SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 2, 149–154
https://doi.org/10.1080/21681805.2021.1885484

ARTICLE

Anorectal application of 5% lidocaine cream reduces pain prior to periprostatic nerve block during transrectal ultrasound guided prostate biopsy: Randomized, prospective controlled study

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ABSTRACT

Objectives: Trans rectal ultrasound guided prostate biopsy with periprostatic nerve block (PPNB) is performed following probe insertion and manipulation leaving these initial maneuvers uncovered in terms of pain control. We evaluated whether topical analgesia reduces pain during early stages of the procedure.

Patients and methods: Seven group prospective, randomized controlled study: groups 1–3: nerve block with 5 ml 1% lidocaine bilaterally plus perianal topical application of 10 ml 5% lidocaine cream. Groups 4–6 as in 1–3 plus digital application of 10 ml 5% lidocaine cream internally on rectal walls. For each approach exposure times were 5 (groups 1 and 4), 10 (groups 2 and 5) and 20 (groups 3 and 6) min, respectively. The control group (7) received PPNB only. Patients filled a 0–10 visual analogue scale (VAS) at five points: after probe insertion, during probe manipulation, following PPNB, after prostate biopsies and a global pain estimation.

Results: Two hundred and fifty-two patients were enrolled. Significant differences in VAS between all study groups and controls were observed at the pre-biopsy stages of the procedure. In multivariate analysis adjusted for prostate specific antigen, diabetes mellitus status, spinal disease, abnormal digital rectal examination and non- benign prostate hyperplasia histology, significance remained for probe insertion and intra-rectal manipulation. For each exposure time no significant differences were observed between topical application and topical + intra-rectal application. After PPNB, differences between study and control groups disappeared.

Conclusion: Topical anesthesia significantly reduces pain during early stages of prostate biopsy. Perianal application sufficed whereas intra-rectal application of local anesthetics does not add to pain control. Perianal application for 10 min seems to be optimal.

Abbreviations: PBx: prostate biopsy; TRUS: transrectal ultrasound; PPNB: periprostatic nerve block; PSA: prostate specific antigen; DRE: digital rectal examination; AS: active surveillance; CVA: cerebral vascular accident; TIA: transient ischemic attack; NVB: neurovascular bundle; VAS: visual analogue scale

ARTICLE HISTORY
Received 19 August 2020
Revised 25 January 2021
Accepted 29 January 2021

KEYWORDS
Anal canal; biopsy; lidocaine; pain; prostate

Introduction

Transrectal ultrasound guided prostate biopsy (TRUS PBx) is often performed in an ambulatory setting under local anesthesia. Previous studies have demonstrated that periprostatic nerve block (PPNB) is the superior analgesic method for TRUS PBx [1–4]. However, PPNB is unable to decrease the pain associated with intrarectal probe insertion and manipulation, nor with needle puncture through the rectal wall used to deliver an anesthetic agent periprostatically [2,5]. Several studies reported the efficacy of the anesthetic combination or perianal-intrarectal local anesthesia in combination with PPNB [2,5–9], suggesting better pain control compared to PPNB alone with no increase in complication rate. The method of pre-PPNB anesthesia differed, with the use of intrarectal lidocaine gel [5] or of lidocaine-prilocaine cream perianal-intrarectaly [6,7] with subsequent massaging of the cream onto the anal canal mucosa and anterior rectal wall. Ideal exposure time is also an issue, as lidocaine cream was exposed to the perianal/intrarectal mucosa for 20–30 min [6,7], adding considerable time to an otherwise short office procedure. Efficacy of topical anesthesia exposure times on normal mucosa was demonstrated with sufficient efficacy achieved within 5–10 min [10]. We studied anesthetic effect of 5% lidocaine cream with exposure times of 5, 10 and 20 min applied to the anal ring as well as to combined exposure to the anal ring and rectal walls, followed by PPNB. These groups were compared to a control group who received PPNB alone.

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Materials and methods

Study design

A randomized, prospective controlled study design was used to compare the pain level during transrectal ultrasound guided prostate biopsy. The study protocol was approved by the relevant ethical committee for experiments in humans and was registered in the Clinical Trials.gov Protocol Registration System (identification no. NCT04064047). All patients signed an informed consent form.

Study setting and population

Adult males aged 18 and over, referred for TRUS PBx were eligible for inclusion. Exclusion criteria were known sensitivity to lidocaine as well as pre-planned biopsy under general anesthesia. All patients had a negative urine culture prior to procedure. Due to a malfunction in the transrectal probe the study was regulatorily concluded by the PI (A.Z.) prior to the conclusion of the randomization process. The reason for that was that the TRUS probe broke down and the alternative probe utilized had a different diameter and different three-dimensional configuration.

Study protocol

Patients referred to TRUS PBx due to elevated prostate specific antigen (PSA), abnormal findings on digital rectal examination (DRE), as well as those referred for repeat biopsies as part of active surveillance (AS) protocol were enrolled. All patients signed an informed consent. Age, indication for biopsy, serum PSA levels, number of repeated biopsies sets, and time elapsed since the last biopsy, DRE findings and prostate size at TRUS examination were recorded after PPNB was performed. Demographics recorded were- presence of diabetes mellitus, cerebral vascular accident (CVA) in the past as well as transient ischemic attack (TIA), neurological disease, vertebral column injury, hypothyroidism and use of analgesic pain medication 48 h prior to biopsy.

All biopsies were performed using the BK pro focus 2202 transrectal ultrasound and the 8808 bi plane transrectal probe (BK medical, Herlev, Denmark).

Biopsy protocol

All patients received prophylactic fluoroquinolones prior to biopsy, starting the day prior to biopsy and concluding at day 3 following the procedure. None reported pain prior to procedure. Patients were randomly assigned, using a computerized random number generator, to one of the seven groups (Table 1). All seven groups received periprostatic nerve block (PPNB) using 1% lidocaine, 5 mL aimed to each neurovascular bundle (NVB). Six study groups were enrolled, groups 1–3 received topical application of 5% lidocaine cream to the anus with exposure times of 5, 10 and 20 min (groups 1–3,respectively). Groups 4–6 had a topical application of lidocaine as in groups 1–3, as well as rectal application of 10 mL 5% lidocaine cream inserted by a blunt syringe and evenly applied by digitization to the rectal walls with similar exposure times of 5, 10 and 20 min (groups 4–6, respectively). Group 7 served as a control group and received a non-anesthetic cream applied topically. A 12-core random template systematic biopsy was performed in all patients.

Pain assessment

Procedure stages: after probe insertion, during probe manipulation and prior to injection of PPNB, during lidocaine PPNB, after sampling, and lastly after probe withdrawal. Patients were informed on the procedure stages by the performing urologist. Pain was reported following each stage, using a 0 (no pain)–10 (worst imaginable pain) visual analogue pain scale (VAS) score. The patients were also asked to report procedure overall pain. All patients reported zero pain level at enrollment.

Data analysis

A sample size of 336 patients (48 per group) was calculated to detect a one point difference of the mean procedural

Table 1. Patient demographics and clinical parameters.

	5 min topical	10 min topical	20 min topical	5 min topical + intrarectal	10 min topical + intrarectal	20 min topical + intrarectal	Control	*p* Value
Number of patients	38	47	27	23	44	32	41	
Age (years, range)	67.5 (61.8–74)	68 (62–71)	68 (60–70)	66 (64–72)	67 (61–71)	66 (61–74)	67 (62–72)	0.99
Diabetes mellitus (%)	5 (13.2)	3 (6.4)	6 (22.2)	3 (13.0)	9 (20.5)	4 (12.5)	2 (5.3)	0.23
CVA/TIA (%)	4 (10.5)	2 (4.3)	1 (3.7)	1 (4.3)	4 (9.1)	1 (3.1)	0 (0)	0.41
Neurologic disease (%)	0 (0)	1 (2.1)	0 (0)	1 (4.3)	3 (6.8)	2 (6.3)	2 (5.3)	0.54
Spinal cord disease (%)	0 (0)	2 (4.3)	1 (3.7)	2 (8.7)	0 (0)	0 (0)	3 (7.9)	0.18
Hypothyroidism	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	0 (0)	1 (2.6)	0.35
Pain meds in past 48 hours (%)	0 (0)	1 (2.1)	0 (0)	2 (8.7)	1 (2.3)	1 (3.1)	2 (7.9)	0.29
Prostate clinical parameters								
PSA	6.4 (5.0–8.2)	5.9 (4.3–8.4)	7.0 (5.5–12.4)	5.5 (4.4–6.8)	6.9 (5.5–10.0)	6.0 (4.6–10.6)	6.3 (4.8–13.0)	0.096
Repeat biopsy (%)	9 (23.7)	12 (25.5)	7 (25.9)	7 (30.4)	9 (20.5)	6 (18.8)	7 (17.5)	0.90
Prostate size (cm^3, IQR)	52 (37–77)	57 (38–76)	44 (28–75)	57 (39–79)	44 (36–91)	52 (35–73)	50 (32–62)	0.56
Abnormal DRE (%)	9 (23.7)	15 (31.9)	7 (25.9)	2 (8.7)	12 (27.3)	14 (43.8)	21 (51.2)	0.05
Non BPH histology (%)	16 (42.1)	13 (27.7)	14 (51.9)	6 (26.1)	19 (43.2)	15 (46.9)	18 (43.9)	0.16

CVA: cerebral vascular attack; TIA: transient ischemic attack; PSA: prostate specific antigen; Kg: kilograms; SD: standard deviation; IQR: interquartile range; DRE: digital rectal examination; BPH: benign prostate hyperplasia.

pain score between the groups, with alpha error level of 5% and beta error level of 5% (corresponds to a 95% statistical power), assuming a standard deviation of one point for the mean procedural pain score. Data are expressed as mean- ± standard deviation (SD), median and interquartile range (IQR) for variables that do not follow a normal distribution, or frequencies for categorical data. Differences in means of groups were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test or chi-square test, as appropriate. Analysis of covariance (ANCOVA) using a general linear model (GLM) was performed to compare differences in VAS scores of pains between the study groups showing $p < 0.25$ in the univariate analysis were adjusted for PSA, diabetes mellitus (DM)status, abnormal DRE, non- benign prostate hyperplasia (BPH) histology and spinal disease. All not-normally distributed variables were log-transformed before insertion to ANCOVA multivariable models. *P* values below 0.05 were accepted as significant and all statistical tests were two-sided. All demographic and clinical variables were further analyzed using univariate and multiple logistic regression models. Data was analyzed using SPSS software (SPSS, version 18, Chicago, IL).

Results

Overall, 252 patients were enrolled and were randomized to one of the seven groups, comprising six study and one control group. Patient distribution, demographic and co-morbidity properties did not differ between study groups and are presented in Table 1. Mean age was 66.7 ± 7.0 years, being similar in all groups. Abnormal DRE had a high incidence in the control group with 21 patients (51%) having a suspicious prostate at palpation, while in the 5 min topical + rectal lidocaine exposure a low incidence was recorded, only two patients (9%) had a palpable abnormality. All together 80 patients (32%) had a suspicious palpable prostate. Palpable abnormality did not correlate directly to malignant pathology as can be seen in the intergroup distribution. Ninety-three patients (36%) were positive for malignancy, two with a neuroendocrine tumor and 91 with a Gleason score ≥6. Eight additional patients had high grade prostatic intraepithelial neoplasia (HGPIN), thus 101 patients (40%) had non-BPH histology. Low incidence of DM, hypothyroidism and prior history of cerebrovascular accident or transient ischemic attack were observed among all study groups. PSA and abnormal DRE were the only prominent potential confounders according to univariate analysis. Significant differences in VAS between all study groups and control were observed at all time frames. In a univariate analysis, significant differences were observed during probe insertion, during intrarectal probe manipulation and while performing PPNB. In a multivariate analysis adjusted for PSA, DM status, spinal disease, abnormal DRE and non-BPH histology, significance remained only for probe insertion and intrarectal manipulation (Table 2).

Comparing the same time exposure, no significant differences were observed between topical applications and topical + intrarectal application (Figure 1). At later procedure stages, after PPNB, the advantage seen previously for study groups over the control group has dissipated.

For each method of analgesia, significant reductions in VAS pain score were achieved in comparison with the controls (Figure 2). A non-significant reduction was seen with 10 and 20 min exposures.

Discussion

Trans-rectal ultrasound prostate biopsy is a common urological procedure, often accompanied by pain and discomfort. Previous studies have established peri-prostatic nerve block as the gold standard for procedural pain reduction, however the earlier stages of the procedure, including TRUS probe insertion to the anus, probe manipulation and anterior rectal wall penetration with PPNB needle is not affected by PPNB itself. We compared pain levels in different stages of the procedure, both prior to and after PPNB to assess both efficacy of anal anesthesia as well as the recommended exposure time. Results demonstrate an advantage in pain levels prior to PPNB in all study groups compared to the control group. Technique for lidocaine cream application did not seem to change pain perception. Comparing exposure times prior to initiation of procedure suggests that a 10 min exposure time is beneficial. This is demonstrated both in univariate and multivariate logistic regression model (Table 3), with, albeit not achieving significance, lower pain levels during anterior rectal wall puncture.

Previous studies demonstrated lack of efficacy of intrarectal lidocaine to reduce overall pain during biopsy [11], different stages of the procedure were not assessed separately, adding to the notion that such analgesia is redundant. Other attempts to reduce pain by using lidocaine suppositories have shown efficacy and improved pain [12,13]. Despite the significant improvement in the lidocaine suppository groups, the anesthesia was administered 30 min to 1h prior to biopsy limiting its practicality in everyday practice. However, in this

Table 2. Median pain VAS scores during different time frames of trans rectal ultrasound prostate biopsy.

Procedure stage	5 min topical	10 min topical	20 min topical	5 min topical + intrarectal	10 min topical + intrarectal	20 min topical + intrarectal	Control	*p* Value	P_{ANCOVA}*
During probe insertion	2.0 (1.0–3.1)	2.0 (1.0–3.0)	2.0 (1.0–3.5)	2.0 (1.0–3.5)	2.0 (1–3.0)	2.0 (1.0–2.5)	4.0 (2.25–5.0)	<0.001	0.07
During probe manipulation	1.0 (0.0–2.0)	0.5 (0–1.0)	0.5 (0–1.0)	1.0 (0.5–1)	0.75 (0.5–1.88)	0.5 (0–1.0)	1.5 (1.0–3.0)	<0.001	0.02
During PPNB	2.5 (2.0–4.5)	2.0 (1.0–3.0)	2.5 (1.0–3.0)	2.0 (2.0–3.0)	1.5 (1.0–2.88)	1.75 (1.0–3.0)	2.5 (1.5–4.0)	0.02	0.11
During biopsy	3.0 (1.5–4.3)	2.0 (1.5–3.5)	2.5 (1.5–3.5)	2.5 (2.0–4.0)	2.0 (1.5–4.0)	1.25 (1.5–3.5)	2.5 (1.0–4.0)	0.72	0.80
Overall estimate	3.0 (2.0–4.1)	2.0 (1.0–3.5)	2.5 (1.5–3.0)	2.5 (1.5–3.5)	2.5 (1.5–3.5)	2.5 (1.5–3.9)	3.0 (1.0–4.0)	0.35	0.58

*Adjusted for PSA, diabetes mellitus status, spinal disease, abnormal digital rectal examination and non-benign histology.
PPNB: periprostatic nerve block.

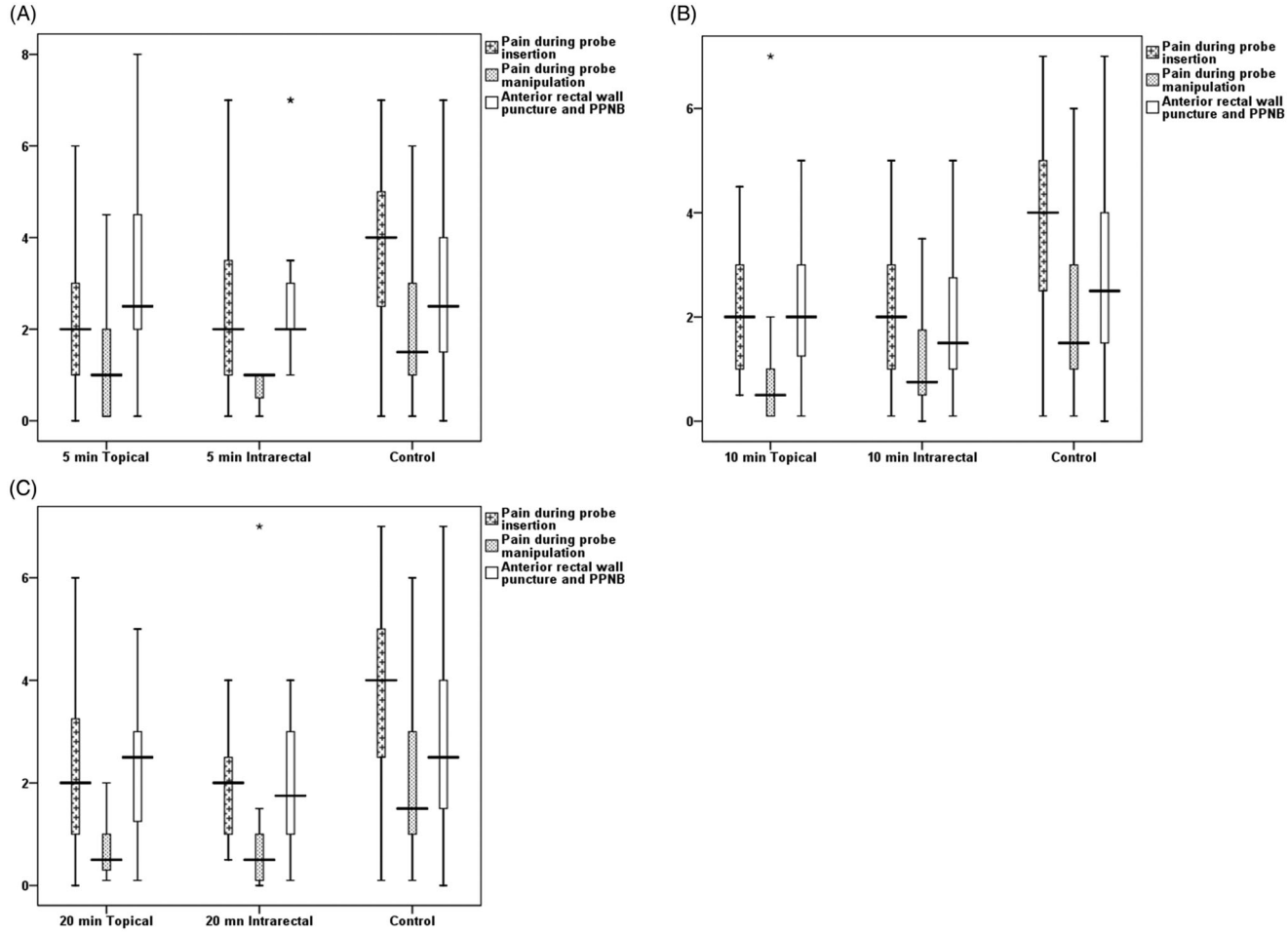

Figure 1. Box and whisker plots of pain level during early stages of transrectal ultrasound guided prostate biopsy (during probe insertion, during intrarectal probe manipulation and during anterior rectal wall puncture of peri-prostatic nerve block). Comparison of pain level between topical exposure, topical plus intrarectal exposure and control in 5 min exposure (A): $p < 0.001$ during probe insertion versus control, $p = 0.01$ during intrarectal probe manipulation versus control and $p = 0.86$ during anterior rectal wall puncture of peri-prostatic nerve block versus control; in 10 min exposure. (B): $p < 0.001$ during probe insertion versus control, $p < 0.001$ during intrarectal probe manipulation versus control and $p = 0.08$ during anterior rectal wall puncture of peri-prostatic nerve block versus control; in 20 min exposure. (C): $p < 0.001$ during probe insertion versus control, $p < 0.001$ during intrarectal probe manipulation versus control and $p = 0.12$ during anterior rectal wall puncture of peri-prostatic nerve block versus control.

study, a group receiving 2% lidocaine gel, prior to PPNB showed no improvement compared to a placebo plus PPNB. The latter suggest that PPNB is sufficient for biopsy anesthesia, although in this study too different TRUS PBx stages were not assessed separately. Results of our study support this notion that in the biopsy part of the procedure, analgesia is achieved by PPNB alone, with no added benefit of anorectal anesthesia.

In a recent study, pain score was compared between PPNB alone and a combination of PPNB with either anal/intrarectal prilocaine-lidocaine cream application, or perineal pudendal nerve block. Exposure time for the prilocaine-lidocaine cream was 5 min prior to probe insertion. Study results failed to demonstrate reduced pain levels during probe insertion and manipulation between the control and topical anesthesia group but showed lower pain score for the PPNB + perineal pudendal nerve block group [14]. In the study however, pain assessment was made after performing PPNB during re-entry of the TRUS probe and not at the initial probe insertion.

Several studies have attempted measures for reducing pain in TRUS PBx, such as pre-biopsy diazepam [15] which showed no difference between study and control group. A study comparing listening to classical music versus no music during the procedure, and which used lidocaine gel intra-rectally in both study and control groups, showed reduced pain and anxiety levels in the music group [16].

Optimal exposure times was also assessed, with similar results during the probe insertion and intra-rectal probe manipulation. During rectal wall puncture results showed a 10en min exposure time to be advantageous. Lack of pain variance between topical and intrarectal application at the rectal wall puncture is an interesting result. A possible explanation might be spreading of the lidocaine cream during probe insertion, thus applying it to the anterior rectal wall as well. This explanation however does not explain the fact that exposure time of the lidocaine cream to the rectal wall is shorter in topical exposure alone.

These results reinforce several previous studies showing efficacy in pain reduction also in shorter anal/rectal

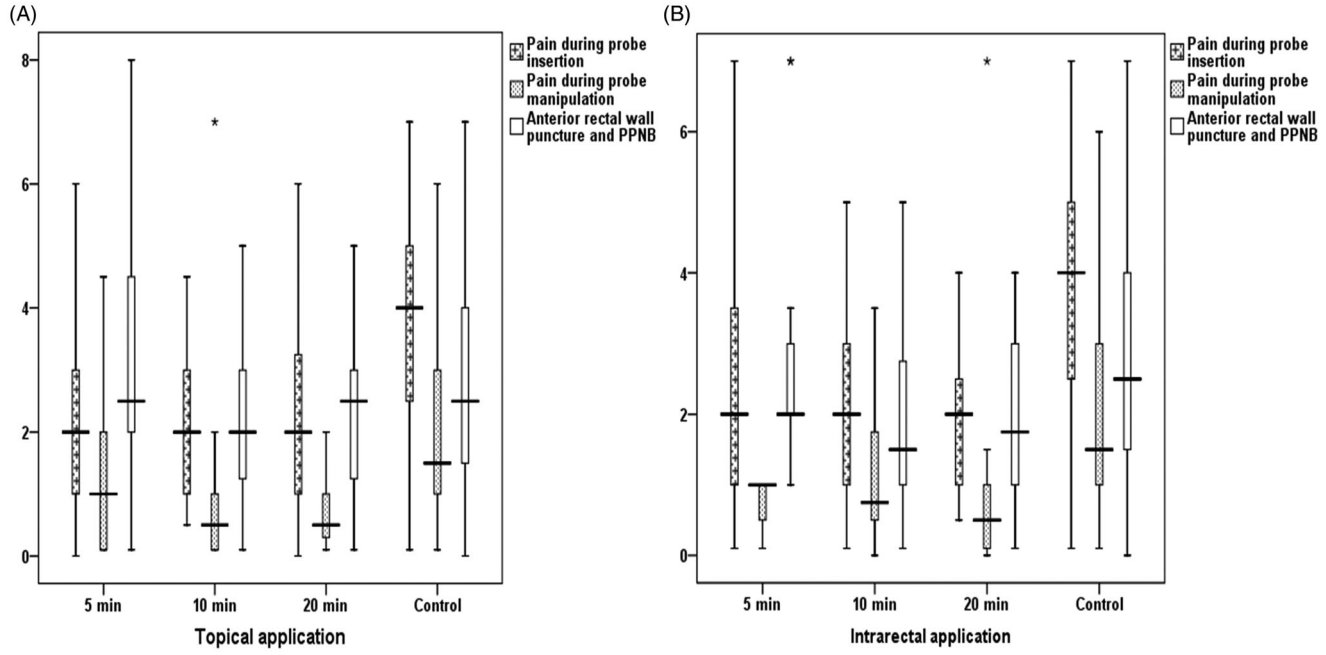

Figure 2. Box and whisker plots of pain level during early stages of transrectal ultrasound guided prostate biopsy (during probe insertion, during intrarectal probe manipulation and during anterior rectal wall puncture of peri-prostatic nerve block) with different exposure times. (A) Topical application. Pain level was significantly lower in case of 5, 10 and 20 min exposures versus control during probe insertion ($p < 0.001$), probe manipulation ($p < 0.001$), but didn't achieve statistical significance during periprostatic nerve block ($p = 0.09$); (B) Topical plus intrarectal application. pain level was significantly lower in case of 5, 10 and 20 min exposures versus control during probe insertion ($p < 0.001$), probe manipulation ($p < 0.001$) and periprostatic nerve block ($p = 0.04$).

Table 3. Univariate and multivariate (multinominal) logistic regression for pain VAS scores during different time frames of trans rectal ultrasound prostate biopsy.

Procedure stage	5 min topical OR (95% CI)	10 min topical OR (95% CI)	20 min topical OR (95% CI)	5 min topical + intrarectal OR (95% CI)	10 min topical + intrarectal OR (95% CI)	20 min topical + intrarectal OR (95% CI)	Control	*p* Value
Pain during probe insertion								
Univariate	0.68 (0.53–0.88)	0.66 (0.52–0.84)	0.67 (0.51–0.89)	0.73 (0.55–0.97)	0.67 (0.53–0.85)	0.68 (0.52–0.88)	Ref	0.002
Multivariate*	0.64 (0.48–0.87)	0.58 (0.43–0.79)	0.61 (0.44-0.85)	0.67 (0.48–0.93)	0.67 (0.51–0.88)	0.64 (0.48–0.87)	Ref	0.003
Pain during probe manipulation								
Univariate	0.78 (0.59–1.03)	0.52 (0.35–0.77)	0.41 (0.23–0.73)	0.54 (0.33–0.88)	0.61 (0.44–0.86)	0.54 (0.35–0.83)	Ref	<0.001
Multivariate*	0.81 (0.57–1.15)	0.42 (0.25–0.71)	0.39 (0.20–0.75)	0.51 (0.28–0.92)	0.64 (0.42–0.96)	0.59 (0.37–0.95)	Ref	0.001
Pain during periprostatic nerve block								
Univariate	1.10 (0.89–1.36)	0.81 (0.64–1.03)	0.90 (0.69–1.18)	0.97 (0.74–1.26)	0.79 (0.61–1.02)	0.78 (0.59–1.04)	Ref	0.049
Multivariate*	1.11 (0.86–1.43)	0.75 (0.55–1.02)	0.92 (0.68–1.25)	0.99 (0.74–1.35)	0.88 (0.67–1.16)	0.83 (0.62–1.12)	Ref	0.12
Pain during biopsy sampling								
Univariate	1.18 (0.94–1.48)	0.98 (0.78–1.24)	1.05 (0.81–1.36)	1.08 (0.82–1.41)	1.02 (0.81–1.29)	0.96 (0.74–1.25)	Ref	0.67
Multivariate*	1.17 (0.87–1.56)	0.89 (0.66–1.21)	1.02 (0.74–1.39)	1.07 (0.77–1.47)	1.02 (0.77–1.36)	0.99 (0.77–1.34)	Ref	0.90
Overall pain estimation								
Univariate	1.10 (0.86–1.39)	0.83 (0.64–1.08)	0.88 (0.66–1.18)	0.86 (0.63–1.18)	0.89 (0.69–1.15)	0.94 (0.72–1.22)	Ref	0.39
Multivariate*	1.07 (0.79–1.44)	0.78 (0.57–1.07)	0.87 (0.61–1.22)	0.87 (0.61–1.23)	0.93 (0.69–1.25)	0.99 (0.73–1.34)	Ref	0.49

*Adjusted for PSA, diabetes mellitus status, spinal disease, abnormal digital rectal examination and non-benign histology.
PPNB: periprostatic nerve block.

anesthesia exposure [17,18], although direct exposure time comparison was not performed in those studies.

As mentioned, due to TRUS probe malfunction, we were unable to reach our goal for patient recruitment.

Study strengths include a relatively large number of patients and maintaining similar procedure protocol in all study and control groups, by which possible confounders were excluded. To our knowledge this is the first study to assess pain levels at different stages of TRUS PBX, thus better establishing efficacy, as well as the recommended exposure times. Our results show that a 10 min peri-anal exposure time is sufficient to significantly reduce pain levels in the early stages of the procedure in comparison to previous studies, which suggested exposure times of 30 to 60 min. It also suggested that intra-rectal insertion of lidocaine is redundant and peri-anal application suffice.

Whether our results demonstrate clinical significance is debatable, taking into consideration that at the termination of the procedure, patients did not report an overall pain level reduction. A non-significant tendency for overall pain level reduction at termination of the procedure was most notable at the 10 min topical exposure group (Table 3). With that being said, we believe that pain level reduction of one or twopoints as in our study, is desirable at any part of the procedure.

Ethics approval

The study protocol was approved by the medical centers ethical committee for experiments in humans (ASF-289-15).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

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