

Running Head: Comparison of the Efficacy of Different Anesthesia Methods in Prostate Biopsy

Comparison of the Efficacy of Local Anesthesia Methods and Caudal Regional Anesthesia in Prostate Biopsy Applied Under Transrectal Ultrasonography: A Randomised Controlled Study

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Key Words: caudal regional anesthesia; pain; prostate biopsy; prostate cancer; periprostatic local anesthesia.

ABSTRACT

Purpose: To evaluate the efficacy of caudal regional anesthesia and local anesthesia methods in prostate biopsy applied under transrectal ultrasonography.

Materials and Methods: This prospective study included a total of 160 patients randomly separated into 4 equal groups as intrarectal local anesthesia (IRLA), periprostatic local anesthesia (PPLA), combined local anesthesia (IRLA+PPLA), and caudal regional anesthesia (CRA). The patients were evaluated using the pain scores on a visual analog scale.

Results: The pain score during anesthesia induction was significantly higher in the CRA group than in the IRLA and IRLA+PPLA groups ($p<0.001$). The pain score during entry of the probe to the rectum and movement was significantly lower in the CRA group than the IRLA groups ($p=0.014$). The pain score on penetration of the needle to the prostate and at 30 mins after the biopsy was significantly higher in the IRLA group ($p<0.001$). At 2 hours after the biopsy, the pain score in the CRA group was significantly lower than IRLA groups ($p=0.015$).

Conclusion: The PPLA alone can be applied more quickly than CRA, causes less pain during the application, and has similar efficacy in reducing pain during and after the prostate biopsy procedure.

Key Words: caudal regional anesthesia; pain; prostate biopsy; prostate cancer; periprostatic local anesthesia.

INTRODUCTION

Prostate cancer is the second most common cancer in males and the fifth most frequent cause of male cancer-related deaths (1). A definitive diagnosis of prostate cancer is determined with prostate biopsy taken under transrectal ultrasonography (TRUS) guidance (2). Most TRUS prostate biopsies are performed under local anesthesia and approximately 20% of these procedures create negative effects of physical pain, stress and anxiety (3). There is a need for repeated biopsies in approximately 21-28% of clinically important cancers (4). In addition, patients under the active observation protocol require repeated biopsies. Minimizing pain during the biopsy procedure increases patient compliance with the follow-up protocol (5).

Research is currently ongoing for the most appropriate form of anesthesia to reduce the pain during TRUS prostate biopsy. Previous studies have shown that patients feel pain at two stages during prostate biopsy: the entry and movement of the TRUS probe inside the rectum, and during penetration of the biopsy needle to the prostate (6). Some studies have reported that periprostatic local anesthesia (PPLA) causes no pain during entry and movement of the TRUS probe (7, 8).

Previous studies have demonstrated that caudal regional anesthesia (CRA) reduces pain both during entry and movement of the TRUS probe, and during penetration of the biopsy needle (9, 10). However, to our knowledge, there is no study in literature that has compared CRA with the all other most frequently used anesthesia methods for prostate biopsy.

The aim of this study was to compare and evaluate the efficacy of CRA and the local anesthesia methods of intrarectal local anesthesia (IRLA), PPLA and IRLA+PPLA in prostate biopsy applied under TRUS.

MATERIALS and METHODS

This prospective randomised control study was carried out in the Ankara Numune Training and Research Hospital, Department of Urology, Ankara, Turkey in 2017-2018. The study protocol was approved by the Institutional Review Board of Ankara Numune Training and Research Hospital (1569/2017) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from all the patients.

Patients were excluded from the study if they had any evident coagulopathy, immunosuppression, prostatitis, neurological disease, previous prostate biopsy, inflammatory intestinal disease, rectal malignancy, anorectal disease, and allergy to local anesthetic.

All patients were evaluated with medical history, international prostate symptom score (IPSS), physical examination, DRE, full blood count, blood biochemistry, urine analysis and serum PSA. The height and weight of all patients were measured and their body mass index (BMI) was calculated. Indication for prostate biopsy were suspicion of malignancy in DRE and/or serum PSA value $>4\text{ng/ml}$.

The patients included in the study were randomly separated into 4 anesthesia groups using the sealed envelope randomization method. Group 1 patients were applied with 10 ml 2% lidocaine gel for IRLA. Group 2 patients were administered 5 ml 1% lidocaine HCL to the area defined as the vascular nerve bundle in the posterolateral of the prostate, using a 22G 25cm chiba needle under TRUS. Group 3 patients were administered 10 ml IRLA then PPLA induction was applied 10 mins later. The prostate biopsy was applied 10 minutes after local anesthesia to these patients in Group 1-3. For patients in Group 4, first a vascular route was opened and 3 ml/kg/hour Ringer lactate solution infusion was started. The patients were monitored and vital signs were followed. The patients were placed in the left lateral decubitus, knee-chest position, then the sacral horns and sacral hiatus were identified. After aseptic

cleaning of the region where the needle was to enter, the same anesthesia specialist in all cases applied local anesthesia with 2ml 2% prilocaine. Entering the skin at a 45° angle with a 22G 9cm spinal needle, the sacrococcygeal ligament was pierced and when it was felt that a space was entered, the needle was brought to a position of 20° to the skin and was advanced 5-6cm into the epidural space. When it was confirmed that no cerebral spinal fluid or blood had appeared with aspiration, a 20 ml solution containing 20mg/ml 2% 15ml lidocaine and 5ml 0.9% isotonic NaCl was injected in 2 doses at a 2-minutes interval. The effect of the CRA was evaluated with the cold test. Motor block status was evaluated bilaterally with the Bromage scale (0= no block, 1=hip cannot be brought into flexion, 2=hip and knee cannot be brought into flexion, 3= hip, knee and ankle cannot be brought into flexion). The prostate biopsy was performed 15 minutes after CRA.

All the prostate biopsy procedures were performed by the same urology specialist using a Hitachi EUB-400 ultrasonography device (Hitachi, Tokyo, Japan) with a 6.5 mHz biplane transrectal probe and an 18G 25cm biopsy needle. Before the procedure, the prostate volume was calculated using the ellipsoid formula. At least a 12-core systematic prostate biopsy was taken from all patients. All of the patients used ciprofloxacin (1000 mg BID) from the day before the TRUS biopsy (5 days) for prophylactic antibiotic treatment .

After insertion of the TRUS probe, the biopsy procedure was completed and the duration of biopsy was recorded as the time until removal of the probe. The durations of applying PPLA and CRA induction were recorded. During PPLA and CRA induction, on entry of the TRUS probe to the rectum and during movement, during penetration of the needle to the prostate, and at 30 mins, 2 hours and 1 day following the biopsy, the pain scores using a Visual Analog Scale (0= no pain- 10= intolerable pain) were recorded by a nurse blinded to the type of anesthesia.

Statistical Analysis

Data obtained in the study were analysed statistically using Statistical Package for Social Sciences (SPSS) version 22.0 software (SPSS Inc. Chicago, IL, USA). In the group comparisons, the Chi-square test was used for determination of prostate cancer, the Kruskal-Wallis test for numerical variables not showing normal distribution, and the One-Way ANOVA test for variables showing normal distribution. A value of $p < 0.05$ was accepted as statistically significant. In the post hoc comparison of variables which were significant in the Kruskal-Wallis test, the Mann Whitney U-test with Bonferroni correction was used.

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RESULTS

TRUS biopsy was performed to the 203 patients in our clinic between October 2017 and October 2018 and 43 of these patients stated that they did not want to be included in the study, and the study continued with the remaining 160 patients. Fourty patients were randomly included to the each group The patients included in the study were determined with a mean age of 63.04 ± 7.47 years, BMI 26.8 ± 4.5 kg/m² and mean number of biopsy cores 12.9 ± 2.4 . Median values of serum PSA, IPSS and prostate volume were 7.37 ng/dl (range 2.7–2035), IPSS 10 (range 0–35) and prostate volume 57.7 mL (range 18.6-174.03), respectively. No statistically significant difference was determined between the groups in respect of mean age, BMI, serum PSA value, IPSS, prostate volume and number of biopsy cores (Table 1). Urine analysis was performed to 156 patients; 113 were normal, 17 patients had microscopic hematuria, 15 patients had leukocyturia and microscopic hematuria + leukocyturia. DRE was performed 157 patients; 78 patients had normal prostate examination, 79 had pathologies (nodule, asymmetry etc.). Full blood count and blood biochemistry were normal for all patients.

The mean pain scores during anesthesia induction were statistically significantly higher in the CRA group ($p < 0.001$). No statistically significant difference was determined between the PPLA and IRLA+PPLA groups (Table 2). The mean pain scores during entry of the TRUS probe and movement were lowest in the CRA group, but a statistically significant difference was only determined between the IRLA group and the CRA group ($p < 0.001$) (Table 2). The mean pain scores during penetration of the needle to the prostate were statistically significantly higher in the IRLA group than the other groups ($p < 0.001$) (Table 2). The mean pain scores at 30 mins after biopsy were statistically significantly higher in the IRLA group than other anesthesia methods ($p < 0.001$) (Table 2). In the pain scores at 2 hours after the biopsy, a statistically significant difference was only determined between the IRLA group and the CRA

group ($p=0.002$) (Table 2). At 1 day after the biopsy, no statistically significant difference was determined between the groups in respect of the mean pain scores (Table 2).

The mean anesthesia induction time before prostate biopsy was determined to be significantly longer in the CRA group than in the PPLA and IRLA+PPLA groups (7.38 ± 2.9 mins, 3.93 ± 1.7 mins, 4.25 ± 1.5 mins, respectively, $p<0.001$). The mean duration of the prostate biopsy procedure was 7.93 ± 2.9 minutes in all the patients and no statistically significant difference was observed between all 4 groups (IRLA: 7.46 ± 2.9 mins, PPLA: 8.10 ± 2.7 mins, IRLA+PPLA: 8.03 ± 2.8 mins, CRA: 8.15 ± 3.2 mins, $p=0.47$). In the CRA patients, motor block was determined as Bromage 0 in 80%, Bromage 1 in 10%, Bromage 2 in 2.5%, and Bromage 3 in 7.5%. Prostate cancer was determined in 31.3% of patients following the prostate biopsy. No statistically significant difference was determined between the groups in respect of the rates of cancer determination with the biopsy ($p=0.57$).

Following the prostate biopsy, hematuria was observed within the first 48 hours in 51.9% of patients, hematuria lasting longer than 48 hours in 37.5%, rectal bleeding within the first 48 hours in 55%, rectal bleeding lasting longer than 48 hours in 7.5%, hematospermia in 35.3%, urinary system infection in 6.9%, and inability to urinate in 6.8%. No statistically significant difference was determined between the groups in respect of these complications ($p=0.12$, $p=0.17$, $p=0.1$, $p=0.86$, $p=0.6$, $p=0.15$, and $p=0.58$, respectively). Early and late complications according to Clavien classification were summarised at Table 3 and 4.

The TRUS biopsy confirmed the presence of prostate cancer in 12 (30%), 9 (22.5%), 13 (32.5%) and 13 (32.5%) patients of group 1,2,3,4, respectively. The TRUS biopsy results of 14 patients were reported as Atypical Small Acinar Proliferation, therefore, a second biopsy was performed.

DISCUSSION

Although prostate biopsy is an effective diagnostic method for prostate cancer, approximately 65%-90% of patients feel pain or discomfort during the procedure (11). It has been determined that pain can be affected by the patient age, prostate volume, serum PSA level, prior application of lavage, a history of biopsy, the prostate section taken in the biopsy and the number of cores taken (12). In the current study, no significant difference was determined between the groups in respect of patient age, prostate volume, PSA level, or the number of cores taken in the biopsy.

Based on the high drug absorption capability of rectal mucosa, IRLA was the first method researched in the reduction of pain related to prostate biopsy (10). However, the effect of IRLA on pain related to prostate biopsy continues to be a subject of debate. In a meta-analysis by Yan et al, IRLA was reported to decrease pain scores but no significant difference was determined between IRLA and the placebo and non-anesthetized groups (13). In another meta-analysis, Yang et al reported that pain during local anesthesia induction and during entry of the TRUS probe was decreased with IRLA. However, the reduction in prostate biopsy-related pain of PPLA was reported to be superior to IRLA (14). The results obtained in the current study showed that IRLA was less effective than PPLA and CRA in the reduction of prostate biopsy-related pain, and IRLA applied before PPLA did not provide any additional benefit to PPLA in the reduction of pain in local anesthesia induction or during entry of the TRUS probe to the rectum and during movement.

PPLA has been determined to reduce pain during needle penetration to the prostate, but doesn't have an effect on pain created by the TRUS probe (7, 8). However, several studies have reported that the epidural anesthesia method of CRA reduces pain during TRUS probe entry and movement and during penetration of the needle to the prostate, by blocking the

sacrococcygeal nerves which innervate the whole perineum (9, 10). To date, there have been 5 prospective studies that have evaluated the effect of CRA on pain during prostate biopsy.

The first of these reported that PPLA was superior to CRA in reducing pain during prostate biopsy. However, it was also stated that when anatomic variations and the anatomic capacity of the sacral canal were taken into consideration, the dose of 10 ml 1% lidocaine used for CRA may not be sufficient (15). The second study reported that the pain scores of the CRA group were determined to be significantly lower than those without CRA, but the anesthesia methods used in the group without CRA were not described in detail (16). In the third study, it was reported that compared to IRLA, CRA significantly reduced pain during placement of the TRUS probe, in probe maneuvers and when taking the biopsy cores (10). In the fourth study the pain score of the CRA group was determined to be at a significantly high level during anesthesia induction compared to the PPLA group, significantly lower during entry and movement of the TRUS probe, and during needle penetration there was no difference. Moreover, at 30 minutes and 1 day after the biopsy, no difference was determined between the pain scores of the two groups (9). In the fifth study the pain scores of the IRLA+CRA group were determined to be significantly higher during anesthesia induction, and significantly lower during TRUS probe entry compared to the scores of the IRLA+PPLA group. During needle penetration there was no difference between the groups. In the sub analyses, the pain scores of patients with BMI ≥ 25 kg/m² in the IRLA+CRA group were significantly higher than the IRLA+PPLA group during anesthesia induction and needle penetration, but there were no difference during TRUS probe entry. This could be attributed to insufficient anesthesia due to the difficulty of identifying bony landmarks in obese patients (17). In recent years, Kim et al. published meta-analysis which included 47 RCT and showed that there are many options for pain control during TRUS biopsy, however, pelvic plexus block + IRLA, PPLA + IPLA, pelvic

plexus block, PPLA + IRLA, and PPLA methods are potentially more acceptable options.(18). The limitations of performing CRA are anesthetist dependent procedure and not cost-effective.

In our study, the duration of anesthesia induction was longer and the pain level during anesthesia induction was higher in the CRA group compared to the other two local anesthesia groups applied with PPLA. The application of IRLA before PPLA did not significantly reduce pain during anesthesia induction, TRUS probe entry and movement and prostate needle penetration. Unlike previous studies, no significant difference was determined between the groups administered CRA, PPLA alone and IRLA+PPLA in respect of the pain scores during probe entry and movement, during prostate needle penetration and at 30 minutes, 2 hours and 1 day after the biopsy.

The current study has some limitations including the lack of placebo group and not performing power analyses prior to the study.

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CONCLUSION

The results of this study demonstrated that the administration of IRLA before PPLA had no effect on pain related to the anesthesia induction or the biopsy procedure. The application of PPLA alone can be applied more rapidly than CRA, causes less pain while administering anesthesia, has a similar effect on reducing pain during and after the biopsy procedure, does not require an anesthesia specialist and does not require monitoring of the patients during and after anesthesia. Therefore it can be considered an ideal anesthesia method in routine urology practice.

Statement of Ethics: The study protocol has been approved by the Local Ethics Committee of the University of Health Sciences (1569/2017).

Disclosure Statement: The authors have no conflicts of interest to declare.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86.
2. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol*. 2017;71(4):618-629.
3. Packiam VT, Nottingham CU, Cohen AJ, Eggener SE, Gerber GS. No Effect of Music on Anxiety and Pain During Transrectal Prostate Biopsies: A Randomized Trial. *Urology*. 2018;117:31-35.
4. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. *JAMA*. 2017;317(24):2532-2542.
5. Zargar H, Marshall D, Siva G, King Q. Topical diltiazem before transrectal ultrasonography-guided biopsy of the prostate: a randomized controlled trial. *ANZ J Surg*. 2015;85(6):430-2.
6. Valdez-Flores RA, Campos-Salcedo JG, Torres-Gomez JJ, et al. Prospective comparison among three intrarectal anesthetic treatments combined with periprostatic nerve block during transrectal ultrasonography-guided prostate biopsy. *World J Urol*. 2018;36(2):193-199.
7. Gurbuz C, Canat L, Bayram G, Gokhan A, Samet G, Caskurlu T. Visual pain score during transrectal ultrasound-guided prostate biopsy using no anesthesia or three different types of local anaesthetic application. *Scand J Urol Nephrol*. 2010;44(4):212-6.
8. Otunctemur A, Dursun M, Besiroglu H, et al. The effectivity of periprostatic nerve blockade for the pain control during transrectal ultrasound guided prostate biopsy. *Arch Ital Urol Androl*. 2013;85(2):69-72.

9. Wang N, Fu Y, Ma H, Wang J, Gao Y. Advantages of caudal block over intrarectal local anesthesia plus periprostatic nerve block for transrectal ultrasound guided prostate biopsy. *Pak J Med Sci.* 2016;32(4):978-82.
10. Cesur M, Yapanoglu T, Erdem AF, Ozbey I, Alici HA, Aksoy Y. Caudal analgesia for prostate biopsy. *Acta Anaesthesiol Scand.* 2010;54(5):557-61.
11. Li M, Wang Z, Li H, et al. Local anesthesia for transrectal ultrasound-guided biopsy of the prostate: A meta-analysis. *Sci Rep.* 2017;7:40421.
12. Nazir B. Pain during transrectal ultrasound-guided prostate biopsy and the role of periprostatic nerve block: what radiologists should know. *Korean J Radiol.* 2014;15(5):543-53.
13. Yan P, Wang XY, Huang W, Zhang Y. Local anesthesia for pain control during transrectal ultrasound-guided prostate biopsy: a systematic review and meta-analysis. *J Pain Res.* 2016;11:9:787-796.
14. Yang Y, Liu Z, Wei Q, et al. The Efficiency and Safety of Intrarectal Topical Anesthesia for Transrectal Ultrasound-Guided Prostate Biopsy: A Systematic Review and Meta-Analysis. *Urol Int.* 2017;99(4):373-383.
15. Horinaga M, Nakashima J, Nakanoma T. Efficacy compared between caudal block and periprostatic local anesthesia for transrectal ultrasound-guided prostate needle biopsy. *Urology.* 2006;68(2):348-51.
16. Ikuerowo SO, Popoola AA, Olapade-Olaopa EO, et al. Caudal block anesthesia for transrectal prostate biopsy. *Int Urol Nephrol.* 2010;42(1):19-22.
17. Urabe F, Kimura T, Shimomura T, et al. Prospective comparison of the efficacy of caudal versus periprostatic nerve block, both with intrarectal local anesthesia, during transrectal ultrasonography-guided prostatic needle biopsy. *Scand J Urol.* 2017;51(4):245-250.
18. Kim DK, Lee JY, Jung JH, et al. What is the most effective local anesthesia for transrectal ultrasonography-guided biopsy of the prostate? A systematic review and network meta-analysis

of 47 randomized clinical trials. Sci Rep. 2019 Mar 20;9(1):4901. doi: 10.1038/s41598-019-41412-w.

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Table 1: Characteristics of Study Population

	IRLA	PPLA	IRLA + PPLA	CRA	p*
Age (years)	64.32±7.97	62.82±7.31	63.67±7.57	62.35±6.99	0.41*
BMI (kg/m²)	27.8±2.5	28.8±6.6	25.9±4.1	26.07±3.3	0.1*
PSA (ng/mL)	97.60±343.67	14.29±31.06	42.56±203	19.01±33.15	0.28**
IPSS	12.82±10.05	12.75±8.4	12.22±9.43	13.27±9.24	0.73**
Prostate volume (mL)	64.39±26.32	64.29±24.23	64.54±26.47	66.41±33.13	0.98**
Number of biopsy cores	13.07±3.07	12.85±2.23	13.20±2.82	12.50±1.03	0.83**

BMI: Body Mass Index; IPSS: International Prostate Symptom Score; PSA: Prostate Specific Antigene; IRLA: Intrarectal local anesthesia; PPLA: Periprostatic local anesthesia, CRA : Caudal regional anesthesia

* One-Way ANOVA test ** Kruskal Wallis test

Table 2: The groups in respect of the pain scores

	IRLA	PPLA	IRLA + PPLA	CRA	p*
During anesthesia induction		2.02±2.00	2.57±1.66	5.15±2.25	<0.001 ^a
During entry and movement of probe to the rectum	3.25±2.19	2.42±1.67	2.65±2.35	1.85±2.21	0.014 ^b
During penetration of the needle to the prostate	5.80±2.61	2.45±1.96	2.52±1.90	2.17±2.81	<0.001 ^c
30 minutes after the biopsy	3.05±1.63	1.62±1.51	1.45±1.28	1.40±1.75	<0.001 ^d
2 hours after the biopsy	2.07±1.54	1.75±1.61	1.37±1.21	1.05±1.23	0.015 ^e
1 day after the biopsy	1.30±1.30	0.87±1.20	0.82±0.95	0.82±1.25	0.197

IRLA: Intrarectal local anesthesia; **PPLA:** Periprostatic local anesthesia, **CRA :** Caudal regional anesthesia

* Kruskal Wallis test

^a PPLA vs CRA , IRLA + PPLA vs CRA (p<0.001, Bonferroni corrected Mann-Whitney test results)

^{b,e} IRLA vs CRA (p<0.001 ve p=0.002, respectively. Bonferroni corrected Mann-Whitney test results)

^{c,d} IRLA vs PPLA, IRLA vs IRLA + PPLA, IRLA vs CRA (p<0.001, Bonferroni corrected Mann-Whitney test results)

Table 3: Early complications of prostate biopsy

	IRLA	PPLA	IRLA + PPLA	CRA
No complications	4 (10%)	8 (20%)	8 (20%)	7 (17.5%)
Clavien 1	34 (85%)	32 (80%)	28 (70%)	26 (65%)
Clavien 2	2 (5%)	0	3 (7.5%)	5 (12.5%)
Clavien 3a	0	0	1 (2.5%)	2 (5%)

IRLA: Intrarectal local anesthesia; PPLA: Periprostatic local anesthesia,

CRA : Caudal regional anesthesia

Kruskal Wallis test was used

All p values were higher than 0.05

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Table 4: Late complications of prostate biopsy

	IRLA	PPLA	IRLA + PPLA	CRA
No complications	32 (80%)	35 (87.5%)	29 (72.5%)	33 (82.5%)
Clavien 1	5 (12.5%)	4 (10%)	8 (20%)	5 (12.5%)
Clavien 2	1 (2.5%)	0	3 (7.5%)	1 (2.5%)
Clavien 3a	0	1 (2.5%)	0	1 (2.5%)
Clavien 3b	1 (2.5%)	0	0	0
Clavien 4a	1 (2.5%)	0	0	0

IRLA: Intrarectal local anesthesia; PPLA: Periprostatic local anesthesia,
CRA : Caudal regional anesthesia
Kruskal Wallis test was used
All p values were higher than 0.05