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ORIGINAL ARTICLE

Prospective comparison among three intrarectal anesthetic treatments combined with periprostatic nerve block during transrectal ultrasonography-guided prostate biopsy

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Abstract

Background Recent trends in prostate biopsy analgesia suggest a combination anesthetic to provide better pain relief than periprostatic nerve block (PPNB) alone. This study aimed to demonstrate the efficacy and safety of three intrarectal local anesthesia (IRLA) combined with PPNB in patients undergoing transrectal ultrasonography (TRUS)-guided prostate biopsy.
Methods In this prospective, randomized study, 120 prostate biopsy patients were equally divided into four IRLA groups: group 1 (placebo) received simple lubrication; group 2 received 2% lidocaine gel; group 3 received 100 mg indomethacin suppository and group 4 received 5% prilocaine/lidocaine (EMLA) cream. PPNB with 2% lidocaine was applied in all groups. A ten-point visual analog scale evaluated both pain associated with the probe insertion and pain associated with prostate sampling. Adverse effects or complications due to anesthesia during and after the procedure were documented.
Results Compared with group 1, groups 3 and 4 had significantly lower pain scores at both probe insertion and prostate sampling while group 2 showed no significant differences at both pain scores. Moreover, group 4 showed significantly lower pain scores at probe insertion compared to group 3, while no significant difference was observed at prostate sampling. Mild complications were observed in all groups with no significant difference in the incidence of complications between groups.
Conclusion Intrarectal application of EMLA cream is a more efficient pain reduction than either 2% lidocaine gel or 100 mg indomethacin suppository when applied combined with PPNB. This combination represents an effective option of pain relief for patients undergoing TRUS-guided prostate biopsy.

Keywords Prostate cancer · Biopsy · Anesthesia · Lidocaine · Prilocaine · Indomethacin

Introduction

Prostate cancer (PCa) is the most common urological neoplasm and the second leading cause of cancer-related death in the western world [1, 2]. Patients presenting with high prostate-specific antigen (PSA) values and/or abnormal digital rectal examination are screened for PCa through prostate histopathology studies. To date, transrectal ultrasonography (TRUS)-guided prostate biopsy, first introduced by Hodge et al. [3] is considered the main diagnostic method for PCa confirmation.

Although TRUS-guided prostate biopsy is the standard procedure for the exact diagnosis of PCa, and it is performed with a generally low complication rate, the procedure can cause significant pain or discomfort [4]. To decrease pain perception and improve patient acceptance of the biopsy, Nash et al. [5] performed for the first time a local anesthesia

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through a periprostatic nerve block (PPNB) by injecting 5 ml 1% lidocaine just lateral to the junction between prostate base and seminal vesicle, blocking the neurovascular bundles near the prostate.

The Nash technique successfully decreased pain, and since then, it has been established by several authors as the gold standard anesthetic method of prostate biopsy [5]. Studies have since shown, however, that the anesthetic effect of Nash technique is only associated with a reduction of the pain when cores are taken during the prostate sampling [5]; no effect has been observed in reducing pain during the probe insertion and its manipulation into the anal canal, particularly in young patients [4]. Additionally, considering that sextant sampling is inadequate and sampling with at least eight cores is suggested [6], and that some patients have to be re-biopsied to get an accurate diagnosis, various modalities of analgesia prescription have been evaluated in literature to be used during TRUS-guided prostate biopsy.

Concerning this, there is an emerging trend of adding a non-invasive intrarectal local analgesia (IRLA) treatment during prostate biopsy in addition to PPNB. Indeed, various studies have shown that a combined anesthetic treatment (IRLA with PPNB) significantly improves pain relief when compared to one of these anesthetic therapies alone [7, 8].

Recent studies have been conducted to evaluate the efficacy and safety of IRLA combined with PPNB [9–11]; however, the best combination remains to be elucidated. In this study, in order to gain more insight into the best combined anesthetic treatment, we have compared pain scores of three IRLA treatments combined with PPNB in a prospective, randomized, study.

Methods

Patient selection

A total of 135 patients who underwent TRUS-guided prostate biopsy at the Central Military Hospital, Mexico City, Mexico over a period of 11 months from January 2013 to November 2013 were enrolled in this study, which was approved by the hospital's ethics committee (No. 040/2013). The main indicators for prostate biopsy were increased serum PSA (≥ 4 ng/ml) and/or abnormal digital rectal examination. The exclusion criteria included patients with a previous transrectal prostate biopsy, treated with anticoagulants, acute prostatitis, active anal/rectal pathology, chronic pelvic/rectal pain, known allergy to local anesthesia, or concomitant analgesic medication. As shown in Fig. 1, 120 patients met the inclusion criteria and agreed to participate in the study, and read and signed a written consent.

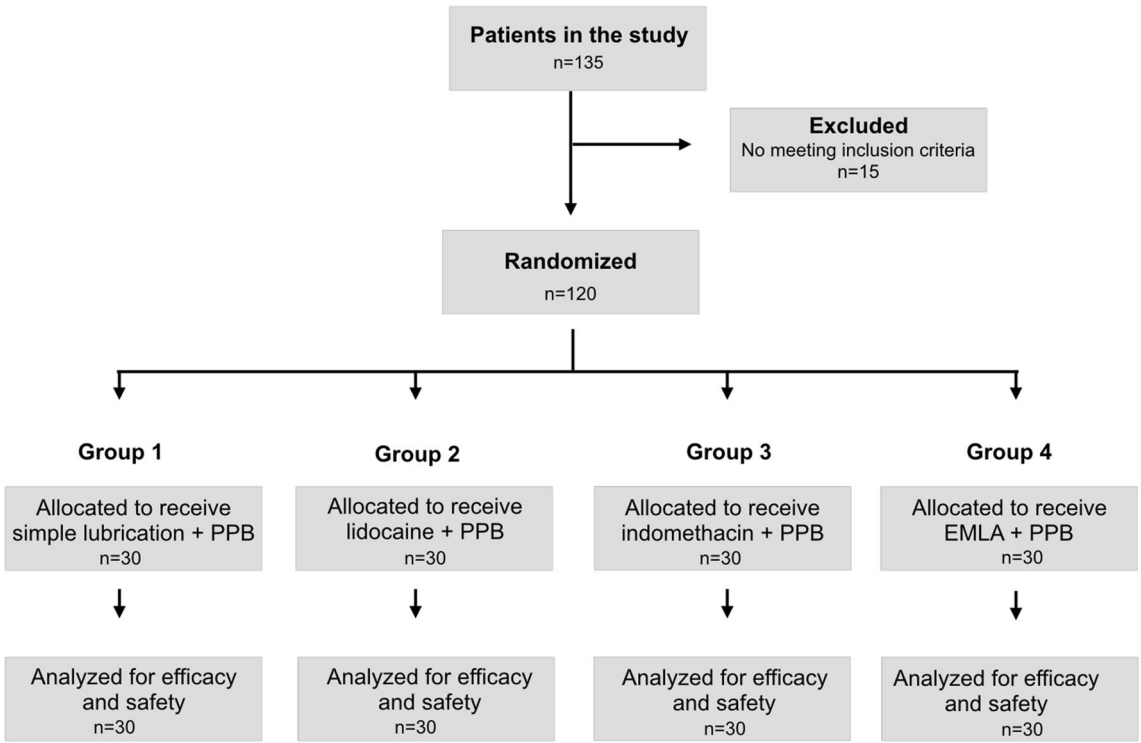

Fig. 1 Flow diagram of the study selection process

Study design and anesthesia

Using block randomisation, participants were assigned to four equal groups [27]. A once-daily oral dose of 500 mg levofloxacin was given to all participants for prophylaxis, beginning 1 day before and for 6 days after the prostate biopsy. Additionally, an experienced nurse administered a cleansing phosphate-based enema 3 h before biopsy. After prophylaxis, group 1 (placebo) received 10 ml non-medicated lubricating gel; group 2 received 10 ml 2% lidocaine gel; group 3 received 100 mg indomethacin suppository; and group 4 received 10 ml of prilocaine/lidocaine (EMLA) cream to reach a final concentration of 5%. An experienced urologist applied all treatments by a suppository or a syringe into the anal canal and perianal skin, as specified for the corresponding treatment. Dosages and exposure times were selected according to the literature and previous knowledge; all groups were administered 30 min of anesthetic treatment except for group 3, which was exposed to 1 h of anesthetic treatment [8, 9, 11, 12] immediately prior to biopsy. Information about each treatment was withheld from the participants.

Prostate biopsy

In the ultrasonography room, patients were placed in the left lateral decubitus position and transrectal ultrasound was performed using an ultrasound scanner (Pro Focus UltraView Ultrasound Scanner BK Medical 2202) with a 7.5 MHz endorectal biplane transducer (8808e). The prostate was imaged for signs of abnormality and prostate volume was measured in the maximum triaxial diameters. Subsequently, using a 20-cm 22-gauge spinal needle (Cook Medical Company, IN, USA), PPNB was performed in all groups by injecting 5 ml 1% lidocaine hydrochloride lateral to the junction between the prostate base and seminal vesicle on each side [5]. After 5 min, the prostate biopsy was performed using the sextant biopsy extended technique, as reported by Bjurkin et al. [6]. In all patients, six core samples per lobe were taken for a total of 12 core samples per patient. For patients with suspected malignancy (defined as the presentation of hypoechoic zones during ultrasound) one or two further core samples were added. All samples were taken using an automatic biopsy gun and a 20-cm 18-gauge Biopty-Cut™ needle. After the procedure, patients were transferred to a surgical room for ambulatory surgery to recover.

Pain questionnaire and safety

10 min after the procedure, patients were asked to complete a questionnaire enquiring about pain perception. Pain was evaluated using a 10-point visual analog scale (VAS, 0 = painless, 10 = severe pain) at two points; (1) pain associated with the probe insertion and (2) pain associated with prostate sampling. A urologist blinded to each IRLA treatment performed the survey.

3 h after procedure, patients were assessed for possible complications. Adverse post-operative events falling under the Clavien-Dindo surgical complications grade 'I' were considered as mild complications, and included: self-limiting rectal bleeding, self-limiting hematuria, dysuria, and acute urinary retention [24]. Events graded as II or above in the Clavien-Dindo classification were considered severe complications, and these included allergic reactions, vasovagal syncope, fever (temperature $\geq$ 38.0 °C), hematuria and/or rectal bleeding requiring any kind of intervention or blood transfusion [24]. Patients with mild complications were kept for 2 h to recover before being discharged home.

Statistical analysis

This study used one-way analysis of variance (ANOVA) to compare patient characteristics including age, PSA values, prostate volume, and number of core samples. Kruskal–Wallis variance analysis was performed to determine differences in pain score at both evaluated levels; non-parametric Mann–Whitney *U* test to determine the best anesthetic treatment; and Chi-square test to evaluate the complication index. Results with a $P < 0.05$ value were considered statistically significant. Statistical analysis was performed using Stata Intercooled software, version 12.1 (StataCorp LP, College Station, Texas, USA).

Results

Study population

Clinical values of participants are shown in Table 1. It can be observed that there are no significant differences in age ($P = 0.718$), PSA levels ($P = 0.094$), prostate volume ($P = 0.654$), and number of core samples ($P = 0.730$) between groups.

Efficacy of pain treatment

To determine efficacy of the pain reliefs under investigation, VAS scores associated with both probe insertion and prostate sampling were evaluated in all groups and compared to group 1 (control). As evident in Table 2, VAS scores associated with the probe insertion and prostate sampling in group 3 and 4 were significantly lower ($P < 0.05$) in comparison to group 1; while group 2 showed no significant difference compared to group 1. To further define the most effective anesthesia, VAS scores

Table 1 Patient characteristics

Variable	Groups				Median	*P* value
	1	2	3	4		
Mean age (years)	61.6 ± 7.8	62.5 ± 5.6	62.9 ± 5.4	63.4 ± 5.8	62.6	NS
Mean PSA (ng ml^{-1})	10.3 ± 7.9	12.9 ± 24.2	19.3 ± 18.3	10.0 ± 6.0	13.1	NS
Mean prostate volumen (cc)	54.7 ± 19.6	51.2 ± 28.3	59.2 ± 25.1	53.1 ± 26.8	54.5	NS
No. of cores biopsies	11.9 ± 0.9	11.9 ± 0.8	11.8 ± 0.6	12.2 ± 0.8	11.9	NS

Values represent the mean ± standard deviation (SD). *P* value calculated by analysis of variance

NS not significant, *PSA* prostate-specific antigen, *CC* cubic centimeters

Table 2 Pain level during the two analised phases of biopsy procedure

	Group 1	Group 2	Group 3	Group 4
Mean pain level during probe insertion	5.0 [2.0]	5.0 [2.0]	3.0 [2.0]*	2.0 [2.0]**
Mean pain level during biopsy punctures	5.0 [1.0]	5.0 [4.0]	3.0 [4.0]*	2.5 [3.0]**

Values are median and interquartile range [IQR]

* Significant difference in comparison to group 1 (control group) (* $P \leq 0.05$; ** $P \leq 0.001$). *P* value calculated by Kruskal–Wallis test

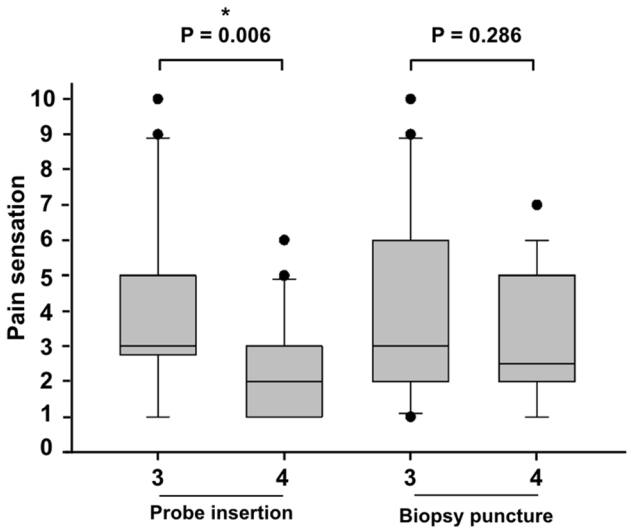

Fig. 2 Comparison of the visual analogue scale (VAS) scores of group 3 versus group 4 during the two phases of the study

of group 3 and group 4 were analyzed and compared each other using the non-parametric analysis Mann–Whitney *U* test. Results show that group 4 had significantly lower VAS scores at probe insertion compared to group 3, while no significant difference was observed for the VAS scores related to the prostate sampling (Fig. 2).

Table 3 Complication incidence in studied groups

	Group 1	Group 2	Group 3	Group 4	*P* value
No. patients	30	30	30	30	
No. severe	0	0	0	0	No applicable
No. mild (%)	2 (6.7)	1 (1.3)	3 (10)	2 (6.7)	NS
Hematuria	2	1	1	1	
Rectal bleeding	0	0	2	1	

No severe complications were observed during and after the biopsy procedure. *P* value calculated by Chi-squared test (Chi^2)

Subsequent complications

Table 3 shows no severe complications associated with the anesthesia during or after the biopsy procedure. There were only mild complications such as self-limiting rectal bleeding, self-limiting hematuria, dysuria, with no significant differences in the incidence between groups ($P = 0.773$).

Discussion

In this study, the use of either 100 mg indomethacin suppository or intrarectally applied 5% EMLA cream significantly reduced pain intensity in patients undergoing a PPNB and TRUS-guided prostate biopsy when compared with a control group of patients receiving non-medicated lubricating gel. This was evaluated using a visual analog scale at the insertion and manipulation of the ultrasound probe, and at prostate sampling itself. The anesthetic 2% lidocaine (used for patients in group 2) was found to be less effective than the other two treatments (received by patients in groups 3 and 4) at reducing pain, showing no significant difference in comparison to the control group. Comparing the two successful pain relief treatments, it was demonstrated that 5% EMLA cream resulted in a larger significant pain reduction at taking biopsy punctures when compared with 100 mg indomethacin suppository; however, no significant difference was observed between the two treatments at probe insertion.

As highlighted by several researchers [13, 14], pain-related prostate biopsy is mainly associated with two factors: (1) the insertion and movements of the ultrasound probe in the rectum, and (2) the core-biopsy needle punctures of the prostate. Both the rectum and prostate contribute to pain sensation. The rectum is richly innervated by splanchnic sensory and somatic nerves. The borderline between these two types of nerves corresponds to the dentate line. At the superior area of the dentate line, there is predominantly splanchnic innervation that is relatively insensitive to pain, while at the inferior there is predominantly somatic innervation of fibers derived from the inferior rectal nerve, in which the prostatic apex overlies, and thus represents an extremely pain-sensitive area [15]. Conversely, prostatic pain can be originated in the stroma or capsule of the prostate gland surrounded by an extensive autonomic innervation, derived from fibers of the pelvic plexus, which travel to the prostate via the cavernous nerves. The cavernous nerves are part of the bilateral neurovascular bundles, which run posterolateral to the prostate and represent the main pain sensory supply of the prostate [14, 16, 17].

Since 1996, the PPNB technique proposed by Nash et al. [5] has been considered the best anesthetic method for prostate biopsy. However, this technique acts by blocking the neurovascular bundles nearby the prostate, having no effect over the anal sphincter and the small segment inferior to the dentate line where overlies the prostatic apex. Therefore, PPNB is reported to be useful only to prevent pain arising from the prostatic capsule or stroma at taking the biopsy punctures, while no effect has been shown in controlling pain arising from probe insertion and its manipulation in the anal canal [18]. IRLA applied combined with PPNB has been observed to exhibit better pain relief than these two maneuvers alone by covering the dual component of pain [11, 12, 19]. In 2004, Obek and colleagues showed for the first time a significant pain reduction using the combined anesthesic method, applying 2% lidocaine gel rectally combined with PPNB. Recently, Skriapas et al. [20] performed a comparison between combined anesthetic methods using two different IRLA (glyceryl trinitrate, GTN and lidocaine gel) with PPNB. Better efficacy was determined using GTN ointment than lidocaine gel; however, this was associated with headache and hypotension, considered as side effects of the anesthesia.

The present study aimed to determine, for the first time, the most effective and safest anesthesia for dual pain control during prostate biopsy. As discussed previously, 100 mg indomethacin suppository and 5% EMLA cream provide better pain control at dual components of pain than 2% lidocaine gel (Table 2) with no severe complications associated to these anesthetics. Only mild complications, such as haematuria and rectal bleeding that did not need intervention or treatment, were the most frequent complications. Moreover, no significant differences were observed in the complications incidences between studied groups (Table 3).

Several factors, including age, prostate volume, enema preparation, patient position, and number of biopsy punctures can interfere in pain scores during TRUS-guided prostate biopsy [11, 21]. Our selected patient populations had no significant differences in age, PSA levels, prostate volume, and biopsy punctures, as shown in Table 1. Moreover, the same patient position and enema preparation were applied in all groups, thereby controlling all the mentioned clinical features that may have an influence on the obtained pain scores.

The positive effect found with 5% EMLA cream is line with the study of Raber et al. [22] in which the superiority of combined EMLA cream was demonstrated through topical placement around the anal canal and the rectal mucosa with PPNB when compared with PPNB alone. Furthermore, Giannarini et al. [11] evaluated the combined use of EMLA cream with a PPNB, reporting markedly better pain relief at the probe insertion and biopsy punctures than when these two methods where applied alone. It is important to highlight that in both the Giannarini et al. [11] and Raber et al. [22] studies, better results were determined in younger (< 65-year-old) and larger prostate size (> 49 cc) patients. Moreover, as stated in the study of Raber et al. [22] the eutectic mixture of lidocaine–prilocaine of EMLA cream has a higher concentration of active substances, and thus allows better drug penetration through the tissue. Under these scenarios, the significant pain control found with 5% EMLA cream is likely due to a direct effect of this analgesia over the small segment of rectum exquisitely sensitive to pain that overlies the prostatic apex and the richly innerved prostatic capsule, in which the effect of the PPNB is insufficient [14].

The pain relief demonstrated by 100 mg indomethacin suppository could be due to its systemic and local anti-inflammatory effect. Indomethacin, as a non-steroid anti-inflammatory drug (NSAID), is associated with the inhibition of prostaglandin synthesis. The release of prostaglandins, along with cytokines and leukotrienes, at the rectal mucosa can lead to edema and the recruitment of other immune cell components including mast cells and lymphocytes triggered to local pain sensation [25]. Furthermore, there is the possibility of a synergic effect of suppositories and PPNB over the visceral nerve supply of the prostate [9]. The pain relief function of indomethacin is in line with the previous reports in the literature using a diclofenac suppository [9, 13].

Interestingly, 5% EMLA cream exhibited a better anesthetic effect than 100 mg indomethacin suppository, showing significantly higher pain reduction at the probe insertion (Fig. 2). This could be explained due to the different mechanism of action; EMLA cream exerts its anesthetic effect locally by blocking neurovascular innervations present in the rectal mucosa, different to indomethacin

suppository that has a local and systemic effect of blocking prostaglandin synthesis. Nevertheless, both anesthetic drugs reduced pain intensity with no significant difference at taking the biopsy punctures during prostate sampling. This suggests that even though these two anesthetics present different mechanism of action, both IRLA have a synergic pain-reducing effect when combined with the PPNB.

In this study, the use of 2% lidocaine gel transrectally did not show any significant difference compared to the placebo control group. Although the 2% lidocaine transrectal anesthetic has been reported to provide pain relief [8, 12], contradictory results demonstrating a lack of pain relief, in line with these findings, have also been observed [26]. Additionally, recent meta-analysis data derived from Li et al. [23] assessing different local anesthesia indicate lidocaine to provide no significant pain reduction. Therefore, the alleviated pain reported by Obek et al. [12] and Yun et al. [8] could be due to the lack of a placebo control group in these studies.

In summary, the combined anesthetic treatment of 5% EMLA cream with PPNB resulted in a larger significant pain reduction in comparison to 2% lidocaine gel and 100 mg indomethacin suppository combined with PPNB. However, this study was limited to measure pain relief in homogeneous groups with respect to age and prostate volume. Therefore, it would be interesting to determine the efficacy of each anesthetic treatment in stratified groups in order to gain more insight into the mechanism of action of each anesthetic. Moreover, this study evaluated only the two main pain-sensitive phases, probe insertion and biopsy punctures, of TRUS-guided prostate biopsy right after procedure. Recording of pain scores at different time-points in the procedure (including 6 and 24 h after biopsy, and in the general procedure itself) would provide further evidence demonstrating the differential efficacy of anesthetic treatments during TRUS-guided prostate biopsy.

Conclusion

In conclusion, when comparing different anesthetic treatments to be used in combination with PPNB prior to TRUS-guided prostate biopsy, this study reveals that the application of 5% EMLA cream decreased pain intensity without increasing the complication incidences. Therefore, this combination represents the best option for pain control in patients who undergo TRUS-guided prostate biopsy.

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Compliance with ethical standards

Conflict of interest Authors have declared no conflict of interest.

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