RESEARCH ARTICLE

Efficacy and safety of three different analgesic methods for patients undergoing transrectal ultrasound-guided prostate biopsy: a prospective, randomized controlled trial

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Abstract

Background: Recent evidence suggests that additional analgesic regimens to periprostatic nerve block (PPNB) anesthesia provide substantial pain relief during transrectal ultrasound-guided prostate biopsy. In this regard, we investigated the efficacy and safety of tramadol alone or in combination with parecoxib as adjunct regimens to PPNB anesthesia.

Material and Methods: A total of 51 participants were randomly allocated into three study groups: Group 1 received PPNB anesthesia, Group 2 received tramadol and PPNB anesthesia, whereas Group 3 received both tramadol and parecoxib as adjunct regimens to PPNB anesthesia. The pain was evaluated at three different time points during biopsy: at the time of probe insertion (NRS1), at the time of PPNB anesthesia (NRS2), and at the time of the actual biopsy itself (NRS3), using a numeric rating scale (NRS) of pain. Safety was evaluated by the occurrence of complications and adverse effects.

Results: The mean NRS1 score was statistically significantly different in Groups 2 and 3 than in Group 1 (2.4 ± 1.3 and 1.1 ± 1.2 vs. 4.5 ± 1.8; $p < 0.0167$). We found a statistically significant difference regarding NRS 2 score in Groups 2 and 3 than in Group 1 (2.6 ± 1.4 and 1.1 ± 1.3 vs. 4.1 ± 1.3; $p < 0.0167$). The mean NRS1 and NRS2 scores were found to be statistically significantly different in Group 3 than in Group 2 (1.1 ± 1.2 vs. 2.4 ± 1.3 as well as 1.1 ± 1.3 vs. 2.6 ± 1.4; $p < 0.0167$). Also, a statistically significant difference was found between Groups 2 and 3 regarding hematuria episodes [0 (0.0) vs. 5 (29.4); $p < 0.0167$].

Conclusion: Tramadol as an adjunct regimen to PPNB anesthesia is a safe and straightforward technique that provides a significant analgesic effect. The effectiveness is even higher when tramadol is combined with parecoxib. HIPPOKRATIA 2020, 24(4): 166-172.

Keywords: Biopsy, analgesia, periprostatic nerve block, tramadol, parecoxib

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Introduction

Transrectal ultrasound (TRUS)-guided biopsy of the prostate gland is one of the most common invasive examinations in the urology setup. Although it is considered a relatively innocuous procedure, the majority of patients perceive it as a physically and psychologically traumatic experience. Various methods have been described to achieve satisfactory pain control, ranging from a simple application of anesthetic gels to complex nerve blocks[1,2]. The current gold standard pain relief method during TRUS-guided biopsy is the injection of lidocaine into the neurovascular bundles of the prostate gland, known as periprostatic nerve block (PPNB) anesthesia[3,4]. However, despite PPNB, some patients report pain; therefore, improving anesthesia is of great importance.

Pain experienced during TRUS-guided biopsy of the prostate gland is cumulative in character and has a threefold origin: i) pain occurring during the ultrasonography probe's insertion into the rectum, which is due to stretching of the anal sphincter; ii) pain that occurs during needle puncture while administering local anesthetic at the PPNB site, and iii) pain that occurs during the biopsy needle's insertion into the prostate gland for the collection of multiple prostate core biopsies (actual biopsy)[5].

According to recent studies, PPNB anesthesia effectively reduces the pain attributed to biopsy needle insertion into the prostate gland, but it is ineffective in reducing the pain caused by the ultrasound probe insertion into the rectum[6-7]. The pain caused by the anesthetic infiltration at the PPNB site was shown in another study[8] to be equivalent to or even comparable to that of the biopsy itself. Therefore, if adjunct regimens are added before the PPNB anesthesia, pain due to the reasons mentioned above might be alleviated.

Material and Methods

The present study is a single-center, prospective, open-label, randomized, three-arm, parallel-group, non-placebo, controlled clinical trial conducted at the 2nd Urology Department of the School of Medicine of Aristotle University of Thessaloniki over a period of five months (October 2017 till March 2018). The scientific review board of Papageorgiou General Hospital approved the Ethical clearance of the study [290/20-12-2017/ (topic 3.3) session]. The trial was registered at the Australian New Zealand clinical trials registry (ANZCTR) and allocated the ACTRN: ACTRN12619001760167. Participants who met the inclusion criteria were randomly allocated into three study-arms using an electronic platform generator[9] of randomized permuted blocks. Group 1 received PPNB anesthesia alone by infiltrating 10 ml (5 ml per side) of 1 % lidocaine hydrochloride solution at the junction between the seminal vesicle and the prostate base (mount Everest sign) as described by Nash et al. Group 2 received a single intramuscular injection of tramadol 100 mg/ml as an adjunct regimen to PPNB anesthesia. In contrast, Group 3 received a single dose of intramuscular injection of both tramadol 100 mg/ml and parecoxib 40 mg/ml as adjunct regimens to PPNB anesthesia. Each participant was asked to give written informed consent for both the TRUS-guided prostate biopsy procedure and their participation in the clinical trial.

Study Population

We considered eligible for the present study, all consecutive patients referred to the urology department for early detection of prostate cancer due to increased serum prostate-specific antigen, and/or abnormal digital rectal examination[10]. We set as exclusion criteria: previous history of prostate biopsy, concurrent analgesia administration, active anorectal pathology (anal fissures, strictures, hemorrhoids), chronic prostatitis and pelvic pain syndrome, known allergy to investigative regimens, contraindications to non-steroidal anti-inflammatory drugs (NSAIDs) such as gastric or duodenal ulcers, patients with bleeding diathesis, and those with impaired intellectual ability.

Prostate Biopsy Technique

All TRUS-guided prostate biopsies were performed in an identical manner to ensure that the groups were as homogeneous as possible. Pre-procedural participants' preparation was performed by self-administered cooper enema (once in the evening before the biopsy) and oral prulifloxacin (600 mg once daily, starting from the day before the biopsy and continued for another four days).

Upon enrollment of participants in the trial, only those randomly allocated into Group 2 and Group 3 received a further preprocedural intramuscular injection of tramadol 100 mg/ml alone or in combination with parecoxib 40 mg/ml, respectively. The duration between preprocedural intramuscular injection and biopsy was one hour, whereas the duration between the PPNB and the actual biopsy (obtaining prostatic core samples) was five minutes.

The biopsies were performed using a biplane 5-10 MHz handheld probe of the Pro Focus Ultrasound System (BK Medical, Copenhagen, Denmark). Participants were placed in a lithotomy position, and initially, digital rectal examination (DRE) was performed, followed by a transrectal ultrasound survey of the prostate gland where the total prostate volume was measured. After completion of the prostate imaging and volume calculation, 10 ml of 1 % lidocaine was injected bilaterally at the PPNB site of the prostate gland. A routine, extended prostate biopsy scheme of 12 prostatic cores, including six parasagittal and six biopsies targeted laterally covering the base, mid zone, and apex, was obtained using an 18-gauge biopsy needle (UNIGUN, MEDAX medical device, Poggio Rusco, Italy) loaded in an automatic reusable biopsy gun (MEDGUN, MEDAX medical device, Poggio Rusco, Italy).

Immediately after completion of each particular step, participants were asked to assess the pain experienced at the time of probe insertion (NRS 1), at the time of PPNB anesthesia (NRS 2), and at the time of the actual biopsy itself (NRS 3). A numeric rating scale (NRS) of pain was used, ranging from zero to ten points, with zero corresponding to no pain or discomfort and ten to worst possible pain or discomfort (Figure 1).

Participants were monitored up to two hours after biopsy completion to record any potential severe complications and/or adverse effects related to the study's interventions. Participants were discharged home only after successful voiding and provided that no major bleeding was evident.

Post-procedural complications and adverse effects were interviewed by telephone seventy-two hours later. We phrased questions to all participants in the same manner to minimize any possible bias during data collection.

Study Outcomes

The primary endpoint was the efficacy of adjunct regimens as assessed by a decreased NRS score compared to the current gold standard technique (PPNB). Based on a literature review and comparing our findings with previous studies, a minimum difference of one point in the 10-point NRS score was considered clinically significant.

The secondary endpoint was safety as evaluated by

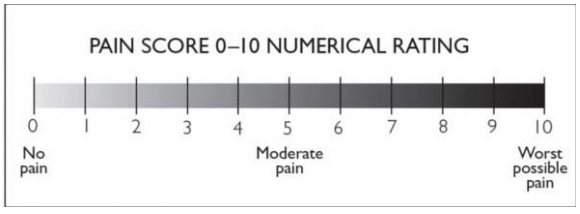

Figure 1: The Numeric Rating Scale used in the current study is a unidimensional measure of pain intensity in adults and represents a segmented numeric version of the visual analog scale and similarly is anchored by terms describing pain severity extremes.

the occurrence of post-procedural complications and adverse effects related to each analgesic study protocol alone and compared to the current gold standard technique (PPNB).

Statistical Analysis

To detect statistically significant differences of such magnitude with 81 % power and a two-sided 5 % significance level using ANOVA with two degrees of freedom contrasts, approximately 11 patients per group were required. All continuous variables of participants' characteristics were checked to be normally distributed according to the Shapiro-Wilk test, and they are reported as the mean ± standard deviation and minimum-maximum values. We calculated the differences in patients' characteristics for continuous variables using one-way analysis of variance (ANOVA) with $\alpha = 0.05$. We report categorical variables as frequencies and relative frequencies. Cochran's rule was accepted; therefore, we used the chi-square test with $\alpha = 0.05$. Assessing normality for NRS scores between participants in Groups 1, 2, and 3 suggested that data were not normally distributed; thus, we used the non-parametric Mann-Whitney U test. Differences in complication rate were reported with frequencies and relative frequencies, and were assessed using Fisher's exact test because Cochran's rule was not accepted. Adjustments for multiple testing were performed using Bonferroni's procedure as indicated. *Post hoc* pairwise comparisons among the three groups were conducted both in ANOVA and Chi-Squared tests, while the adjustment of the Type I error was made by Holm's sequential Bonferroni method (comparison-wise $\alpha = 0.0167$). All analyses were performed using R®, version 3.5.0.[11].

Results

A total of 100 consecutive patients that were referred to the urology department were screened for complying with the eligibility criteria. Of those patients, only 51 (51.0 %) were eligible to participate in the study. The main reasons for patients' exclusion were a history of previous prostate biopsy (32.0 %), impaired intellectual ability (6.0 %), and anorectal pathology (6.0 %). The discontinuation rate of the participants was zero among all groups. Figure 2 demonstrates the participants' allocation in the research study.

Eligible participants were, further, randomly allocated into three study groups. Each study group consisted of 17 patients. Table 1 summarizes the general characteristics of participants. No statistically significant differences were seen between the three study groups with respect to age ($p = 0.24$), DRE ($p = 0.70$), and prostate volume ($p = 0.27$).

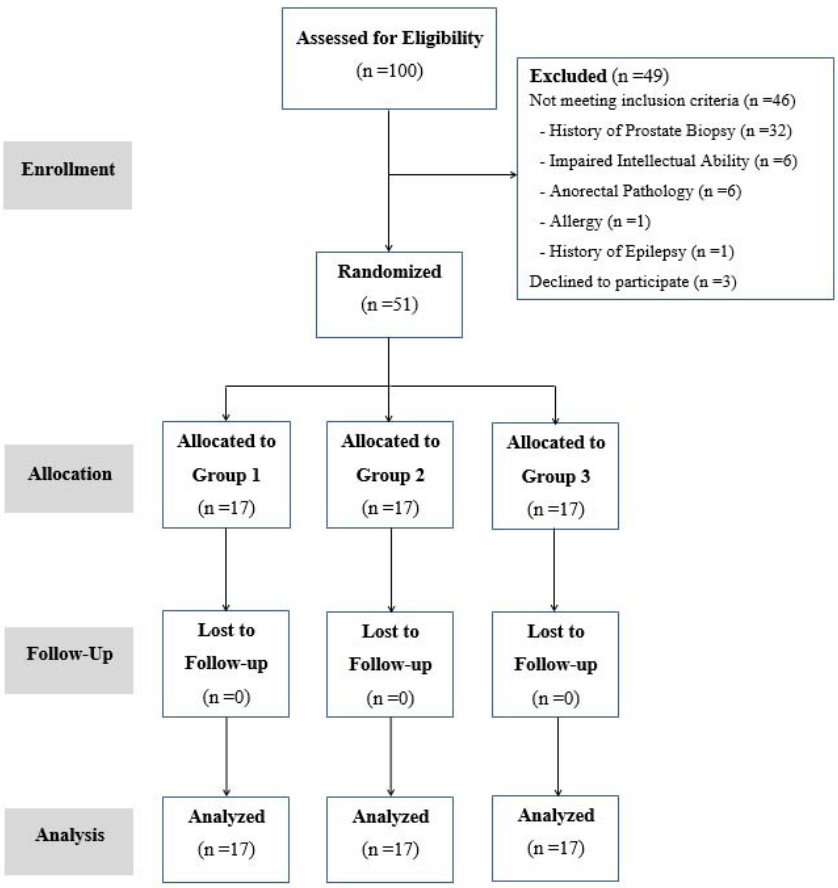

Figure 2: Consort Flow Diagram of the study showing the participants' allocation in the research study.

Table 1: Summary of participants' characteristics who underwent TRUS-guided prostate biopsy and were included in the study.

General Characteristics	Group 1 (n =17)	Group 2 (n =17)	Group 3 (n =17)	Total (n =51)	p-value
Age (years)					
Mean ± SD	67.53 ± 9.48	65.88 ± 8.20	62.65 ± 7.75	65.35 ± 8.58	0.245
Min-Max	51 - 85	51 - 79	49 - 79	49 - 85	
DRE, n (%)					
Positive	5 (29.4%)	5 (29.4%)	7 (41.2%)	17 (33.3%)	0.703
Negative	12 (70.6%)	12 (70.6%)	10 (58.8%)	34 (66.7%)	
PSA plasma level (ng/ml)					
Mean ± SD	10.27 ± 6.75	6.07 ± 2.86	7.27 ± 3.26	7.87 ± 4.88	0.032
Min-Max	3.90 - 32.80	2.08 - 12.19	2.83 - 14.35	2.08 - 32.80	
Prostate volume (cm^3)					
Mean ± SD	65.92 ± 38.12	57.94 ± 28.79	49.39 ± 19.49	57.75 ± 29.97	0.279
Min-Max	20.2 - 174.1	25.7 - 140.6	25.4 - 88.6	20.2 - 174.1	
Prostate biopsy cores, n (%)					
12	17 (100 %)	17 (100 %)	17 (100 %)	51 (100 %)	-
≠ 12	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	

The one-way analysis of variance (ANOVA) was used to determine whether there are any significant differences between the means of study groups; TRUS: transrectal ultrasound, PSA: prostate-specific antigen, DRE: digital rectal examination, n: number, SD: standard deviation.

The primary outcome was to investigate statistically significant differences in mean NRS scores between the three study groups. Table 2 summarizes the mean values of each study group at three different points in time during prostate biopsy. The mean pain score during the ultrasound probe's insertion into the rectum (NRS 1) was statistically significantly different in Groups 2 and 3 than it was in Group 1 (2.4 ± 1.3 and 1.1 ± 1.2 vs. 4.5 ± 1.8; $p < 0.0167$). A statistically significant difference was also found in the mean pain score (NRS 2) during lidocaine infiltration at the PPNB site in Groups 2 and 3 than in Group 1 (2.6 ± 1.4 and 1.1 ± 1.3 vs. 4.1 ± 1.3; $p < 0.0167$). Moreover, the mean pain score (NRS 1) during the ultrasound probe's insertion into the rectum as well as the mean pain score (NRS 2) during lidocaine infiltration at the PPNB site was found to be statistically significantly different in Group 3 than it was in Group 2 (1.1 ± 1.2 vs. 2.4 ± 1.3 as well as 1.1 ± 1.3 vs. 2.6 ± 1.4; $p < 0.0167$). No statistically significant differences were found between the three study groups regarding pain relief during actual biopsy itself (NRS 3).

The second outcome was to investigate the safety of each study group alone, as well as in comparison with the control group. Table 3 summarizes the complication episodes occurring in each study group. Based on the safety results presented in Table 3, no statistically significant differences (all $p > 0.05$) were seen between the three study groups regarding syncope episodes, allergic reactions, rectal bleeding, acute urinary retention, and fever. Hematuria was the only complication with a statistically significant difference ($p = 0.04$) between the three study groups. Consequently, a further statistical analysis was pursued to investigate which pairs of groups demonstrate statistically significant differences. Table 4 summarizes the statistical results between study groups, expressed as p-values. Hematuria episodes were found to be statistically significantly different between Group 2 and Group 3 [0 (0.0) vs. 5 (29.4); $p < 0.0167$]. No other statistically significant differences were found between the three study groups concerning hematuria episodes.

Discussion

Although TRUS-guided prostate biopsy is a well-tolerated diagnostic examination for many patients, it can provoke significant pain and discomfort. As it was mentioned before, the pain during TRUS-guided prostate biopsy has a three-fold origin: i) the pain caused during the ultrasonography probe's insertion into the rectum that is due to the stretching of the anal sphincter, ii) the pain caused during needle puncture while depositing local anesthetic at PPNB site, and iii) the pain caused during the biopsy needle's insertion into the prostate gland in order to collect multiple core biopsies (actual biopsy). Various methods have been described to achieve satisfactory pain control, including general anesthesia, intrarectal local anesthesia (IRLA) by the use of lidocaine gel[12], intravenous administration of propofol[13], inhalation of nitrous oxide[14], intravenous conscious sedation by the use of fentanyl and midazolam[15], orally administration of rofecoxib[16], and the intrarectal administration of diclofenac suppositories[1] before prostate biopsy. However, some of those methods have doubtful efficacy, while others require a trained team and an operating theater; therefore, they are considered impractical to perform in an outpatient setting.

In 1996 Nash et al were the first who reported considerable pain relief after injection of a local anesthetic agent at the PPNB site. After that, several studies[4,17] have examined the efficacy and safety of PPNB anesthesia, thus suggesting PPNB as the most effective and safe technique for providing substantial pain relief during TRUS-guided prostate biopsy. However, even though there is a broad consensus over the effectiveness of PPNB anesthesia on

Table 2: Comparison of pain by the use of numeric rating scale scores at three different points in time during transrectal ultrasound-guided prostate biopsy between three groups that were included in the study.

Numeric Rating Scale	Group 1	Group 2	Group 3	p-value		
				Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
NRS 1	4.5 ± 1.8	2.4 ± 1.3	1.1 ± 1.2	0.001	<0.001	0.008
NRS 2	4.1 ± 1.3	2.6 ± 1.4	1.1 ± 1.3	0.013	<0.001	0.005
NRS 3	3.8 ± 1.3	3.2 ± 0.6	2.9 ± 1.1	0.322	0.026	0.122

Values are reported as mean ± standard deviation. The Mann-Whitney U test is used to compare two unrelated or independent samples when there is violation of normality or small sample size. NRS: numeric rating scale, assessing the pain experienced at the time of probe insertion (NRS 1), at the time of PPNB anesthesia (NRS 2), and at the time of the actual biopsy itself (NRS 3).

Table 3: Comparison of participants' complications and adverse effects that underwent transrectal ultrasound-guided prostate biopsy and were included in the study.

Complications	Group						Total		p-value
	1		2		3				
	Count	n %	Count	n %	Count	n %	Count	n %	
Syncope Episode									
No	17	100 %	17	100 %	17	100 %	51	100 %	-
Yes	0	0 %	0	0 %	0	0 %	0	0 %	
Allergic Reactions									
No	17	100 %	17	100 %	17	100 %	51	100 %	-
Yes	0	0 %	0	0 %	0	0 %	0	0 %	
Hematuria									
No	15	88.2 %	17	100 %	12	70.6 %	44	86.3 %	**0.043**
Yes	2	11.8 %	0	0 %	5	29.4 %	7	13.7 %	
Rectal Bleeding									
No	17	100 %	16	94.1 %	16	94.1 %	49	96.1 %	-
Yes	0	0 %	1	5.9 %	1	5.9 %	2	3.9 %	
Urinary Retention									
No	16	94.1 %	16	94.1 %	16	94.1 %	48	94.1 %	-
Yes	1	5.9 %	1	5.9 %	1	5.9 %	3	5.9 %	
Fever									
No	16	94.1 %	17	100 %	17	100 %	50	98 %	0.361
Yes	1	5.9 %	0	0 %	0	0 %	1	2 %	

Cochran's rule was not accepted; therefore, Fisher's exact test was used to determine whether there is a significant association between two categorical variables. n: number.

Table 4: Comparison of hematuria episodes between 51 participants that underwent transrectal ultrasound-guided prostate biopsy and were included in the study.

Complication	Group 1 (n =17) Count (%)	Group 2 (n =17) Count (%)	Group 3 (n =17) Count (%)	p-value		
				Group 1 vs. 2	Group 1 vs. 3	Group 2 vs. 3
Hematuria Episodes	2 (11.8)	0 (0.0)	5 (29.4)	0.145	0.203	**0.015**

Cochran's rule was not accepted; therefore, Fisher's exact test was used to determine whether there is a significant association between two categorical variables. n: number.

alleviating pain during the collection of multiple prostate core biopsies, recent studies[18,19] have concluded that PPNB anesthesia provides an only minor effect on the pain that is associated with the ultrasonography probe's insertion into the rectum and with the infiltration of local anesthetic at the PPNB site.

The results of our study confirm the effectiveness and safety of the PPNB anesthesia for pain management during prostate biopsy by reporting a mean pain score of 3.8 points in NRS, which is considered an effective pain alleviation according to the international association for the study of pain[20]. However, the injection of 1 % lidocaine at the PPNB site provides only a remarkable pain relief during the collection of multiple prostate biopsy cores.

The first randomized controlled trial that investigated the efficacy and safety of tramadol as an adjunct regimen to PPNB anesthesia for pain management during TRUS-guided prostate biopsy was published in 2006 by Pendleton et al[21]. The authors concluded that the administration of 75 mg tramadol and 650 mg acetaminophen orally with periprostatic 1 % lidocaine before the prostate biopsy procedure is an easy, effective, and safe method of pain

control during all steps of the prostate biopsy. After that, Olmez et al[22] investigated the efficacy of tramadol and its combination with lornoxicam, an NSAID of the oxicam class, to manage pain during TRUS-guided prostate biopsy, and concluded that the use of lornoxicam or tramadol for pain relief is an effective and comfortable method.

It is now well established that even though there is a widely held view among clinicians that 1 % lidocaine infiltration at the PPNB site is an adequate method for a painless prostate biopsy procedure, there is clear evidence that tramadol as an adjunct regimen to PPNB anesthesia provides substantial pain relief during TRUS-guided prostate biopsy. Furthermore, there is also considerable evidence that tramadol is a safe regimen with only minimal adverse effects[23]. The overwhelming consensus of our study with the aforementioned clinical trials is that tramadol as an adjunct regimen to PPNB anesthesia was proven to be a safe and effective regimen for the management of pain during the prostate biopsy procedure, especially at the time of ultrasound probe insertion into the rectum and at the time of lidocaine infiltration at the PPNB site. The effect size was even larger when tramadol was combined with parecoxib as adjunct regimens to PPNB anesthesia. However, a considerable increase in hematuria episodes was observed in the co-medication of these drugs.

Parecoxib is a selective NSAID that belongs to a class of medicines called cyclooxygenase-2 (COX-2) inhibitors, which in contrast to other NSAIDs, do not affect platelet aggregation, as proved by previous studies[24-26]. Nevertheless, when combined with warfarin, parecoxib has been shown to increase the propensity to bleeding[27], which might be due to the inhibitory effect of parecoxib on the CYP2C9 enzyme also metabolizing warfarin. Moreover, we assume that COX-2 inhibitors may affect fibrinolysis similarly to aspirin[28] or that an increased number of hematuria episodes in Group 3 might be procedure-specific.

Even though our research reached its aims, there are few unavoidable limitations. First, it was conducted only on a small number of patients referred for prostate biopsy at our urology department. Therefore, to generalize the results, the study should have involved more patients at various urology departments.

Second, the pain is a complex perceptual experience that remains difficult to quantify, so inaccurate pain evaluation may have occurred with the pain intensity scale.

Third, the pain experienced during the prostate biopsy is largely dependent on the dexterity of the physician. In our study, prostate biopsies were performed by seven randomly allocated physicians in each study group, thereby may influence the internal validity of the study.

Fourth, participants were asked to think back on possible adverse effects that have been occurred during the last three days, which may have introduced recall bias. Lastly, although some studies have already investigated the effect of tramadol for pain management during TRUS-guided prostate biopsy, there is still major literature need to verify both the effectiveness and the safety of tramadol alone or in combination with parecoxib as an adjunct regimen to PPNB anesthesia.

Conclusion

Our findings indicate that intramuscular injection of 100 mg tramadol as an adjunct regimen to PPNB anesthesia is a simple and safe technique that provides significant analgesic effect during TRUS-guided prostate biopsy, especially at the time of the ultrasound probe's insertion into the rectum and at the time of lidocaine infiltration at the PPNB site. The effect size is even larger when tramadol is combined with intramuscular injection of 40 mg parecoxib one hour before the PPNB anesthesia.

Conflict of interest

The authors have nothing to disclose.

Acknowledgements

The study constitutes the first author's Master of Science Thesis (supervised by the last author) in Medical Research Methodology (May 2018) titled "Comparative study of different analgesia protocols for prostate biopsy", at the School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, and as such the full text was deposited and is freely available through the Institutional Repository (https://ikee.lib.auth.gr/). A Certificate (No 49/31.5.21), issued by the MSc Medical Research Methodology program, declares that this is not considered published work and the author reserves the right to submit this study for peer review and publication. The study has been reported in abstract form at 24th Pan-Hellenic Urology Congress in Athens (11-13 October 2018) under the title "Comparative study of different analgesia protocols for prostate biopsy".

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