain, and 10 representing unbearable pain and discomfort. Separate VAS scores were recorded during the probe insertion, biopsy procedure, and 30 minutes after the procedure. The patients also answered whether they would be willing to return for another procedure if necessary. The secondary outcome variables were biopsy-related complications and the rate of prostate cancer detection. All patients were asked to report the extent of dizziness, nausea, or vomiting after the procedure. Complications were defined as events requiring active treatment. These included allergic reaction, severe hematuria, and rectal bleeding requiring hospitalization, acute urinary retention, fever greater than 39°C, and hypotension or lipothymia requiring intravenous therapy. Self-limiting hematuria, rectal bleeding, and hematospermia were considered expected side effects, and thus not recorded.

Statistical analysis. Calculation of the sample size was based on data from a previous pilot study of 50 patients treated with PNB. A minimum one-point difference in the 10-point VAS score is generally considered clinically significant when scores are assigned by patients.^{6,11,12} It was determined that 62 patients would need to be enrolled in each study arm to detect a decrease in the VAS pain score of 1.0 at a standard deviation of 1.7, a significance of 5%, and a power of 90%. Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0. Numerical data that were normally distributed are represented as the mean \pm standard deviation, and the differences

Table 1 - The clinical and demographic characteristics of patients in the 3 transrectal-guided needle biopsy of the prostate treatment groups in a study conducted at the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, People's Republic of China.

Variable	PNB	Meperidine	Control	P-value
Patients, n	62	62	62	-
Age (years)	68.7 \pm 9.3	67.1 \pm 7.4	67.5 \pm 8.3	0.511
Prostate-specific antigen (ng/mL)	11.4 \pm 6.1	11.3 \pm 7.4	11.8 \pm 8.6	0.923
Prostate volume (mL)	66.4 \pm 18.7	66.5 \pm 19.6	67.0 \pm 20.0	0.982
Family history of prostate cancer, n (%)	3 (4.8)	4 (6.5)	3 (4.8)	1.000
Abnormal digital rectal examination, n (%)	21 (33.8)	25 (40.3)	19 (30.6)	0.516
Cancer detection, n (%)	18 (29.0)	22 (35.5)	17 (27.4)	0.588

PNB - periprostatic nerve block

Table 2 - Pain scores at different phases of the procedure and positive responses in the 3 transrectal-guided needle biopsy of the prostate treatment groups in a study conducted at the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, People's Republic of China.

Variable	PNB	Meperidine	Control	P-value
VAS, during probe insertion	3.61 ± 2.17	2.55 ± 2.04	3.51 ± 2.07	0.009 ^a , 0.005 ^b , 0.797 ^c , 0.011 ^d
VAS, during biopsy	3.66 ± 1.89	3.08 ± 1.97	5.81 ± 2.08	<0.001 ^a , 0.105 ^b , <0.001 ^c , <0.001 ^d
VAS, 30 min after biopsy	1.21 ± 0.94	1.18 ± 0.82	1.32 ± 0.81	0.614 ^a
Positive responses to rebiopsy, n (%)	51 (82.2)	59 (95.2)	32 (51.6)	<0.001 ^a , 0.044 ^b , 0.001 ^c , <0.001 ^d

^aPNB compared with meperidine compared with control, ^bPNB compared with meperidine, ^cPNB compared with control; ^dMeperidine compared with control, PNB - periprostatic nerve block, VAS- visual analog pain scale

Table 3 - Complications requiring active treatment in the 3 transrectal-guided needle biopsy groups in a study conducted at the First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, People's Republic of China.*

Variable	PNB	Meperidine n (%)	Control
Acute urinary retention	0 (1.6)	1 (1.6)	2 (3.2)
Persistent hematuria	1 (1.6)	0 (0.0)	0 (0.0)
Fever up to 39 °C	2 (3.2)	1 (1.6)	2 (3.2)
Severe rectal bleeding	1 (1.6)	1 (1.6)	0 (0.0)
Total	4 (6.5)	3 (4.8)	4 (6.5)

*P-value = 1.000 for all comparisons, PNB - periprostatic nerve block

between the groups at different observation times were evaluated by ANOVA followed by a post-hoc least significant difference comparison test to show which group differed from others. Non-parametric numerical data were expressed as the median and range (minimum and maximum) and were analyzed using the Kruskal-Wallis test. Pearson's chi-squared test and Fisher's exact test was used to compare categorical data. Statistical significance was set at $p < 0.05$, and all p -values were two-tailed.

Results. There were no significant differences among the 3 treatment groups (PNB, meperidine, and control) with respect to age, PSA level, prostate volume, family history of prostate cancer, abnormal digital rectal examination, or the prostate cancer detection rate (Table 1). During probe insertion, patients who received meperidine reported the minimum mean VAS score. This was significantly lower than the scores of the PNB and control groups. During the prostate biopsy, the VAS pain score was similar in the PNB and meperidine groups, and both were significantly lower than that of the control group. Thirty minutes after the biopsy, there

were no significant differences in VAS scores among the 3 groups. Fifty-nine (95.2%) patients in the meperidine group were willing to undergo biopsy again under the same conditions, compared with 51 (82.2%) patients in the PNB group, and 32 (51.6%) in the control group (Table 2). No major adverse events related to anesthesia were observed in any of the treatment groups, and there were no other major complications (Table 3). Mild side effects occurred in ~5% of the patients in the meperidine group, including dizziness, nausea, vomiting, and drowsiness. These changes were transient and did not require any intervention. A total of 5 patients in the 3 groups developed fever ($>39^{\circ}\text{C}$) and were treated with intravenous antibiotics. Hematuria and rectal bleeding that required hospitalization was observed in 2 of the PNB group, one patient in the meperidine group, and no patients in the control group. Complications requiring active treatment were not significantly different among the 3 groups.

Discussion. The main findings in the present study were that intramuscular injection of meperidine was more effective than PNB in controlling pain associated

with transrectal prostate biopsy, in particular the probe insertion. It also increased patients' willingness to undergo the procedure again if indicated.

Many studies have shown PNB to be the preferred method and gold standard for pain relief during the procedure.^{1,3,4,13} However, the pathophysiology of pain accompanying prostate biopsy is not completely understood. Pain during prostate biopsy is due to the insertion and manipulation of the TRUS probe into the rectum, as well as the needle puncture into the prostate capsule. The nerve supply of the prostate is autonomic and originates from the inferior hypogastric plexus. The nerves pass along the plane between the prostatic capsule and rectum. The pain associated with prostate biopsy is thought to be due to direct contact of the biopsy needle with these nerves within the stroma and the prostatic capsule.^{3,14-16} Therefore, PNB does not completely eliminate pain that originates from inserting a transrectal probe or the initial rectal wall puncture.^{4-7,12,17-19} Some drugs are used to reduce the pain caused by inserting the transrectal probe. Jindal et al^{15,16} found that diltiazem or nitroglycerine can relax the anal sphincter, and the pain at the insertion of the rectal probe is significantly decreased by application of either diltiazem or nitroglycerine. McCabe et al¹⁴ reported that topical glyceroltrinitrate (GTN) ointment can reduce the discomfort associated with TRUS-guided biopsy of the prostate, in particular during the insertion of the ultrasound probe.

During many invasive diagnostic procedures, the simultaneous use of a sedative or analgesia improves patient cooperation and the quality of the examination.²⁰⁻²² The study of Awsree et al²³ addressed the use of propofol for sedation during prostate biopsy. The authors concluded that sedation can significantly reduce patients' pain and make prostate biopsy a more acceptable experience for the patient. Meperidine is a synthetic opioid that provides analgesia and sedation for most moderate-to-severe pain syndromes.⁸ In a prospective randomized study, Lujan et al⁹ compared the efficacy of intravenous analgesia with meperidine to that of periprostatic plexus infiltration with lidocaine. They concluded that periprostatic plexus block with lidocaine does not have the advantages of meperidine. In another study, Tobias-Machado et al¹⁰ reported that a combination of meperidine and midazolam was beneficial in significantly reducing pain during prostate biopsy. The pethidine was administered by an intravenous route in the 2 studies, and the patients required monitoring to minimize cardiorespiratory events. In the present study, meperidine was injected intramuscularly instead of intravenously.

The patients in our treatment groups underwent the procedure safely without serious adverse effects. Adverse side effects occurred in approximately 5% of the patients in the meperidine group, and included dizziness, nausea, vomiting, and drowsiness. These effects were transient and self-limited, and did not require any intervention. The patients required bed rest for an average of 30 minutes longer. The low rate and mildness of adverse side effects may be due to low dosing and intramuscular injection of the drugs. The patients were fully awake during the biopsy procedure and did not require monitoring or assistance from the anesthesiologist.

There have been several studies regarding the correlation between patient's pre-procedural anxiety and pain perceptions during various radiological interventions. Patient anxiety is an important consideration in invasive interventions and has been shown to intensify acute pain. It has also been shown that patients who are soon to undergo prostate biopsy experience high anxiety levels.^{24,25} The alleviation of anxiety by meperidine can enhance its analgesic effect and make prostate biopsy a more satisfactory experience for the patient.

This study had certain limitations. Firstly, although the VAS is commonly used to assess pain, its accuracy and repeat validity have occasionally been questioned.²⁶ The VAS at different stages of the procedure was evaluated retrospectively and all patients were asked to grade their pain after the whole procedure. In this way the potential pitfall of recall bias (recalling the most painful part of the procedure, and not giving absolute value to the others) is circumvented.^{27,28} Secondly, the sample size is small and based on results from a single center. A large sample, multi-center, randomized study will be required to evaluate the most appropriate anesthesia method to control pain during prostate biopsy. Thirdly, the use of a combination of intramuscular meperidine and PNB may produce the best analgesia, but this combination was not tested in the present study.

In conclusion, our study shows that intramuscular meperidine injection is an easy, safe, and effective method to provide analgesia during TRUS prostate biopsy, and better analgesia than PNB during the probe insertion.

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