Title	Intrarectal administration of lidocaine gel versus plain lubricant gel for pain control during transrectal ultrasound-guided extensive 10-core prostate biopsy in Hong Kong Chinese population: prospective double-blind randomised controlled trial
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Intrarectal administration of lidocaine gel versus plain lubricant gel for pain control during transrectal ultrasound-guided extensive 10-core prostate biopsy in Hong Kong Chinese population: prospective double-blind randomised controlled trial

以前瞻性雙盲隨機對照方式，試驗香港華籍人士在進行經直腸超聲波導引的前列腺活組織切除術時，使用含利多卡因的凝膠與純粹潤滑劑在止痛效用上的分別

Objective. To compare the level of pain experienced by patients during transrectal ultrasound-guided prostatic biopsy using intrarectal 2% lidocaine gel versus plain lubricant gel.

Design. Prospective double-blind randomised controlled trial.

Setting. Regional hospital, Hong Kong.

Patients. From March 2002 to December 2003, patients who underwent ultrasound-guided prostate biopsy at a Geriatric Urology Centre.

Main outcome measures. Pain and discomfort scores measured by horizontal visual analogue scales.

Results. A total of 338 consecutive patients were randomised to lidocaine gel or plain lubricant gel groups. The two groups were statistically similar in demographic and disease characteristics. There were no significant statistical differences in pain or discomfort score in the lidocaine gel and plain lubricant groups—pain score: 1.75 versus 1.79 (P=0.66) on day 0 and 0.21 versus 0.15 (P=0.97) on day 1; discomfort score: 0.79 versus 0.77 (P=0.86) on day 0 and 0.12 versus 0.12 (P=0.76) on day 1. No major complications were recorded in this cohort.

Conclusions. Transrectal ultrasound-guided trucut biopsy of the prostate can be safely performed with no anaesthesia in Chinese patients. Pain and discomfort are minimal. It was found that 2% lidocaine gel has no statistical therapeutic or analgesic benefit over plain lubricant gel.

目的：比較病人在進行經直腸超聲波導引前列腺活組織切除術時，在直腸內使用含2% 利多卡因凝膠或純粹潤滑劑，所經歷的痛楚程度的分別。

設計：前瞻性雙盲隨機對照試驗。

安排：地區醫院，香港。

患者：2002年3月至2003年12月期間，在一所老人泌尿科中心進行超聲波導引前列腺活組織切除術的病人。

主要結果測量：以水平視覺模擬度數，量度痛楚和不適的程度。

結果：共有338位連續的病人以隨機方式分為兩組，每組分別使用含利多卡因凝膠和純粹潤滑劑。兩組別在人口特徵和病徵上都很相近。兩組別的痛楚和不適指數亦沒有明顯的統計差別：痛楚程度方面，第0日是1.75比1.79（P=0.66），第1日是0.21比0.15（P=0.97）；不適程度方面，第0日是0.79比0.77（P=0.86），第1日是0.12比0.12（P=0.76）。這些病人都沒有嚴重併發症紀錄。

結論：華籍病人在無需麻醉的情況下，可安全進行經直腸超聲波導引前列腺活組織

Key words:
Anesthesia;
Lidocaine;
Pain measurement;
Prostatic neoplasms;
Ultrasonography, interventional

關鍵詞：
麻醉；
利多卡因；
痛楚量度；
前列腺腫瘤；
超聲描記術，治療性的

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切除術。痛楚和不適僅屬輕微。試驗亦顯示含 2% 利多卡因的凝膠並不比純粹潤滑劑有更大的治療和止痛作用。

Introduction

Transrectal ultrasound (TRUS)-guided needle biopsy of the prostate gland is considered a simple and accurate method by which prostatic tissue is obtained for histological evaluation.[1-3] It was estimated that 232 090 new cases of prostate cancer would be diagnosed in 2005[4] in the United States and TRUS-guided biopsy is the current diagnostic gold standard. With an average positive biopsy rate of 30%, more than 770 000 biopsies will be performed annually. In Hong Kong, 912 new cases of prostate cancer were diagnosed in 2002; prostate cancer was the fourth most common cancer in men.[5] Various forms of anaesthesia, including lidocaine nerve blockade,[6-8] intrarectal lidocaine gel,[9] and nitrous oxide inhalation,[10,11] have been reported to effectively decrease patient pain and discomfort during TRUS-guided prostate biopsy. Nonetheless, there is no consensus on optimum analgesia during the procedure. Many studies have not been prospective, measurement of pain has not been standardised or objective, and urologists have not been blinded to the type of anaesthesia used. In addition, previous experience of biopsy and cultural factors may affect patient perception of pain and discomfort. We evaluated the pain and discomfort levels associated with TRUS-guided prostate biopsy with intrarectal administration of 2% lidocaine gel versus plain lubricant gel alone in a prospective double-blind randomised controlled trial.

Methods

Patients

In this prospective study, patients at the Geriatric Urology Centre, Department of Surgery, University of Hong Kong Medical Centre, Tung Wah Hospital were enrolled between March 2002 and December 2003. The study population consisted of consecutive patients referred for urology advice because of a raised prostate-specific antigen (PSA) level on screening or lower urinary tract symptoms and raised PSA or abnormal digital rectal examination (DRE). All patients with PSA level of above 4 ng/mL or abnormal DRE were enrolled in the study. Patients were excluded from analysis if they had a history of previous biopsy, were non-Chinese, or were currently prescribed analgesia.

Study design

A clinical history was obtained from all patients. Following physical examination, patients were randomly assigned, by drawing a pre-sealed envelope, to a group who would receive 2% lidocaine gel 10 mL or plain lubricant gel 10 mL intrarectally. The procedure was explained to patients by a nurse specialist and they were given written information for future reference. All patients commenced a 3-day course of oral antibiotic prophylaxis 1 day prior to the procedure: ciprofloxacin 250 mg twice a day and metronidazole 400 mg 3 times a day. Patients were instructed to use fleet enema (sodium biphosphate) to clear the lower bowel before biopsy. Informed consent was obtained from all patients.

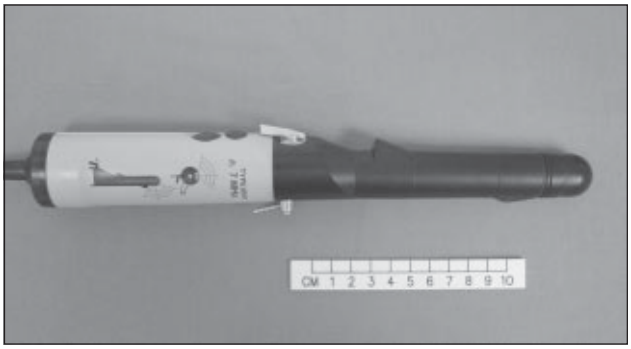

Fig 1. Scaled illustration of the 7-MHz ultrasound probe (Falcon 2002; B & K), 22 mm in diameter which was used to examine, measure, and guide biopsy of the prostate gland

Patients were placed in the left lateral decubitus position with the knees and hips fully flexed. Plain lubricant gel or 2% lidocaine gel (Instillagel; Farco-Pharma GmbH, Cologne, Germany) was gently instilled into the rectal vault and onto the perianal area. After 5 minutes, a 7-MHz ultrasound probe (Falcon 2002; B & K, Copenhagen, Denmark), 22 mm in diameter (Fig 1), was used to examine and measure the prostate gland. Total prostate volume was determined using a computer-generated elliptical estimation of volume (volume=0.52 x transverse diameter [W] x anteroposterior diameter [H] x cranial caudal diameter [L]). The TRUS-guided systematic biopsies were performed during sagittal scanning with an 18-gauge biopsy cut needle (ACN Biopsy needle; MDTECH, Florida, US) driven by a spring-loaded Bard Biopsy gun (CR Bard Inc, Covington, Georgia, US). A systematic sextant pattern was used with biopsies taken at the base, middle, and apex of the right and left lobes at the parasagittal plane. In addition, two lateral horn biopsies were performed on each side. The biopsy gun was reloaded by an assistant after each biopsy. The gun was fired with the needle pointing to the mouth of an empty, appropriately labelled specimen container. The specimen was expelled, by firing the gun, into the sterile container intact with no contamination and further manipulation. On completion of the biopsy procedure, formalin solution was poured into the specimen bottle inside the fume cupboard to fix the tissue. The whole procedure including ultrasound examination and biopsy took 5 minutes on average. All procedures were done by or in the presence of one of the authors in order to ensure the correct method was employed throughout the study.

Within 5 minutes of completion of the procedure, patients were asked to grade the pain associated with the ultrasound and biopsy experience on a horizontal visual analogue scale (VAS) [Fig 2] and a 4-point discomfort scale

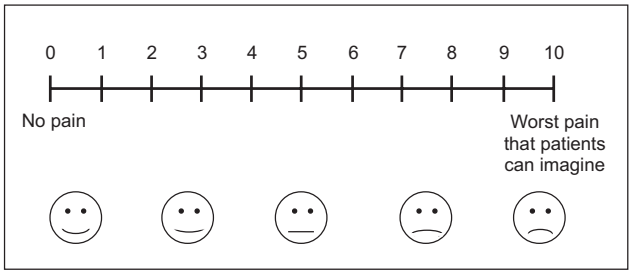

Fig 2. Pain scale (0-10 visual analogue pain scale)

Table 1. Discomfort scale

Score	Degree of discomfort
0	None
1	Mild
2	Moderate
3	Severe

(Table 1). This was done in another room with the help of a nurse who had no knowledge on the anaesthesia used. No attempt was made to separate the grading of pain and discomfort for different parts of the procedure, such as DRE, ultrasound probe insertion, or firing of biopsy gun. Patients were followed up by telephone by the nurse the following day and asked to report pain and discomfort scores and whether they experienced any complications related to the biopsy.

Statistical analysis

The Mann-Whitney *U* non-parametric rank sum test (two-tailed) was used to compare continuous variables and Pearson Chi squared (X^2) test (two-sided) was used to compare dichotomous variables. A P value of less than 0.05 was considered statistically significant. The number of patients included corresponded to a 95% power (β=0.05), an alpha risk of 5% (α=0.05, two-sided), and a standardised effective size of 0.4, when a difference in pain score of 0.5 was sought. At least 164 patients were required for each group. Statistical analysis was performed with the commercially available Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], US).

Results

From March 2002 to December 2003, a total of 386 consecutive TRUS-guided biopsies of the prostate were performed. Non-Chinese (n=7) and patients with a history of previous biopsy (n=41) were excluded. There were 338 eligible patients who were divided into two groups to receive plain lubricant gel (NA group) or 2% lidocaine gel (LA group) with 169 patients in each group. Four urologists performed the biopsies. Each patient received an extended 10-core biopsy of the prostate with additional biopsies taken from abnormal sites. The mean age of the patients was 71.33 years (standard deviation [SD], 7.49 years; range, 49-91 years). The median PSA level was 8.40 ng/mL. The mean volume of prostate was 53.07 mL (SD, 27.17 mL). Digital rectal examination was normal in 207 (61.2%) patients. Pathological findings were normal in 210 (62.1%) cases, 107 (31.7%) had malignancy, 18 (5.3%) had high-grade prostatic intraepithelial neoplasm (PIN), and three (0.9%) had evidence of inflammatory changes (Table 2).

There were no statistical differences between the two groups in terms of age, PSA level, and prostate volume by Mann-Whitney *U* test, or pathological findings and DRE by Pearson Chi squared test (Table 2). The VAS pain scores and discomfort scores on days 0 and 1 for the two groups were shown in Fig 3 and 4, respectively. Mann-Whitney *U* test showed no statistical difference between the two groups with the sensitivity of detection of VAS 0.5 points (Table 2).

Table 2. Demographic data, and pain and discomfort scores

	Plain gel group, n=169	Lidocaine gel group, n=169	P value
Mean age (range) [years]	70.99 (49-91)	71.67 (50-91)	0.45
Median serum PSA* (ng/mL)	8.40 (1.80-4735.00)	8.00 (0.17-6740.00)	0.75
Prostate volume (mL)			
Mean (SD)	55.02 (29.63)	51.11 (24.38)	0.29
Range	14.00-257.40	14.23-140.00	
Digital rectal examination (No. of patients)			
Normal	108	99	0.35
Abnormal	61	70	
Histology (No. of patients)			
Negative	108 (63.9%)	102 (60.4%)	0.81
Cancer	50 (29.6%)	57 (33.7%)	
Prostatic intraepithelial neoplasm	9 (5.3%)	9 (5.3%)	
Inflammation	2 (1.2%)	1 (0.6%)	
Mean pain score on day 0 (SD)	1.79 (1.51)	1.75 (1.55)	0.66
Mean pain score on day 1 (SD)	0.15 (0.45)	0.21 (0.69)	0.97
Mean discomfort score on day 0 (SD)	0.77 (0.60)	0.79 (0.62)	0.86
Mean discomfort score on day 1 (SD)	0.12 (0.32)	0.12 (0.36)	0.76

* PSA denotes prostate-specific antigen

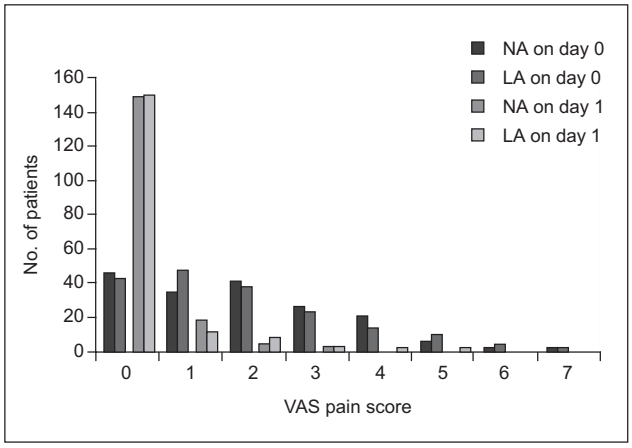

Fig 3. Visual analogue scale (VAS) pain scores of the plain lubricant gel (NA) and 2% lidocaine gel (LA) groups after transrectal ultrasound-guided trucut biopsy of the prostate gland on day 0 (P=0.66) and day 1 (P=0.97)

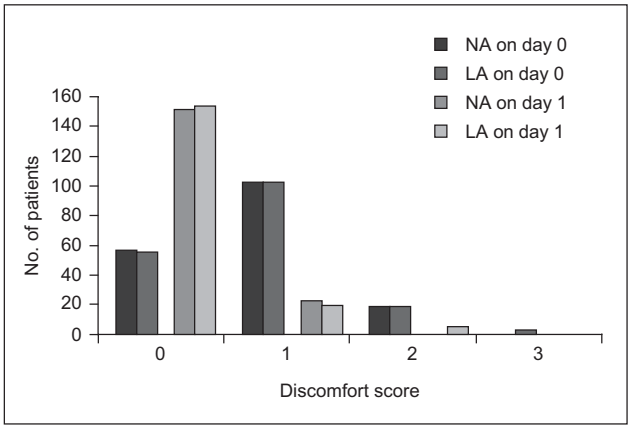

Fig 4. Discomfort scores of the plain lubricant gel (NA) and 2% lidocaine gel (LA) groups after transrectal ultrasound-guided trucut biopsy of the prostate gland on day 0 (P=0.86) and day 1 (P=0.76)

Discussion

In 1963, Takahashi and Ouchi[11] first performed transrectal ultrasonography of the prostate gland, and in 1981 Holm and Gammelgaard[12] described transperineal biopsy of the prostate guided by TRUS. It was not until 1989 that Torp-Pedersen and Lee[13] reported the results of TRUS-guided biopsy of the prostate using a spring-loaded 18-gauge biopsy needle. To date, TRUS-guided biopsy of the prostate remains the gold standard in diagnosing prostate cancer. It is estimated that more than 770 000 prostate biopsies would be performed in 2005 in the United States. Although TRUS-guided biopsy of the prostate is frequently performed, there is no consensus on optimal anaesthesia during the procedure. Anaesthetic modalities such as periprostatic lidocaine block, transrectal lidocaine gel, intravenous sedation, nitrous oxide inhalation, and plain lubricant gel are widely used. In this prospective double-blind randomised study, we identified no statistical significant difference in the pain and discomfort scores following intrarectal administration of 2% lidocaine gel or plain lubricant gel alone.

A 10-point linear VAS is generally considered the best instrument for assessing pain intensity. It is independent of language and ethnic differences, provides a sensitive measurement, and enables statistical comparison. The mean VAS pain scores were 1.79 (SD, 1.51) and 1.75 (SD, 1.55) on day 0, and 0.15 (SD, 0.45) and 0.21 (SD, 0.69) on day 1 for NA and LA groups, respectively. These scores indicate mild pain while a pain score of greater than 5 would be considered to be moderate-to-severe. Mann-Whitney *U* test showed no statistical difference between the two groups with the sensitivity of detection of VAS 0.5 points. Other studies have reported similar findings.[14,15] Nonetheless our cohort groups reported less pain compared with other studies and this may have been due, in part, to ethnic differences. Our cohort consisted of exclusively ethnic Chinese patients, recruited consecutively and prospectively. Other studies have demonstrated that acute and chronic pain perception is influenced by ethnic and cultural factors.[16-20] Our cohort of ethnic Chinese patients were more tolerable to pain with a low mean VAS pain score.

Redelmeier et al[21] demonstrated that patients who experienced pain during colonoscopy may recall the experience as unpleasant. A repeated procedure would be biased and preclude the patient from a subsequent procedure. Repeated TRUS-guided prostate biopsy, similar to colonoscopy, is significantly influenced by the previous experience. In the current trial, we excluded patients with a history of previous biopsy in order to allow a more objective assessment of pain and discomfort scores.

The second end-point of the current study was discomfort score for the whole procedure. As instrumentation and manipulation at the anal canal may not cause pain but discomfort, the 4-point discomfort scale (Table 1) measured patient's general feeling for the whole procedure. The mean discomfort scores were 0.77 (SD, 0.60) and 0.79 (SD, 0.62) on day 0, and 0.12 (SD, 0.32) and 0.12 (SD, 0.36) on day 1 for NA and LA groups, respectively. Mann-Whitney *U* test showed P values of 0.86 and 0.76 on day 0 and day 1, respectively. There was no statistical significant difference between two groups.

In this trial, we did not purposely stratify pain and discomfort for various parts of the procedure, namely DRE, introduction of ultrasound probe into the rectum, trucut biopsy of the prostate, and withdrawal of the ultrasound probe. Nevertheless urologists who performed the procedure had the general impression that the introduction of the ultrasound probe caused the most discomfort or pain during the whole procedure. As the current ultrasound probe is 22 mm in diameter, it would be worth investigating

whether use of a smaller size probe can minimise pain and discomfort.

Each tube of 2% lidocaine gel (Instillagel; Farco-Pharma GmbH) costs HKD25. As there were no benefits to using this gel, financial savings are possible if only plain gel is used.

The data in this study demonstrated that TRUS-guided biopsy of the prostate without anaesthesia is safe and well tolerated by Chinese patients. No patient experienced a vasovagal attack, hypotension, severe bleeding, sepsis, or loss of consciousness during or after the procedure. Further studies are required to determine whether use of a smaller ultrasound probe reduces the minimal pain and discomfort experienced.

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