Kaohsiung Journal of Medical Sciences (2015) 31, 572–579

Available online at www.sciencedirect.com

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journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Intravenous paracetamol for relief of pain during transrectal-ultrasound-guided biopsy of the prostate: A prospective, randomized, double-blind, placebo-controlled study

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Received 23 April 2015; accepted 4 September 2015
Available online 21 October 2015

KEYWORDS
Analgesia;
Biopsy;
Paracetamol;
Prostate;
Transrectal ultrasound

Abstract Transrectal-ultrasound-guided prostate biopsy (TRUS-PBx) is the standard procedure for diagnosing prostate cancer. The procedure does cause some pain and discomfort; therefore, an adequate analgesia is necessary to ensure patient comfort, which can also facilitate good-quality results. This prospective, randomized, double-blinded, placebo-controlled study aimed to determine if intravenous (IV) paracetamol can reduce the severity of pain associated with TRUS-PBx. The study included 104 patients, scheduled to undergo TRUS-PBx with a suspicion of prostate cancer, that were prospectively randomized to receive either IV paracetamol (paracetamol group) or placebo (placebo group) 30 minutes prior to TRUS-PBx. All patients had 12 standardized biopsy samples taken. Pain was measured using a 10-point visual analog pain scale during probe insertion, during the biopsy procedure, and 1 hour postbiopsy. All biopsies were performed by the same urologist, whereas a different urologist administered the visual analog pain scale. There were not any significant differences in age, prostate-specific antigen level, or prostate volume between the two groups. The pain scores were significantly lower during probe insertion, biopsy procedure, and 1 hour postbiopsy in the

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2015.09.003

paracetamol group than in the placebo group. In conclusion, the IV administration of paracetamol significantly reduced the severity of pain associated with TRUS-PBx.

Introduction

Transrectal-ultrasound (TRUS)-guided prostate biopsy (PBx; TRUS-PBx) is the standard procedure for diagnosing prostate cancer (PCa). The procedure is recommended for patients with abnormal digital-rectal-examination (DRE) findings or an elevated prostate-specific antigen (PSA) level [1]. TRUS-PBx is known to cause pain and/or discomfort with various different and conflicting ratios ranging from 7% to 96% [2]. An interesting result has been observed from the study of Irani et al [3] mentioning that 19% of the patients that have undergone TRUS-PBx would refuse to undergo the procedure again without any analgesia.

The severity of pain/discomfort is correlated with the number of cores taken; thus, an adequate analgesia can improve patient comfort during biopsy and increase the diagnostic value of the procedure [4,5]; however, it was also reported that the number of the cores and the severity of pain are not correlated [6,7]. In addition, Kaver et al [8] hypothesized the concept of pain accumulation, that is, pain during TRUS-PBx gradually increases in severity from the first core to the last.

Many factors are associated with pain during TRUS-PBx, such as anal discomfort due to the TRUS probe and insertion of needles into the prostate gland [9,10]. Periprostatic local anesthetic infiltration is regarded as the best method for managing pain during TRUS-PBx [11]; however, this method is invasive, and a randomized trial reported that needle punctures for lidocaine infiltration were more painful than probe insertion and biopsy [12].

Intravenous (IV) paracetamol (acetaminophen) is considered the first-line non-opioid analgesic for treating mild to moderate pain. Although paracetamol's central analgesic effect is well known, its primary mechanism of action, which may be inhibition of prostaglandin synthesis or via an active metabolite influencing cannabinoid receptors, remains unknown [13].

The present prospective, randomized, double-blinded, placebo-controlled study aimed to determine if IV paracetamol can reduce the severity of pain associated with TRUS-PBx.

Methods

Between December 2009 and February 2011, 140 consecutive patients underwent TRUS-PBx in our department, of which 104 qualified for inclusion in the study. The study flowchart is shown in Figure 1. The indications for PBx included abnormal DRE findings and/or a PSA concentration $\geq$ 4 ng/mL. The exclusion criteria were painful conditions of the prostate, rectum, and anus (such as acute prostatitis or prostadynia, hemorrhoid, and anal fissure or stricture); neurological conditions that can affect the perception of pain; history of liver and/or kidney disease; and allergy to paracetamol. In addition, patients who had undergone PBx previously and/or were using any oral analgesic or narcotic medication were excluded due to their potential to interfere with the perception of pain. A written informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Selcuk University School of Medicine, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Antibiotic prophylaxis was achieved via oral administration of 500-mg ciprofloxacin, one tablet every 12 hours starting 2 days prior to TRUS-PBx and 3 days postprocedure. The patients were randomly assigned to receive 100-mL (10 mg/mL) IV paracetamol (Perfalgan, Bristol-Myers Squibb, Itxassou, France) for 15 minutes before TRUS-PBx (paracetamol group), or 100-mL IV saline for 15 minutes before TRUS-PBx (placebo group). The solutions in both groups were infused from within a special black bag, so as to blind the patients to which treatment they received. TRUS-PBx was performed 30 minutes after the injection of the solutions.

The patients were placed in the left lateral decubitus position. The transrectal imaging was performed using a LOGIQ 200 PRO Series ultrasonography device equipped with a 6.5-MHz probe (GE Healthcare, Seoul, Korea). After the insertion of the TRUS probe, the prostate gland was imaged in longitudinal and sagittal planes for morphologic evaluation and volume measurement. A standard of 12 cores were sampled from each patient by using an automatic spring-loaded biopsy gun with an 18-gauge 22-cm biopsy needle. All biopsies were performed by the same urologist (O.K.) that was blinded to the preprocedure analgesic treatment.

Following TRUS-PBx, each patient spent at least 1 hour in the recovery room, during which time they were asked to report the severity of their pain. Pain was evaluated by using a 10-point visual analog scale (VAS) during probe insertion and biopsy, and 1 hour after biopsy by a urologist other than the one that performed the biopsies. All patients had a follow-up visit at the outpatient clinic 1 week after the TRUS-PBx to monitor for complications.

Data were analyzed with SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) and NCSS 2007 (NCSS Inc., Kaysville, UT, USA). Shapiro–Wilk analysis was used to analyze the distribution of the age, PSA concentration, and prostate volume. The descriptive analyses were given as mean $\pm$ standard deviation and range for the continuous quantitative variables. The differences between the two groups were analyzed with Student *t* test and

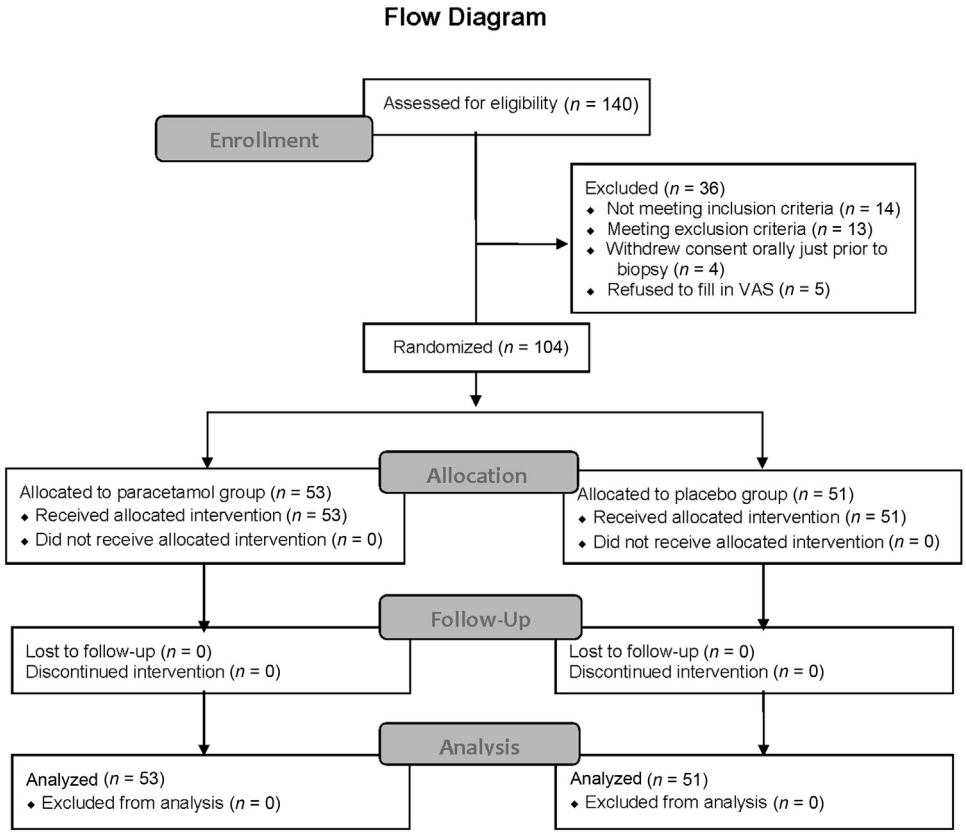

Figure 1. Flow diagram of the study. VAS = visual analog scale.

Mann–Whitney *U* test. Variance analysis was used to analyze the VAS scores within each group. The level of statistical significance was set at $p < 0.05$.

Results

The paracetamol group included 53 patients, versus 51 patients in the placebo group. There were not any significant differences in age, body-mass index, PSA value, and prostate volume between the two groups ($p > 0.05$ for all). The descriptive statistics are given in Table 1. The VAS pain scores during probe insertion and TRUS-PBx, and 1 hour after the procedure in both groups are shown in Table 2.

The VAS pain scores were highest in the paracetamol group during TRUS-PBx and the lowest 1 hour post-TRUS-PBx. There was no significant difference in the VAS pain score during probe insertion or during TRUS-PBx ($p > 0.05$) in the paracetamol group, whereas the VAS pain score 1 hour after TRUS-PBx was significantly lower than during both probe insertion and TRUS-PBx ($p < 0.001$). In the placebo group, the VAS pain score was also highest during TRUS-PBx. In contrast to the paracetamol group, the VAS

Table 1 Baseline demographic and clinical characteristics of the groups.

	Paracetamol group ($n = 53$)	Placebo group ($n = 51$)	*P*
Age (y)	67.9 ± 8.2 (46–82)	67.1 ± 9.1 (49–91)	>0.05
BMI (kg/m^2)	26.4 ± 3.4 (21.6–32.3)	26.0 ± 2.9 (22.2–34.1)	>0.05
PSA (ng/mL)	24.1 ± 40.6 (2–152)	21.8 ± 40.1 (5–158)	>0.05
TRUS prostate volume (mL)	55.4 ± 27.8 (17–155)	59.2 ± 23.1 (17–132)	>0.05
Complications			>0.05
Hematuria	18 (33.9)	20 (39.2)	
Rectal bleeding	12 (22.6)	14 (27.4)	
Urinary infection	4 (7.5)	4 (7.8)	
Fever	1 (1.8)	2 (3.9)	
Urinary retention	2 (3.7)	1 (1.9)	
Hematospermia	6 (11.3)	5 (9.8)	

Data are presented as mean ± standard deviation (range) or *n* (%).
BMI = body-mass index; PSA = prostate-specific antigen; TRUS = transrectal ultrasonography.

Table 2 Distribution of visual-analog-scale scores between the two groups.

Pain	Paracetamol group ($n = 53$)	Placebo group ($n = 51$)	p
During probe insertion	0.82 ± 0.48 (0–2)	1.54 ± 0.86 (0–5)	<0.001
During the procedure	0.91 ± 0.32[a] (0–3)	2.59 ± 0.79[d] (1–6)	<0.001
1 h after the procedure	0.12 ± 0.03[b,c] (0–1)	0.78 ± 0.53[e,f] (0–2)	<0.001

Data are presented as mean ± standard deviation (range).
[a] Pain during probe insertion versus procedure: $p > 0.05$.
[b] Pain during probe insertion versus after procedure: $p < 0.001$.
[c] Pain during procedure versus after procedure: $p < 0.001$.
[d] Pain during probe insertion versus procedure: $p < 0.01$.
[e] Pain during probe insertion versus after procedure: $p < 0.01$.
[f] Pain during procedure versus after procedure: $p < 0.001$.

pain score during TRUS-PBx was significantly higher than during probe insertion in the placebo group ($p < 0.01$). The VAS pain score 1 hour post-TRUS-PBx in the placebo group was significantly lower than during probe insertion ($p < 0.01$) and during TRUS-PBx ($p < 0.001$).

Minor complications, including hematuria, rectal bleeding, urinary infection, fever, urinary retention, and hematospermia, were observed in both groups at similar rates (Table 1). All complications were treated appropriately on an outpatient basis without squeal.

Discussion

PCa is the most common cancer among men when skin cancer is excluded, and is the second leading cancer-related cause of death [14]. Moreover, the number of the newly and incidentally diagnosed PCa cases is increasing due to the widespread use of PSA monitoring. For this purpose, TRUS-PBx has become the gold standard procedure, which is recommended for patients with abnormal DRE findings or an elevated PSA concentration [1]. Anal discomfort due to insertion and movements of the TRUS probe, and insertion of needles into the prostate gland are the most common causes of pain during TRUS-PBx [9,10]. It was reported that the rectal wall above the dentate line, which is pierced by the biopsy needle, has a decreased sensorium, and most of the pain associated with TRUS-PBx is caused by the penetration of the prostatic capsule, which results in the stimulation of the sensory receptors located in the capsule [9]. Therefore, an adequate analgesia is necessary to ensure patient comfort, which can facilitate good-quality results.

Paracetamol (acetaminophen), a widely prescribed drug for the relief of pain, has a central analgesic effect mediated via the activation of the descending serotonergic pathways. Debate exists about its primary site of action, which might be the inhibition of prostaglandin synthesis or via an active metabolite affecting cannabinoid receptors. It is assumed that paracetamol acts as a reducing cosubstrate on the peroxidase site of prostaglandin H_2 synthetase, and decreases the availability of the ferryl protoporphyrin IX radical cation involved in the conversion of arachidonic acid to prostaglandin G_2. Alternatively, it has also been postulated that paracetamol's mechanism of action might be mediated by an active metabolite (*p*-aminophenol) that is conjugated with arachidonic acid to effect cannabinoid receptors [13]. Paracetamol interferes less with platelet function and does not prolong bleeding time, as compared to nonsteroidal anti-inflammatory drugs (NSAIDs). It is inexpensive and well tolerated, and has a safe therapeutic dose. The analgesic efficacy of IV administration of 1-g paracetamol was reported in patients following orthopedic surgery [15] and elective ambulatory surgery [16].

Periprostatic nerve block (PPNB), with bilateral injections of a local anesthetic agent at the junction of the base of the prostate and seminal vesicles, was first described by Nash et al [17] in 1996. Although it is accepted as the gold standard for pain relief, it does not prevent the pain caused by the insertion of the TRUS probe into the rectum, TRUS probe movements, or during transcapsular infiltration of the local anesthetic agent. As such, various doses of local anesthetic agent, injection locations, and combinations of medications have been described for this method, including injection only at the base of the prostate, both at the base and the apex, and only at the apex [8,17–19]. A prospective, randomized, controlled study by Ozden et al [20] compared different doses (2.5 mL, 5 mL, and 10 mL) of 1% lidocaine injection at the base only, or at the base and apex of the prostate to saline injection. They reported that PPNB with injection of 10-mL lidocaine resulted in better pain relief than lower doses of lidocaine, and that there was not a significant difference between basal only versus basal plus apical injection. Despite all the research performed to date, there remains a lack of consensus on the optimal local anesthetic technique.

As PPNB may not always be sufficient to reduce pain, several multimodal approaches that combined PPNB with other pain medications have been studied, including intrarectal anesthetic gel [21,22] or anesthetic–myorelaxant cream [23]; diclofenac administered intramuscularly [24], dermally [25], or intrarectally [26,27]; IV ketorolac [28]; oral rofecoxib [29]; paracetamol plus codeine [30]; and tramadol versus intramuscular midazolam [31]. In general, these studies conclude that additional pain-relief methods lower pain and/or discomfort experienced during insertion and movements of the TRUS probe, as PPNB alone is not always effective [11,32].

It was reported by two randomized studies that administration of intrarectal lidocaine–prilocaine or lidocaine–nifedipine cream in addition to standard PPNB lowered pain during TRUS-PBx, especially during insertion and

movements of the TRUS probe [21,23]. Both studies concluded that the combination of PPNB and lidocaine—prilocaine/nifedipine cream was more effective than PPNB alone, and that the combination treatment should be the standard regimen. These findings were subsequently supported by those of Anup et al [22], who reported that the combination of PPNB and perianal—intrarectal lidocaine—prilocaine cream was more effective than either of the two regimens alone.

The administration of diclofenac via intramuscular injection, dermal patch, or rectal suppository was evaluated for pain relief during TRUS-PBx. Bhomi et al [24] reported that there was a significant difference between the PPNB group and the control group, and between the PPNB group and the diclofenac group. Interestingly, they did not observe a difference between the diclofenac and control groups, and concluded that PPNB improves patient tolerance of TRUS-PBx better than diclofenac. By contrast, Griwan et al [25] reported that a diclofenac patch significantly reduced pain 1 hour, 2 hours, and 4 hours post-TRUS-PBx, but not during the procedure. They concluded that diclofenac could be used as an adjunct treatment, and that PPNB together with a diclofenac patch might provide adequate analgesia during and after TRUS-PBx. A randomized, controlled trial reported that the combination of PPNB with levobupivacaine and diclofenac suppository was superior to PPNB only and diclofenac suppository only [26].

Apart from these studies, Haswir and Umbas [27] evaluated the efficacy of oral morphine sulfate only or diclofenac suppository only for pain relief during TRUS-PBx, and reported no difference between the methods. In another study with a similar setting, Olmez et al [33] observed that pain associated with TRUS-PBx was higher in their saline group, that both their tramadol and lornoxicam groups had significantly lower pain scores than the saline group, and that the tramadol group had the lowest score; as in the study by Haswir and Umbas [27], PPNB was not used. The tramadol group also had the lowest level of discomfort than the other two groups, and the percentage of patients that reported they would not undergo another TRUS-PBx in the future was lower in the tramadol and lornoxicam groups than in the saline group.

Moinzadeh et al [29] compared the oral administration of 50-mg rofecoxib (a selective inhibitor of cyclooxygenase-2) only and placebo, and did not observe a decrease in pain between the two methods. Based on their findings, they suggested that systemic administration of NSAIDs may not be suitable for pain relief during TRUS-PBx. In contrast, 60-mg IV ketorolac before TRUS-PBx significantly reduced pain [28]. The author concluded that a single dose of IV ketorolac was efficient for pain relief without any adverse effects, despite its NSAID properties.

The literature includes a few studies on the use of paracetamol during TRUS-PBx, but none have examined the IV route of administration [30,34,35]. Pendleton et al [34] randomized patients scheduled to undergo TRUS-PBx into two groups: Group 1 received the combination of tramadol plus acetaminophen together with PPNB, and Group 2 received placebo with PPNB. They reported that the combination of tramadol plus acetaminophen together was associated with lower pain scores. Subsequently, Visapää and Taari [30] studied the effect of the combined oral administration of 500-mg paracetamol and 30-mg codeine together with PPNB, and reported that the VAS pain scores were lower in the combination treatment group. A recent prospective, randomized, single-blinded study compared oral paracetamol and rectal EMLA cream to conventional PPNB [35]. The pain scores in these two groups were significantly lower than in the PPNB group, and the percentage of patients that reported they would undergo TRUS-PBx again using the same pain relief method was significantly higher in the paracetamol and rectal EMLA groups. A summary of the prospective, randomized, controlled studies is listed in Table 3.

Based on the similar thoughts from these studies [30,34,35], earlier findings that paracetamol is a good choice for pain relief [15,16], and our limited experience using paracetamol during TRUS-PBx (only 2 patients in whom PPNB could not be used due to allergy to local anesthetics), we performed the present study to determine the efficiency of a single dose of 1-g IV paracetamol for pain control during TRUS-PBx. In the present study, paracetamol significantly decreased the severity of pain during probe insertion and biopsy, as well as 1 hour postbiopsy. In contrast to some of the previous studies, in the present study the VAS pain scores were highest during TRUS-PBx, not during probe insertion, which is consistent with some other reports [9]. This might be due to the assumption that movements of the TRUS probe while obtaining biopsy samples from lateral parts of the prostate and piercing of the prostatic capsule cause the most pain.

The present study has certainly some limitations. Firstly, the patient population was small. Although we sought to recruit at least 60 patients for each group, due to the use of exclusion criteria, only 53 patients and 51 patients were enrolled in the paracetamol and placebo groups, respectively. Secondly, it might have been more useful to have included a PPNB group for comparing the efficacy of IV paracetamol not only to placebo, but also to a standard regimen (PPNB). Thirdly, we did not evaluate the liver and kidney functions of the patients with laboratory tests; we only asked if the patients had a history of any disease that may interfere with paracetamol usage. It should be kept in mind that paracetamol should not be used in patients with a liver and/or kidney disease, as in rare cases it can cause hepatic or renal insufficiency.

In contrast to its limitations, this study has some strength. Firstly, all biopsies were performed by the same urologist that was blinded to the analgesic method used, and the VAS pain scores were evaluated by a different urologist. Secondly, a readily available, inexpensive, and well-tolerated analgesic agent—paracetamol—was evaluated. Thirdly, although the duration of TRUS-PBx in the paracetamol group was not compared to that of the conventional method (PPNB), we think that the use of IV paracetamol, as described herein, reduces the duration of TRUS-PBx, as no time is required for periprostatic injection, which might also decrease patient anxiety. Lastly, as there is a risk of vasovagal syncope during TRUS-PBx, opening an IV line for paracetamol administration can facilitate management of a hypotensive attack in a timely manner.

In conclusion, to the best of our knowledge, the present study is the first to evaluate the efficacy of paracetamol for control of pain associated with TRUS-PBx. Based on the

Table 3 List of prospective, controlled studies that have compared different analgesia methods during transrectal-ultrasound-guided prostate biopsy.

Study	Year	Study type	Treatments	Results & notes
Giannarini et al [21]	2009	PRC	PILP cream + PPNB versus PILP cream only versus PPNB only versus no anesthesia	(1) The combination treatment provides better pain control than the other 2 modalities alone, as well as the no-anesthesia group. (2) The magnitude of better pain control is higher in men $\leq$ 65 y, with larger prostate $\geq$ 49 cc, & with lower anorectal compliance. (3) The complication rates are similar.
Anup et al [22]	2013	PRC	PILP cream + PPNB versus PPNB only versus PILP cream only	(1) The combination provides better analgesia, especially in patients $<$ 60 y, prostate volume $>$ 50 cc, & lower anorectal compliance. (2) There was no increase in complication rates.
Cantiello et al [23]	2009	PRC	PPNB versus PPNB + intrarectal anesthetic—myorelaxant cream	(1) The combination group had lower pain scores during probe insertion, during periprostatic infiltration, 30 min after the biopsy, & in the evening of the biopsy. (2) No difference was observed during the procedure & on the day after biopsy.
Bhomi et al [24]	2007	PC	PPNB versus 75-mg diclofenac sodium intramuscularly versus control	(1) The difference was significant between PPNB & diclofenac, & between PPNB & control. (2) There was no difference between the diclofenac & control groups.
Griwan et al [25]	2012	PRC	PPNB versus diclofenac patch versus control	(1) The diclofenac patch is better after TRUS-PBx, but not during the procedure. (2) The authors advise that the combination would be better.
Aktoz et al [26]	2010	PRC	PPNB + diclofenac suppository versus PPNB only versus diclofenac suppository only	(1) The combination therapy was better than the other 2 groups. (2) TRUS-PBx lowers the mean IIEF-5 scores 1 mo after biopsy, but medium-term erectile function (IIEF-5 3 mo after biopsy) is not affected.
Haswir & Umbas [27]	2008	PRC	Oral morphine sulfate 10 mg only versus diclofenac suppository 100 mg only	No difference was observed between the 2 groups.
Olmez et al [33]	2008	PRC	Tramadol 100 mg intramuscularly versus lornoxicam 8 mg intramuscularly versus saline intramuscularly	(1) The tramadol group had the lowest pain & discomfort. (2) The lornoxicam group was better than the control group. (3) The percentage of patients who refused to undergo another TRUS-PBx was lower in tramadol & lornoxicam groups.
Moinzadeh et al [29]	2003	PRC	Oral rofecoxib 50 mg versus placebo	(1) No difference was observed in pain scores. (2) The authors concluded that systemic administration of NSAIDs may not be suitable.
Mireku-Boateng [28]	2004	PRC	Ketorolac 60 mg intravenously versus control	Ketorolac was efficient without side effects.

(*continued on next page*)

Table 3 (*continued*)

Study	Year	Study type	Treatments	Results & notes
Visapää & Taari [30]	2009	PRC	Oral paracetamol 500 mg + oral codeine 30 mg + PPNB versus PPNB only	The combination treatment was better with lower pain scores.
Pendleton et al [34]	2006	PRC	Oral tramadol 75 mg + oral paracetamol 650 mg + PPNB versus placebo + PPNB	The addition of tramadol + paracetamol lowered the pain scores significantly.
Kim et al [35]	2011	PRC	Oral paracetamol 650 mg versus rectal EMLA cream versus PPNB	(1) Both paracetamol & EMLA cream groups had similar VAS scores; those are both lower than PPNB alone. (2) The patients willing to undergo another TRUS-PBx with the same analgesia method were the higher paracetamol & EMLA cream groups. (3) All patients were given 50-mg tramadol intravenously 30 min before the procedure.

IIEF = International Index of Erectile Function; NSAIDs = nonsteroidal anti-inflammatory drugs; PC = prospective, controlled; PILP = perianal—intrarectal lidocaine and prilocaine; PPNB = periprostatic nerve block; PRC = prospective, randomized, controlled; TRUS-PBx = transrectal-ultrasound-guided prostate biopsy; VAS = visual analog scale.

present findings, we think that a single IV dose of 1-g paracetamol can be safely and effectively used to decrease the severity of pain experienced during and after TRUS-PBx.

Acknowledgments

Part of this study was presented as a poster presentation (poster number P-252) at the 21st National Congress of Urology, October 30—November 3, 2010, Istanbul, Turkey. Dr. Ozcan Kilic and Dr. Murat Akand have contributed equally to this study and are the first co-authors of the article.

References

[1] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—Update 2013. Eur Urol 2014;65:124—37.
[2] Autorino R, De Sio M, Di Lorenzo G, Damiano R, Perdona S, Cindolo L, et al. How to decrease pain during transrectal ultrasound guided prostate biopsy: a look at the literature. J Urol 2005;174:2091—7.
[3] Irani J, Fournier F, Bon D, Gremmo E, Dore B, Aubert J. Patient tolerance of transrectal ultrasound-guided biopsy of the prostate. Br J Urol 1997;79:608—10.
[4] Zisman A, Leibovici D, Kleinmann J, Siegel YI, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of pain, anxiety and erectile dysfunction. J Urol 2001;165:445—54.
[5] Davis M, Sofer M, Kim SS, Soloway MS. The procedure of transrectal ultrasound guided biopsy of the prostate: a survey of patient preparation and biopsy technique. J Urol 2002;167:566—70.
[6] Chang SS, Alberts G, Wells N, Smith Jr JA, Cookson MS. Intrarectal lidocaine during transrectal biopsy: results of a prospective double-blind randomized trial. J Urol 2001;166:2178—80.
[7] Naughton CK, Ornstein DK, Smith DS, Catalona WJ. Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. J Urol 2000;163:168—71.
[8] Kaver I, Mabjeesh NJ, Matzkin H. Randomized prospective study of periprostatic local anesthesia during transrectal ultrasound guided prostate biopsy. Urology 2002;59:405—8.
[9] De Sio M, D'Armiento M, Di Lorenzo G, Damiano R, Perdona S, De Placido S, et al. The need to reduce patient discomfort during transrectal ultrasonography-guided prostate biopsy: what do we know? BJU Int 2005;96:977—83.
[10] Han KS, Lee KH, Korean Urologic Oncology Society Prostate Cancer Study Group. Factors influencing pain during transrectal ultrasonography-guided prostate biopsy. Prostate Cancer Prostatic Dis 2008;11:139—42.
[11] Lee C, Woo HH. Current methods of analgesia for transrectal ultrasonography (TRUS)-guided prostate biopsy—A systematic review. BJU Int 2014;113(Suppl. 2):48—56.
[12] Schostak M, Christoph F, Müller M, Heicappell R, Goessl G, Staehler M, et al. Optimizing local anesthesia during 10-core biopsy of the prostate. Urology 2002;60:253—7.
[13] Anderson BJ. Paracetamol (acetaminophen): mechanisms of action. Paediatr Anaesth 2008;18:915—21.
[14] Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, et al. Cancer treatment and survivorship statistics. CA Cancer J Clin 2012;2012(62):220—41.
[15] Sinatra RS, Jahr JS, Reynolds L, Groudine SB, Royal MA, Breitmeyer JB, et al. Intravenous acetaminophen for pain after major orthopedic surgery: an expanded analysis. Pain Pract 2012;12:357—65.
[16] Göröcs TS, Lambert M, Rinne T, Krekler M, Modell S. Efficacy and tolerability of ready-to-use intravenous paracetamol solution as monotherapy or as an adjunct analgesic therapy for postoperative pain in patients undergoing elective ambulatory surgery: open, prospective study. Int J Clin Pract 2009;63:112—20.
[17] Nash PA, Bruce JE, Indudhara R, Shinohara K. Transrectal ultrasound guided prostatic nerve blockade eases systemic needle biopsy of the prostate. J Urol 1996;155:607—9.
[18] Soloway M, Obek C. Periprostatic local anesthesia before ultrasound guided prostate biopsy. J Urol 2000;163:172—3.
[19] Seymour H, Perry MJA, Lee-Elliot C, Dundas D, Patel U. Pain after transrectal ultrasonography-guided prostate biopsy: the

advantages of periprostatic local anesthesia. BJU Int 2001;88:540—4.
[20] Ozden E, Yaman O, Gogus C, Ozgencil E, Soygur T. The optimum doses of and injection locations for periprostatic nerve blockade for transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, placebo controlled study. J Urol 2003;170:2319—22.
[21] Giannarini G, Autorino R, Valent F, Mogorovich A, Manassero F, De Maria M, et al. Combination of perianal—intrarectal lidocaine—prilocaine cream and periprostatic nerve block for pain during transrectal ultrasound guided prostate biopsy: a randomized, controlled trial. J Urol 2009;181:585—93.
[22] Anup K, Pawan V, Niraj K, Biswajit N, Nayan MK. A prospective randomized trial comparing three different analgesic techniques for pain control during transrectal ultrasound guided prostate biopsy: a single center experience. Minerva Urol Nefrol 2013;65:77—82.
[23] Cantiello F, Imperatore V, Iannuzzo M, Scibelli G, Di Meo S, Fusco F, et al. Periprostatic nerve block (PNB) alone vs PNB combined with an anaesthetic—myorelaxant agent cream for prostate biopsy: a prospective, randomized double-arm study. BJU Int 2009;103:1195—8.
[24] Bhomi KK, Lim HH, Consigliere DT, Tiong HY. Control of pain during transrectal ultrasound-guided prostate biopsy: a prospective study comparing two methods. Urol Int 2007;79:332—5.
[25] Griwan MS, Kumar A, Sen J, Singh SK. Comparative evaluation of periprostatic nerve block and diclofenac patch in transrectal ultrasound-guided prostatic needle biopsy. Nephrourol Mon 2012;4:560—4.
[26] Aktoz T, Kaplan M, Turan U, Memis D, Atakan IH, Inci O. "Multimodal" approach to management of prostate biopsy pain and effects on sexual function: efficacy of levobupivacaine adjuvant to diclofenac sodium—A prospective randomized trial. Andrologia 2010;42:35—40.
[27] Haswir H, Umbas R. Comparison of efficacy between oral morphine sulphate and diclofenac suppository for analgesia during transrectal ultrasound-guided prostate biopsy. Acta Med Indones 2008;40:124—8.
[28] Mireku-Boateng AO. Intravenous ketorolac significantly reduces the pain of office transrectal ultrasound and prostate biopsies. Urol Int 2004;73:123—4.
[29] Moinzadeh A, Mourtzinos A, Triaca V, Hamawy KJ. A randomized double-blind prospective study evaluating patient tolerance of transrectal ultrasound-guided biopsy of the prostate using prebiopsy rofecoxib. Urology 2003;62:1054—7.
[30] Visapää H, Taari K. Combination of paracetamol, codeine and lidocaine for pain relief during transrectal ultrasound guided biopsy of the prostate. Scan J Surg 2009;98:55—7.
[31] Ozok HU, Sagnak L, Ates MA, Karakoyunlu N, Topaloglu H, Ersoy H. The efficiency of a sedative or analgesic supplement to periprostatic nerve blockage for pain control during transrectal ultrasound-guided prostate biopsy—A prospective, randomized, controlled, double blind study. Arch Med Sci 2010;5:787—92.
[32] Maccagnano C, Scattoni V, Roscigno M, Raber M, Angiolili D, Montorsi F, et al. Anesthesia in transrectal prostate biopsy: which is the most effective technique? Urol Int 2011;87:1—13.
[33] Olmez G, Kaya S, Aflay U, Sahin H. Comparison of lornoxicam versus tramadol analgesia for transrectal prostate biopsy: a randomized prospective study. Int Urol Nephrol 2008;40:341—4.
[34] Pendleton J, Costa J, Wludyka P, Carvin DM, Rosser CJ. Combination of oral tramadol, acetaminophen and 1% lidocaine induced periprostatic nerve block for pain control during transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, controlled trial. J Urol 2006;176:1372—5.
[35] Kim S, Yoon BI, Kim SJ, Cho HJ, Kim HS, Hong SH, et al. Effect of oral administration of acetaminophen and topical application of EMLA on pain during transrectal ultrasound-guided prostate biopsy. Korean J Urol 2011;52:452—6.