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A novel method for pain control: infiltration free local anesthesia technique (INFLATE) for transrectal prostatic biopsy using transcutaneous electrical nerve stimulation (TENS)

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Abstract

Purpose To describe a novel method for the control of pain during prostate biopsies, infiltration free local anesthesia technique (INFLATE) for transrectal prostatic biopsies with no further needle insertions for local anesthetic infiltration.

Methods A total of 138 men with elevated prostate-specific antigen levels and/or abnormal digital rectal examination findings were included in the study. Of the patients, 73 were assigned to the INFLATE group and 65 to the TRUS-PNB group. Demographic data, PSA levels, findings of digital rectal examinations, and multiparametric prostatic magnetic resonance imaging were recorded. In the INFLATE group, a two-channel TENStem eco basic device with two electrodes was used for pain control during the biopsy. For the TRUS-PNB group, 60 mg lidocaine gel was given intrarectally in addition to infiltration of a prilocaine and bupivacaine mixture (5 mL of 2% prilocaine + 5 mL of 0.25% bupivacaine). Pain perception was assessed using a linear numeric rating scale.

Results The mean ages, BMIs, prostate volumes, and PSA levels were similar between the two groups ($p > 0.05$). Of the 56 participants with prostate adenocarcinoma, 28 were in the INFLATE group, and 28 were in the TRUS-PNB group with a 40.6% overall cancer detection rate. The mean preoperative and post-operative pain scores during probe insertion, biopsy and post-biopsy were similar between the groups ($p > 0.05$).

Conclusion The results of the study confirmed that INFLATE for transrectal prostate biopsy using a TENS device could safely and effectively be used for pain control with the advantage of two fewer needle attempts with no increase in significant complications.

Keywords Depression · Pain · Prostate biopsy · Transepidermal nerve stimulation

Introduction

Prostate cancer is one of the most diagnosed tumors among older men [1]. A prostate biopsy is one of the most commonly used outpatient procedures for diagnosis in the prostate. Astraldi first described the finger-guided prostate biopsy [2]. Since then, the technique has evolved to its current form of transrectal ultrasound-guided prostate biopsy with a periprostatic nerve block (TRUS-PNB), which is recommended by the European Association of Urology. Moreover, the use of multiparametric MRIs has increased in recent years to obtain higher clinically significant prostate cancer diagnoses by targeting prostatic lesions [3]. Despite its diagnostic importance, taking a prostate biopsy may be a bothersome procedure in which patients may suffer from fear of pain and feelings of discomfort [4]. Although some researchers have reported low rates of infection [5], it is reasonable

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to assume that an increased risk of systemic infection due to the administration of rectal route. Jeon et al. showed that the number of the biopsy was one of the factors that increased infectious complications [6]. Many studies have investigated different techniques to reduce the pain associated with biopsy. The EAU proposed the TRUS-PNB as the latest technique (level of evidence: 1b). Also, intrarectal local anesthetic gel applications have been reported to have a significantly lower impact than PNB applications [7, 8].

The transcutaneous electrical nerve stimulation (TENS) is a safe, effective, and easily applicable alternative to nonpharmacological pain management for clinical circumstances such as neuropathic pain, migraines, headaches, or surgery-related pain. Previous studies have investigated the impact of TENS on chronic prostatitis or pelvic pain syndrome [9]. In a TENS application, the adjustable power and frequency of electrical current generate a sensory intensity without motor contraction via endogenous opioid release [10].

In the present study, we proffer a safe and novel method for control of pain with less invasive characteristics during prostate biopsies: infiltration free local anesthesia technique (INFLATE) for transrectal prostatic biopsy with no further needle insertions (usually two) for local anesthetic infiltration.

Action mechanism of the TENS

TENS is a non-invasive peripheral stimulation technique used for pain control. During TENS, pulsed electrical currents stimulate the nerves under the skin. This device consists of a battery-powered hand-held component and electrode pads for attachment to the skin surface. Advantages include easy administration, easy titration of power, rapid onset of effect, and low side effects or little drug interactions [11]. Even in maximal power, TENS generates a strong but non-painful electrical paraesthesia at the site of electrode. Three TENS techniques are defined in the literature: conventional TENS (low intensity, high frequency), acupuncture-like TENS (high intensity, low frequency) and intense TENS (high intensity, high frequency) [12]. Our preference was the conventional TENS due to its high frequency (50–100 Hz), low intensity (paraesthesia, not painful), and small pulse width (50–200 µs). Conventional TENS relieves pain by a segmental mechanism. According to the segmental mechanism, TENS reduces ongoing nociceptor cell activity and sensitization in the central nervous system when applied to somatic receptive fields [11]. According to the pain gate mechanism, stimulation of the A-beta sensory fibers inhibits the C fibers that carry noxious stimuli and inhibits its transport throughout the spinal cord and to the higher centers. Adjusting the TENS frequency at higher rates (80–130 Hz) activates the pain control mechanism. Alternatively, stimulation of the A-delta fibers with lower frequencies (2–10 Hz) provides pain relief via activation of the endogenous opioid mechanisms in the spinal cord. Application of the 100 Hz stimulation with continuation with an interruption at the rate of 2–3 per second activates both the pain gate mechanism and endogenous opioid mechanisms [13].

Materials and methods

After obtaining the Institutional Board approval of the Ondokuz Mayis University Local Ethics Committee, the present study was conducted among the cohorts of patients at the Gazi State Hospital between January 2018 and March 2019. Written informed consent was obtained from the participants before the procedure. All the biopsies were taken by the same surgeon (M.S.B.).

Patient selection and evaluation

After a power analysis was performed, a total of 148 men with high prostate-specific antigen (PSA) levels and/or abnormal digital rectal examination findings were included in the study. Random sampling was done by tossing up a coin. However, two patients using cardiac pacemakers, defibrillators or electronic devices for the central nervous system were directly recruited into the TRUS-PNB group. Ten participants were excluded due to lack of complete data. Of the patients, 73 were assigned to the INFLATE group and the remaining 65 to the TRUS-PNB group. Demographic data, comorbidities, total and free PSA, free-to-total PSA ratio, findings of digital rectal examinations, transrectal ultrasonic prostate volume estimations were acquired. The cognitive biopsy was taken under the light of multiparametric prostatic MRI findings, where present. Participants in the groups were given ciprofloxacin 500 mg twice a day, starting 1 h before the procedure and continued for 3 days. For patients receiving anticoagulant therapy, the medication was discontinued 5 days before the procedure.

INFLATE for transrectal prostate biopsy

In the INFLATE group, we used a two-channel TENStem eco basic device with two electrodes on both sides (Pierenkemper GmbH, Hoernsheimer Eck 19, 35,578 Wetzlar, Germany). According to the Medical Device Regulation (MDR) classification system in accordance under Annex IX of the EU Directive 93/42/EEC, this device carries an IIa classification (low–medium risk).

For this study, we attached one of the adhesive electrodes connected to the first channel to the right anterior suprapubic skin surface, and the corresponding electrode to the right posterior presacral skin surface. Similarly, one of the electrodes connected to the second channel was attached to the

left anterior suprapubic skin surface, and the corresponding electrode was attached to the left posterior presacral skin surface, as shown in Fig. 1a, b. At least 3–6 min before the biopsy, bipolar stimulation (TENS stimulation) was started from lower energy increasing to 60 mA with 100 Hz frequency and 150 µs pulse width. Total biopsy time for this group was defined as the sum of placement of TENS electrodes plus biopsy retrieval time in seconds (Fig. 1c). Amplitude was individually adjusted for each participant to a level that they could tolerate. In both groups, none of the patients received non-steroidal or opioid analgesic before and after the biopsy. The patients were positioned in the left lateral decubitus position with hip flexion and were routinely given 60 mg of lidocaine gel intrarectally. We attached the electrodes on the level of the thoracic 11 dermatomes (Fig. 2a, b). Additional suspected areas were identified and recorded with digital rectal examination before the end-firing TRUS probe was inserted into the rectum (Fig. 3). Prostatic volume was automatically calculated using the formula "height × width × length × π/6". Using an automatic biopsy gun (18 G × 25 cm, Bard Max-Core, Bard Peripheral Vascular Inc., Tempe, AZ, USA), a standard 10-core systematic prostate biopsy was taken for the patients with no history of prostatic biopsy, and an 18-core biopsy was performed for those who had a prior history of negative biopsy.

In the TRUS-PNB group, following the intrarectal administration of 60 mg lidocaine gel, an additional infiltration of 5 mL of prilocaine and bupivacaine mixture (5 mL of 2% prilocaine and 5 mL of 0.25% bupivacaine) was applied to each prostate–seminal vesicle junction. Total biopsy time for this group was defined as the sum of local anesthetic infiltration 4–6 min before biopsy plus biopsy retrieval time in seconds. Following probe insertion, prostatic volume and possible suspected areas were recorded. Prostate volume was calculated with transrectal ultrasound using the formula as mentioned earlier. A total of ten needle insertions were made for prostatic tissue sampling and an 18-core biopsy for those who had a negative history in addition to two needle insertions for local anesthetic infiltration was performed in this group.

Patients were asked about their pain perception based on previous pain experiences using a 10-point linear numeric

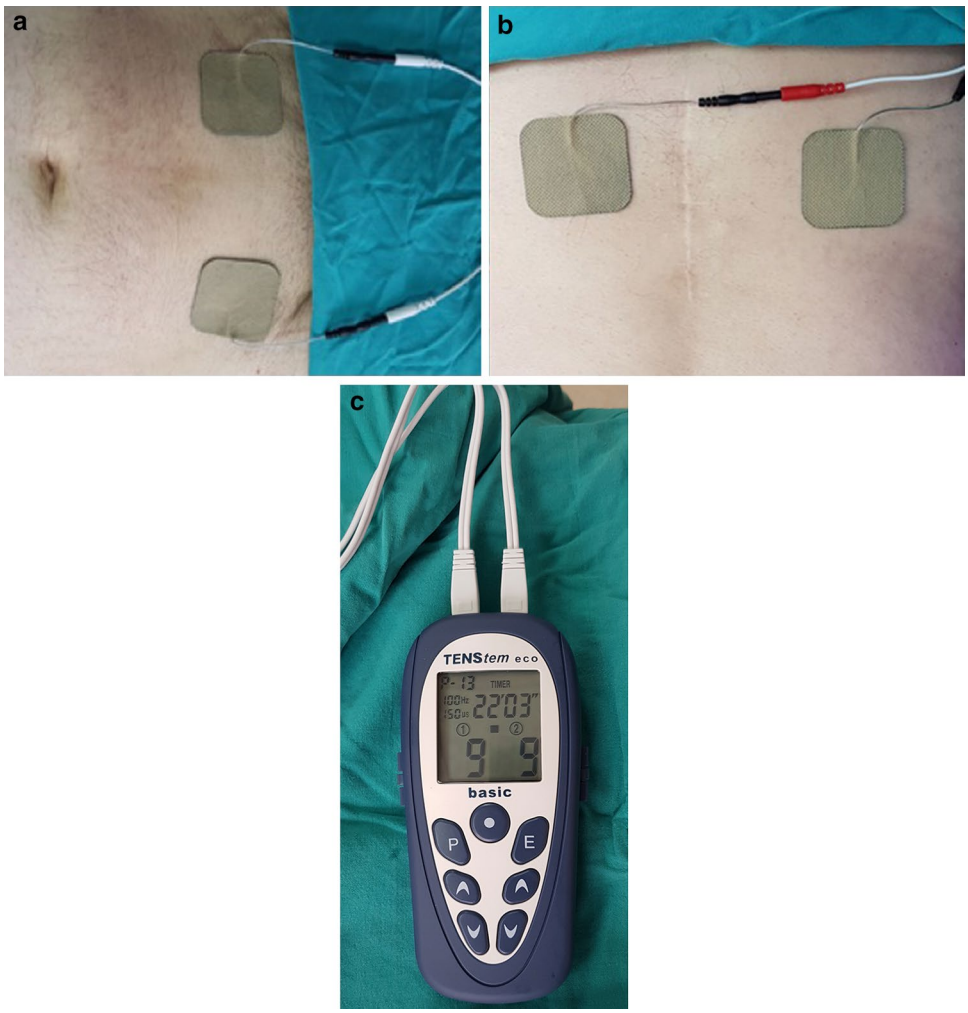

Fig. 1 **a** TENStem electrode placement anteriorly right and left inguinal skin. **b** TENStem electrode placement posteriorly right and left presacral skin. **c** TENStem eco basic device (Pierenkemper GmbH, Hoernsheimer Eck 19, 35,578 Wetzlar, Germany)

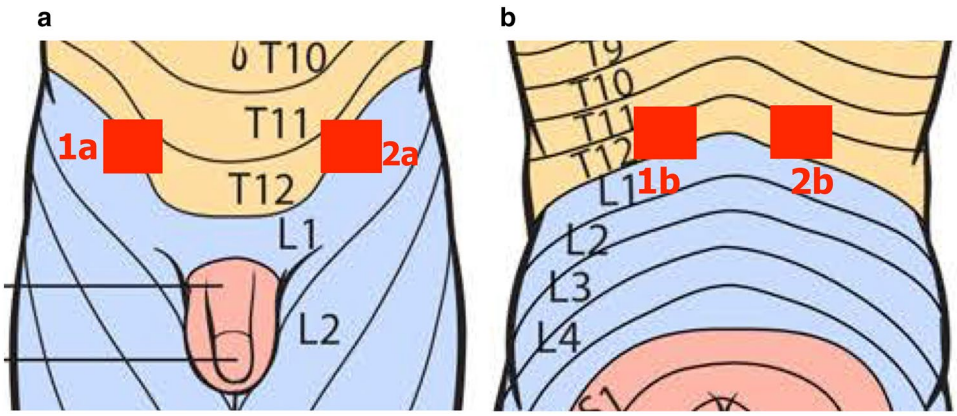

Fig. 2 **a** Attachment points of the electrodes corresponding to the skin dermatome lines, anteriorly (1a—right side, 2a—left side). **b** Attachment points of the electrodes corresponding to the skin dermatome lines, posteriorly (1b—right side, 2b—left side)

Fig. 3 Appearance of end-firing transrectal biopsy probe

rating scale (NRS). The NRS is a segmented numeric scale that reflects the intensity of pain in which a respondent can select a whole number (0–10) [14]. The NRS questionnaire was applied for each participant during rectal probe insertion, biopsy retrieval and 15 min after the procedure. Concerning different age categories (40–49 years, 50–59 years, 60–69 years, 70–79 years and over 80 years), the numerical pain scores were evaluated in the groups. Lower ratings reflect less pain. The patients reported the pain scores. For avoiding bias, the patients were informed about their histopathological diagnosis after they completed the NRS questionnaire.

Inclusion criteria

- Patients with PSA values higher than 2.5 ng/mL according to the European Randomized Study of Screening for Prostate Cancer (ERSPC) [15].
- Any suspicious lesions on DRE.
- Any suspicious lesions on multiparametric prostatic MRI (PIRADS III, IV or V).

Exclusion criteria

- Uncorrected coagulopathy.
- Patients with a cardiac pacemaker or defibrillator.
- Arrhythmia or use of any electronic device for the central nervous system.
- Subjects with significant anorectal disease.
- Epileptic patients taking treatment.
- Alcoholic patients.
- Narcotics abusers.
- Patients with a skin lesion on the electrode attachment sites.

Procedure

The primary outcome measures were arrived at by comparing the pain perception, complication rates, and psychogenic statuses of the groups.

Statistical analysis

The Statistical Package for the Social Sciences v. 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Data were given as mean ± standard deviation (SD), percentages, or numbers. Differences were calculated using an independent samples *t* test, Mann–Whitney *U* test, or Chi square test. Pearson's correlation test was used for BMI and the NRS score. A p value < 0.05 was accepted as significant.

Results

The mean ages of the participants were 66.3 ± 8.3 and 65.6 ± 9.9 years old ($p = 0.63$); the mean BMIs were 26.2 ± 4.9 and 27.7 ± 3.7 kg/m^2 ($p = 0.08$); and the mean prostate volumes were 64.3 ± 55.5 and 57.4 ± 37.7 mL ($p = 0.43$) in the INFLATE and TRUS-PNB groups, respectively. The mean biopsy times were similar between the groups ($p = 0.08$) (Table 1). The mean total PSA, free PSA levels, and free-to-total PSA ratios were 11.2 ± 15.5, 3.0 ± 8.3, and 0.5 ± 2.3 ng/mL in the INFLATE group and 9.6 ± 9.3, 3.8 ± 10.8, and 0.2 ± 0.1 ng/mL in the TRUS-PNB group ($p > 0.05$). A total of 56 patients (40.6%) were

Table 1 Demographic and clinical variables in the groups

	INFLATE group ($n=73$)[a]	TRUS-PNB group ($n=65$)[b]	p
Age (mean ± SD, years)	66.3 ± 8.3	65.6 ± 9.9	0.63
BMI (mean ± SD, kg/m^2)	26.2 ± 4.9	27.7 ± 3.7	0.08
Digital rectal examination findings (n, %)			–
Normal	61 (55.0)	28 (23.4)	
Nodule in a lobe	9 (8.1)	3 (2.7)	
Nodules in both lobes	3 (5.1)	3 (2.7)	
Hard and irregular	2 (2.5)	2 (1.8)	
Biopsy time (mean ± SD, s)	465.9 ± 107.1	411.5 ± 52.1	**0.001**
PSA (mean ± SD, ng/mL)			
Total	11.2 ± 15.5	9.6 ± 9.3	0.47
Free	3.0 ± 8.3	3.8 ± 10.8	0.67
Free/total	0.5 ± 2.3	0.2 ± 0.1	0.29
Prostate volume (mean ± SD, mL)	64.3 ± 55.5	57.4 ± 37.7	0.43
Number of biopsy cores (mean ± SD)	10.7 ± 2.1	10.6 ± 2.3	0.80
TENStem preset energy level (mean ± SD, min–max)			–
Left side	9.8 ±2.4 (6–17)	–	
Right side	9.8 ± 2.4 (6–17)	–	
Histopathological findings (n, %)			
Benign prostatic hyperplasia	37 (50.7)	29 (44.6)	
Suspected malignancy	6 (8.2)	4 (6.2)	
Prostatic intraepithelial neoplasia (high-grade PIN)[c]	2 (2.7)	4 (5.6)	
Prostatic adenocarcinoma	28 (38.4)	28 (43.1)	
Complications required hospitalization (n, %)			
Intraoperative complication	–	–	–
Systemic infection	3 (4.1)	2 (3.1)	0.67
Minor complications (n, %)			
Hematuria	13 (17.8)	6 (9.2)	0.09
Hematospermia	3 (4.1)	1 (1.5)	0.33
Rectal bleeding	2 (2.7)	–	–
Urinary retention	1 (1.4)	1 (1.5)	0.97

A p-value less than 0.05 is accepted statistically significant (in bold)

[a]*INFLATE* infiltration free local anesthesia technique

[b]*TRUS-PNB* transrectal ultrasound-guided periprostatic nerve block

[c]*PIN* prostatic intraepithelial neoplasia

diagnosed with prostate cancer, of whom 28 were in the INFLATE group (38.4%) and 28 were in the TRUS-PNB group (43.1%). The mean numbers of the biopsy core were 10.7 ± 2.1 and 10.6 ± 2.3 (p = 0.80). Post-biopsy hospitalization was required in three (4.1%) and two (3.1%) patients due to high fever in the INFLATE and TRUS-PNB groups, respectively. Nonsignificant hematuria was recorded in 13 patients (17.8%) in the INFLATE group and 6 in the TRUS-PNB group. Three patients experienced nonsignificant hematospermia in the INFLATE group, and only one patient was in the TRUS-PNB group. Findings of digital rectal examination are summarized in Table 1.

The mean preset TENS energy level was 9.8 ± 2.4 for both two sides in the INFLATE group. The mean probe insertion, biopsy, and post-biopsy NRSs were 0.9 ± 0.8, 1.9 ± 1.2, and 0.6 ± 0.6 in the INFLATE group and, 1.2 ± 1.5, 1.9 ± 1.8, and 0.4 ± 0.8 in the TRUS-PNB group, respectively ($p > 0.05$) (Table 2). Pain scores were similar between the INFLATE group and the TRUS-PNB group, for those who are 40–49 years, 50–59 years, 60–69 years, 70–79 years, and over 80 years ($p > 0.05$) (Table 3). Aborting the procedure was required in none of the participants due to pain, except in one with anal stenosis in TRUS-PNB group.

Table 2 Changes in pain sensation using numeric rating scale in the groups

	INFLATE group[a]	TRUS-PNB group[b]	*p*
Stage of the procedure			
Rectal probe insertion (mean ± SD)	0.9 ± 0.8	1.2 ± 1.5	0.25
Tissue sampling with biopsy needle (mean ± SD)	1.9 ± 1.2	1.9 ± 1.8	0.90
Post-biopsy (following 15 min after the procedure) (mean ± SD)	0.6 ± 0.6	0.4 ± 0.8	0.40

[a]*INFLATE* infiltration free local anesthesia technique

[b]*TRUS-PNB* transrectal ultrasound-guided periprostatic nerve block

Table 3 Pain perceptions according to numeric rating scores in different age categories

Age groups (patient number)	Numeric rating scores		*p*
	INFLATE group (mean ± SD)	TRUS-PNB group (mean ± SD)	
During probe insertion (mean)			
40–49 (4)	–	1.0 ± 0.8	–
50–59 (25)	1.0 ± 0.8	1.4 ± 1.2	0.50
60–69 (56)	0.9 ± 0.8	1.4 ± 2.1	0.25
70–79 (38)	0.9 ± 0.8	0.8 ± 0.7	0.66
Older than 80 (1)	0.4 ± 0.6	1.3 ± 0.6	0.15
During prostate biopsy retrieval			
40–49 (4)	–	0.5 ± 1.0	–
50–59 (25)	1.7 ± 0.9	2.2 ± 1.8	0.44
60–69 (54)	2.2 ± 1.6	2.6 ± 1.9	0.14
70–79 (35)	1 ± 0.8.8	1.2 ± 1.1	0.58
Older than 80 (1)	1.5 ± 0.6	2.7 ± 3.0	0.08
15 min after the procedure			
40–49 (4)	–	0	–
50–59 (25)	0.7 ± 0.5	0.4 ± 0.5	0.66
60–69 (54)	0.7 ± 0.8	0.7 ± 0.9	0.30
70–79 (35)	0.3 ± 0.5	0.3 ± 0.5	0.73
Older than 80 (1)	0.5 ± 0.6	0.7 ± 1.2	0.07

Discussion

The prostate biopsy technique in prostate cancer diagnosis has evolved to its present form. Due to the different perspectives of patients and clinicians, this diagnostic procedure is still a challenge. For patients, a prostate biopsy is a stringent stage due to pain and fear expectations. On the other hand, clinicians aim to diagnose clinically significant prostate cancer and to keep their patients away from recurrent biopsies and biopsy-related serious complications.

Biopsy-related pain may occur through a complex mechanism with psychological, physical and social aspects. Pain threshold, fear of cancer diagnosis, anxiety and social inhibition towards biopsy position are psychosocial factors, whereas the prostate size and the number of biopsy core are among the physical factors. A painless and complication-free procedure may ease future biopsy decisions of patients [16]. Our results showed that the mean prostatic volumes and the mean number of the biopsy taken were similar between the INFLATE and TRUS-PNB groups ($p > 0.05$). Our results concerning mean prostate volumes and the number of biopsies clearly showed no statistically significant difference between the INFLATE and TRUS-PNB groups. Also, the above-mentioned physical factors did not affect pain ($p > 0.05$) (Table 2).

Since PNB is more effective in pain control than intrarectal lidocaine gel alone [8, 17], the PNB + intrarectal local anesthetic gel use has become the gold standard [18]. However, the PNB requires two additional needle insertions for bilateral local anesthetic infiltration. The introduction of a biopsy needle into the prostatic–seminal vesicular junction for local anesthetic infiltration is a painful procedure for routine TRUS-TRIB procedure itself. The use of intrarectal local anesthetic gel in the TRUS-PNB group contributed to pain control by lubrication and decreased friction, in addition to superficial anesthesia of the rectal mucosa. However, it was an advantage of the INFLATE procedure to provide adequate pain control without the need for two additional needle punctures for local anesthetic infiltration. In the INFLATE technique, neurons controlling the pain travel within the superior hypogastric plexus originated from T10–12 segments and the pelvic plexus originated from S2–4 spinal nerves [19]. Our results on pain control have clearly shown that the INFLATE technique activated endogenous pathways with the advantage of two less needle entries. Proper placement of the TENS electrodes and adjustment of TENS intensity and frequency are critical factors for adequate analgesia and prevention of unpleasant feelings or complications. A reddish coloration and burning or itching at the electrode–skin junction can occur due to increased blood circulation. However, we observed none of these side effects in the present study.

From the physician's perspective, to provide higher cancer detection rate (CDR) rate, a greater number of biopsy core, use of computerized biopsy systems, and multiparametric

prostate MRI may be needed [20–22]. The CDR for prostate is reported in the range of 27–60% according to the preferred technique, the number of the biopsy cores obtained, and PIRADS scoring system [20, 23]. Our preference was to take a 10-core prostate biopsy for patients who would undergo a prostate biopsy for the first time. For those who had PIRADS 3 or higher scores according to multiparametric prostate MRI, we performed a cognitive prostate biopsy. Our results showed that individual CDRs were 38.4% and 43.1% in the INFLATE and TRUS-PNB groups, respectively, and the overall CDR was 40.6%. Because the present study was not based on a new imaging model, we predicted that CDRs might be similar for the INFLATE and TRUS-PNB groups. The INFLATE technique did not negatively affect the overall CDR in this study (Table 2).

Different measures, such as prophylactic antibiotic use or enema before the biopsy, may decrease infectious complications. However, more needle insertions carry a higher risk of infectious complications [6, 24]. In the classical TRUS-PNB method, the number of needle biopsies planned to be taken plus two additional needle insertions for local anesthetic infiltration are all responsible for the infectious complications. When the biopsy gun is triggered, a prostate biopsy is obtained in a velocity of 25 m/s. On the other hand, local anesthetic infiltration using additional two needles is used under pressure for a few seconds to the prostatic–vesicular angle. However, which one is more responsible for the bacterial inoculation has not been studied to date.

In a prospective randomized study, severe febrile complications were reported between 4.2% and 5.6%, of which at least 4/5 required hospitalization [25]. Our results showed that the rate of infection requiring hospitalization after biopsies was similar in the INFLATE (4.1%) and TRUS-PNB (3.1%) groups, as were other minor complications (Table 1).

With respect to the procedure time, the INFLATE technique required slightly higher procedure times compared to the TRUS-PNB group due to the additional period between the attachment of the electrodes to the skin and biopsy retrieval ($p = 0.08$).

Strengths of this study

1. This report is the first study investigating the impact of TENS on pain management during prostate biopsy.
2. The less invasive nature of the INFLATE procedure due to the need for two fever needle applications.

Limitations of this study

1. Lack of data investigating the effect of TENS on pain management during the prostate biopsy, and lack of comparison between the data.
2. The absence of a third group due to the small number of participants (patients in the INFLATE group that previously underwent TRUS-PNB) and lack of comparison between the two different experiences.
3. Absence of the question "What technique would you prefer if you had to have a biopsy again?" was not asked the patients, who had rebiopsy in both groups.

Conclusion

The results of this study confirmed that in selected cases, the INFLATE technique which has been described as a novel transrectal prostate biopsy method provided effective pain control with the advantage of two fewer needle attempts, did not lead to an increase in serious septic complications requiring hospitalization with similar cancer detection rates. The INFLATE technique is an acceptable method concerning the patients and physicians' perspectives, but further comprehensive, randomized, prospective controlled studies are needed to reach a satisfactory conclusion.

Author contribution MSB: Protocol/project development, data collection or management, data analysis, manuscript writing/editing. OC: Data analysis, manuscript writing/editing, protocol/project development. RB: Data analysis, manuscript writing/editing. RA: Data analysis, manuscript writing/editing. This study has been approved by the appropriate institutional and/or national research ethics committee (21.01.2019/B.30.2.ODM.0.20.08/1913-67) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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