ORIGINAL RESEARCH

Comparing the Efficacy of Periprostatic Nerve Block Alone versus Periprostatic Nerve Block Plus Oral Tramadol Plus Paracetamol Tablet for Pain Control of Patients During and After Transrectal Biopsy of the Prostate Gland: A Randomized Controlled Trial

Eric Roudel C. Ecalnir, MD; Kathleen R. Gonzales, MD, FPUA and Eduardo M. Anonuevo, MD, FPUA

Urology Service, Victoriano Luna Medical Center

Objective: To compare the efficacy of periprostatic nerve block (PPNB) alone versus periprostatic nerve block plus oral Tramadol+Paracetamol Tablet for pain control during and after transrectal ultrasound-guided (TRUS) biopsy of the prostate gland.
Methods: This was a double-blind, placebo-controlled randomized clinical trial. The authors randomized 40 male patients each to either PPNB or PPNB plus oral tramadol and paracetamol (37.5mg/325mg) an hour prior to prostate biopsy. A ten-point visual analog scale was used to measure pain intensity and was recorded upon insertion of the ultrasound probe, during the biopsy, and one hour after the procedure.
Results: The two groups were similar in terms of baseline characteristics. Reductions in pain scores were statistically significantly different ($p<.001$) for each group when comparing pain from at point of insertion of the probe versus during biopsy and versus one-hour post-operatively. However, when comparing the two groups, the pain scores were not statistically significantly different upon insertion of the probe ($p=.68$), during the biopsy ($p=.26$) and one-hour post-operatively ($p=.54$).
Conclusion: Tramadol and paracetamol combination in addition to periprostatic nerve block produces pain relief similar to standard periprostatic nerve block alone.

Keywords: periprostatic nerve block, transrectal ultrasound, prostate biopsy

Introduction

Prostate cancer is the second most common cancer and the sixth leading cause of cancer deaths worldwide, with an estimated 899,000 cases and 258,000 deaths annually.[1] Transrectal ultrasound-guided prostate biopsy is essential in the diagnostic investigation of patients with clinical suspicion of prostate malignancy due to gland alterations on digital rectal examination, or elevation of the prostatic specific antigen (PSA).[2] The indications for prostatic biopsy has increased in the last decade owing to increase in life expectancy, better diagnostic methods, and Public Health Campaign intensification.[3] This procedure is performed in most medical centers by trained urologists and radiologists. However, this exam is almost always accompanied by pain sensation, because of the transrectal ultrasonography (TRUS) probe introduction, or by the biopsy itself.[4] Some series have shown that almost 90% of patients have pain during the procedure, making the experience with this diagnostic procedure traumatic.[4] However, the methods of pain measurement by these previous

studies have been subjective, underestimating the real level of upset being suffered by the patients. Recently, there has been an increasing interest in various methods for providing local anesthesia during the procedure. The aim was to evaluate the efficacy of local anesthetic using periprostatic block alone or a combination of a block and systemic anesthesia in decreasing the pain and discomfort experienced by patients undergoing TRUS-guided biopsy of the prostate.

Methods

This was a double-blind, randomized controlled trial comparing periprostatic nerve block alone (Group A) versus periprostatic nerve block plus oral Tramadol+Paracetamol tablet (Group B) for pain control during and after TRUS-guided biopsy of the prostate gland. This study included patients who consulted at the out-patient department clinic from May 2018 to May 2019.

The authors included males aged 45 years and above who had indications for prostate biopsy such as abnormal digital rectal exam (DRE), elevated prostate-specific antigen (PSA) (>4 ng/ml) levels and abnormal ultrasound findings.

Excluded were those patients with allergy to Lidocaine, Tramadol and Paracetamol, patients with acute prostatitis, inflammatory diseases, and other rectal conditions such as mixed hemorrhoids and fistula-in-ano, patients with fever, taking anti-coagulants, and patients with deranged bleeding parameters.

Sample Size

For this superiority trial, it was assumed that the mean difference in the pain score pre and post procedure in Group B was 2.89 ± 1.63 versus Group A which was 4.32 ± 1.9. These values were estimated from the study of Seckiner, et al.[5] An allowance of 20% is added to the total sample size to account for possible drop outs. This sample size is able to detect a statistically significant difference in pain scores at 0.05 level of significance, yielding a study power of 80%. The formula for difference of 2 means was utilized in the sample size calculation. This study utilized a total of 80 patients (40 per arm).

Patients were randomly assigned to each group by using the restricted randomization method to achieve a balance in the group size. Group A patients were given 1 Multivitamins Tablet while Group B patients were given 1 Tramadol+Paracetamol 37.5 mg/325 mg tablet 1 hour prior to procedure. Both patients and urologist were blinded as to the kind of medication given. Patients were put on non per orem diet (NPO) 8 hours prior to procedure. All patients were given antibiotic prophylaxis of Fosfomycin 3 g sachet dissolved in 1 glass of water on the night prior to the procedure. Bowel preparations were made using 2 tablets Dulcolax on the night prior to the procedure and 2 Dulcolax suppositories per rectum given 6 hours prior to the procedure. During the formal biopsy, patients assumed the lithotomy position. A TRUS of the prostate was performed using a 7.5-MHz transrectal/transvaginal probe, and the prostate was evaluated in both sagittal and transverse planes to calculate the volume. Local anesthesia was given by infiltration of 10 cc of 2% Lidocaine into the prostate, 5 cc in each side (Mount Everest Sign). An 18-gauge, 25-cm automatic biopsy gun was used to obtain a standard of twelve core biopsies. The Universal Pain Assessment Tool (UPAT) (Figure 1) was used to assess the pain scale of each patient.[13] The verbal descriptor scale of the UPAT (VAS: 0 for no pain and 10 for excruciating pain) was used to assess the pain scores during insertion of trans-rectal probe (VAS 1), during formal biopsy (VAS 2), and one hour after (VAS 3) the needle biopsy procedure. Pain scores were measured and recorded for analysis by an assigned nurse independent of the physician who performed the biopsy. After observation for more than an hour, the patient was discharged and advised to take an oral antibiotic for 7 days. Complications such as hematuria, hematospermia, rectal bleeding, and infection were determined by interviewing each patient on his follow-up to the hospital 1 week after the prostate biopsy.

Statistical Methodology

All analyses were done using Statistical Package for the Social Sciences (Version 21). Analysis using intention to treat principle was done. Testing for baseline homogeneity of sample was carried out using independent t-test for continuous numerical data and chi-square test for categorical data.

Comparison of pre-procedural pain score within each group was done using Wilcoxon Signed Ranks Test. Comparison of post procedural scores between 2 groups was done using non-parametric Mann Whitney Test. All tests with p values <0.05 were considered statistically significant. The analyses were carried out by a blinded statistician.

Ethical Considerations

The investigators sought the approval of the Ethics Review Board of the institution. All provisions regarding patient recruitment, participation, safety, autonomy, and confidentiality were embodied in the informed consent. The provisions of the proposal were in accordance with the declaration of Helsinki and the National Ethical Guidelines of the PCHRV Version 2017. Patient anonymity was ensured by coding the data forms and the informed consent form. Only the following people had access to the data: the principal investigator and the junior residents. All electronic data were stored in an encrypted format in Microsoft excel with a password. The soft copy of the data will be stored perpetually in the department's central computer with a security password. All hard copies of the data form and informed consent form will be stored for a maximum of 5 years and shall be incinerated afterwards. Patients were oriented that the collated results will be orally reported in different scientific symposia and gatherings of different medical communities in the future.

Results

This clinical trial randomized 80 patients to either receive periprostatic nerve block plus oral tramadol and paracetamol or periprostatic nerve block plus placebo. The two groups were similar in terms of age (mean 66.7 versus 65.5, p=.43), PSA level (mean 36.5 versus 27.5, p=.38), and prostate size (mean 38.2 grams versus 42.1 grams, p=.35). (Table. 1) Likewise, there was no significant difference in the final biopsy findings of both groups (p=.34). Lastly, there were no complications, drop out of participants, losses or exclusions after randomization that took place during the conduct of this study.

Comparison of Pain Scale Scores

Table. 2 summarizes the pain scale scores of the two groups. Reduction in pain scores were significantly (p<.001) noted for both groups when comparing the point of insertion of the probe, during biopsy and at one-hour post-operative. (*Treatment arm*, mean= 6.8, 2.1 and 1.3, respectively; *Placebo arm*, mean=6.7, 2.3 and 1.2, respectively). However, differences in the pain scores during

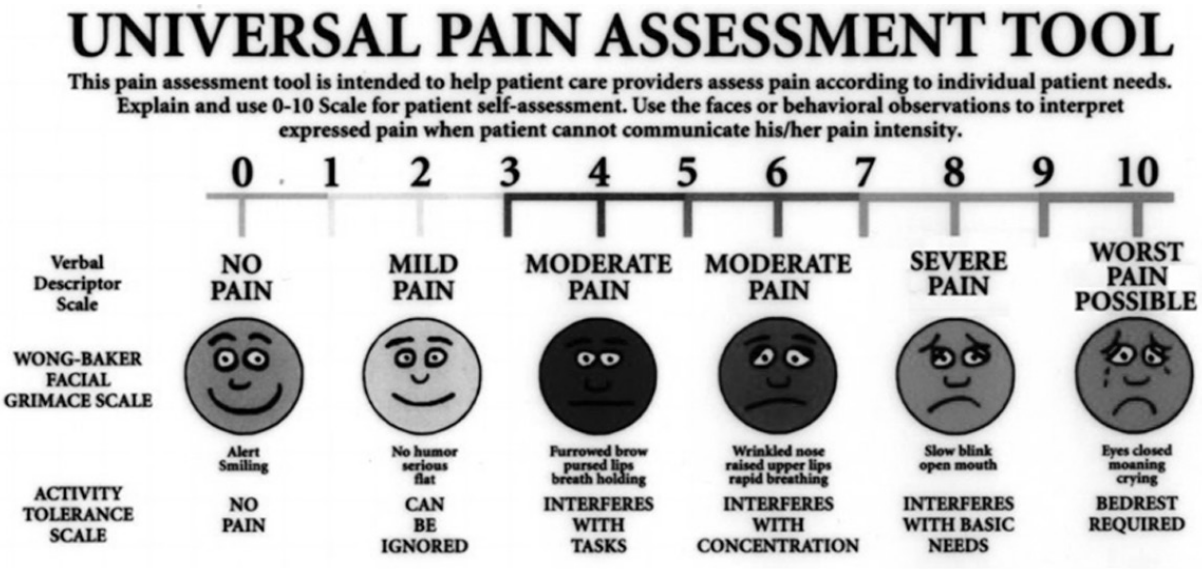

Figure 1. Universal Pain Assessment Tool (UPAT)

insertion of the probe (p=.68), biopsy (p=.26) and one-hour post-operatively (p=.54), were not statistically significant.

Discussion

Transrectal Ultrasound Guided (TRUS) Biopsy of the prostate gland is a reliable procedure in the diagnosis of prostate malignancy following the determination of abnormal prostate-specific antigen (PSA) in conjunction with a digital rectal examination (DRE).[4] The introduction of TRUS by Takahashi and Ouchi (1963) and the standardization of transrectal biopsy technique by Torp-Pedersen, et al. revolutionized prostate biopsy as this approach caused less morbidity.[6] The current practice is using an extended biopsy protocol that requires at least 12 cores. However, pain is the most common morbidity and anxiety experienced by the patient

Table 1. Characteristics of males undergoing TRUS biopsy of the prostate gland.

Characteristics	Periprostatic Nerve Block with Oral Tramadol and Paracetamol N=40	Periprostatic Nerve Block with placebo N=40	p-value*
Mean age ± SD	66.7 ± 7.8	65.5±6.1	0.43
Age range	49-85	51-74	
Mean PSA level ± SEM, ng/dl	36.5 ±5.8	27.5±8.5	0.38
PSA range	5.9 - >100	4.1-320	
Mean prostate size ± SD, g	38.2±7.8	42.1 ±24	0.35
Size range	20-55	10-181	
Biopsy findings (%)			
BPH	11 (27)	20 (50)	0.34
Adenocarcinoma	17 (42)	9 (22)	
High Grade PIN	1 (2.5)	0 (--)	
Atypical acinar proliferation	1 (2.5)	2 (5)	
Not indicated	10 (26)	9 (23)	

*Significant p-value if <0.05
SD=standard deviation; PSA=prostatic specific antigen; SEM=standard error of the mean

Table 2. Comparison of pain scores between males undergoing TRUS-guided prostate biopsy using periprostatic nerve block alone versus using periprostatic nerve block plus oral tramadol plus paracetamol.

	Mean Pain Score (Standard Deviation)			
Group	Upon Insertion of the Probe	During Biopsy	One-Hour Post-operatively	p-value**
Periprostatic Nerve Block plus oral Tramadol and Paracetamol	6.8 (0.9)	2.1 (0.9)	1.3 (0.56)	.001
Periprostatic Nerve Block plus placebo	6.7 (0.74)	2.3 (0.85)	1.2 (0.53)	.001
p-value*	0.68	0.26	0.54	

* Mann Whitney U Test (between groups comparison)
** Wilcoxon signed ranks test (within-groups comparison)

during the procedure.[7] A painful experience during prostate biopsy has an important bearing on the patient's well-being and compliance and reduces procedure acceptability. Incorporating a painful diagnostic procedure as a routine practice is not only unwarranted but can also be considered unethical, particularly when it is performed in a predominantly older age group of patients harboring a low-grade, clinically insignificant disease that does not need aggressive management or treatment at all.[6] Several published literature cited the use different anesthesia to control the pain and discomfort experienced by the patient during the procedure and yet, no standard technique has been proven to be most effective.[7]

Despite an increase in the number of cores and the concomitant pain, the urologists and radiologists did not adopt active pain relief interventions during TRUS-guided prostate biopsy, probably because the rectum was considered to be an insensate structure. The early attempts to mitigate pain evaluated several methods that included general anesthesia, intrarectal local anaesthetic application, pudendal and caudal nerve blocks, rofecoxib, intravenous propofol, nitrous oxide inhalation, intravenous conscious sedation (fentanyl and midazolam), intrarectal glyceryl trinitrate, intrarectal diclofenac, and 40% dimethyl sulfoxide.[6] Some of these methods are of doubtful efficacy, while for intravenous propofol and general anesthesia, a trained team and operating room set-up are needed and they carry inherent risk of respiratory depression which makes it impractical in an office and out- patient setting.[8]

Until Nash, et al. introduced periprostatic nerve infiltration of local anesthesia (such as Lidocaine) in 1996. It resulted to a better pain control among other methods to the extent of becoming the gold standard in prostate biopsy.[9] But others still found the whole procedure very painful. According to Kumar, et al., combining local anesthesia with other analgesia will provide better pain control to the patient.[7] Thus, optimal pain control during TRUS-guided biopsy of the prostate will alleviate the burden of the procedure and improve the psychosocial well-being of the patient.

Tramadol/paracetamol 37.5mg/325mg is an orally administered fixed-dose combination of the atypical opioid tramadol and paracetamol, which is indicated for the symptomatic treatment of moderate to severe pain. Fixed-dose tramadol/paracetamol is a rapidly-acting, longer-duration, multi-modal analgesic, which is effective and generally well-tolerated in patients with moderate to severe pain.[10] In several well-designed, clinical studies, single- or multiple-dose tramadol/paracetamol was effective in providing pain relief in adult patients with postoperative pain after minor surgery, musculoskeletal pain (acute, subacute or chronic), painful diabetic peripheral neuropathy or migraine pain.[11]

This is a double blind clinical trial comparing the effectiveness of periprostatic nerve block (PPNB) alone with multivitamins as placebo versus periprostatic nerve block plus oral tramadol–paracetamol treatment combination in patients undergoing transrectal ultrasound guided biopsy of the prostate. The clinical trial involved 80 patients with half receiving the treatment arm and placebo. The two groups were similar as to baseline characteristics indicative of adequacy of randomization.

Care was taken to follow all anesthesia procedures mentioned in the protocol to prevent procedural bias. The recording of the standard pain scale scores (using visual analog scale of 0 to 10 points) were recorded by independent raters to eliminate social desirability and measurement bias.

The current study showed that both methods of periprocedural anesthesia reduced pain even during the insertion of the ultrasound probe, during the biopsy and an hour after the biopsy. As earlier noted, the pain reduction was significant each arm. However, the pain scores were not significantly different when the two groups were compared. This implies non-superiority of the intervention arm over the placebo.

Several factors might explain why there was no difference in the pain scores noted with PPNB plus paracetamol-tramadol combination. First, the dose of tramadol-paracetamol combination was low. A clinical trial done by Pendleton, et al.[12] who successfully observed superior pain relief utilized 75 mg tramadol/650 mg paracetamol. A similar optimal dose of tramadol had been utilized in the past in the trial of Seckiner, et al.[5]

The element of subjectivity of VAS scores as main factor cannot be dismissed. Standardization by training of personnel recording the pain scores is always a pre-requisite. Continued training by

emphasizing how patients perceive the intensity of pain in comparison to the scale is also necessary.

Although side effects were not observed in this study, Pendleton noted itchiness and lightheadedness when using the combination of oral medications.[12]

In this study, the authors showed that the local anesthetic effect of tramadol in decreasing pain in periprostatic nerve block during TRUS-guided biopsy. The use of tramadol-paracetamol combination for pain relief in transrectal ultrasound-guided prostate biopsy is a practical, effective, and comfortable method. However, its real benefit and cost-effectiveness cannot be determined fully in this study.

Future clinical trials about pain during prostate biopsy can be conducted using higher doses of tramadol and paracetamol. Other measures, such as additional use of pain relievers for breakthrough pain, should also be documented in future studies.

Conclusion

Tramadol and paracetamol combination in addition to periprostatic nerve block produces pain relief similar to standard periprostatic nerve block alone.

Funding/Budget Information

The professional fees of the statistician and cost of medicinal supplies (such as multivitamins and tramadol plus paracetamol tablets) were shouldered by the researchers. The biopsy guns and the 2% Lidocaine injections came from the researchers' institution as part of their regular supplies for such minor procedures. No other financial entity was involved in this study.

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