PJSS Vol. 67, No. 1, January-March, 2012

PJSS PHILIPPINE JOURNAL OF SURGICAL SPECIALTIES

Premedication with Celecoxib Plus Tramadol and Intrarectal 2% Lidocaine vs Lidocaine Alone for Pain Control During Transrectal Ultrasound Guided Prostate Biopsy: A Randomized Controlled Trial

John Mark Arcayera, M.D.; Lester A. Garcia, M.D., F.P.C.S. and Ponciano M. Bernardo Jr., M.D., F.P.C.S.

Department of Urology, East Avenue Medical Center

Objective: Transrectal ultrasound guided biopsy is the diagnostic of choice in detecting carcinoma of the prostate. The biopsy can be painful and many would refuse the procedure again without adequate analgesia. The combination of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids work synergistically in relieving pain. The investigators determined that the premedication of celecoxib and tramadol with 10ml intrarectal 2% lidocaine gel would significantly decrease the pain score of patients undergoing prostate biopsy compared to lidocaine gel alone.

Methods: Thirty one patients who underwent 12-core prostate biopsy were randomly assigned into two groups. The control received 10ml 2% intrarectal lidocaine gel alone and the experimental group was given celecoxib 400mg and tramadol 50 mg 2 hours before biopsy plus intrarectal lidocaine gel. Immediately after biopsy, patients were asked to rate the pain score using visual analog scale (VAS).

Results: A total of 15 patients assigned for control group and 16 patients for the experimental group, showed similar characteristics in terms of age, prostate volume and prostate specific antigen (PSA) value. The overall mean pain score using visual analog pain scale was 4.1 +/- 1.7 in the experimental group compared to 5.5 +/- 1.9 in the control group with significant P value of 0.034 using chi-square test. There was a mean pain score decrease of 1.5 from the scale of 1 to 10 in the experimental group compared to the control.

Conclusion: The addition of oral administration of celecoxib 400 mg and tramadol 50 mg 2 hours before intrarectal 10ml 2% lidocaine gel significantly reduced the pain experienced by patients during ultrasound guided prostate biopsy as compared to lidocaine gel alone.

Key words: celecoxib, tramadol, lidocaine, transrectal ultrasound

Ultrasound guided prostate biopsy is the procedure of choice for diagnosing prostate cancer. However, 19 percent to 25 percent of men who undergo this procedure find it painful. Approximately, 20 percent of men reported that the pain associated with the procedure was significant and they would refuse to undergo the procedure again without some form of analgesia.[1,2]

Methods of analgesia that have been suggested in the recent literature include the rectal administration of lidocaine gel which is simple, safe and effective for providing satisfactory anesthesia during transrectal prostate biopsy. This approach is more convenient, better tolerated and less invasive.[2] However, other studies showed conflicting benefit with regard to pain relief and found it to be inferior to periprostatic block. Transrectal ultrasound (TRUS) guided nerve blockade using lidocaine infiltration into the periprostatic area has been suggested as the standard, although operator variability and the increased risk of infection are of significant concern.[3,10] In addition, intravenous sedation analgesia and inhalational agents have also been practiced, but also carries inherent risk of respiratory depression which makes it impractical in an office and out- patient setting.

Tramadol is a centrally acting analgesic used for many pain disorders. This drug uniquely combines opioid receptor binding activity with the inhibition of serotonin/ norepinephrine reuptake. In several comparative studies, its overall analgesic efficacy was similar to that of morphine or alfentanil and superior to that of pentazocine. Tramadol is generally well-tolerated in clinical trials.

The most common reported adverse events were nausea, vomiting and dry mouth with an incidence of 1.6% to 6.1%.[5,6]

Celecoxib, on the other hand, belongs to a group called NSAIDs which act by inhibiting the cyclooxygenase type-2. The classic NSAIDs block the synthesis of prostaglandins by inhibiting both cyclooxygenase type-1 (COX-1) and cyclooxygenase type-2 (COX-2). In effect, these drugs may produce operative site and gastrointestinal bleeding, as well as renal tubular dysfunction. The COX-2-specific drugs have been recently introduced as alternatives to the classic NSAIDs, producing comparable analgesia without NSAIDs-like side effects.[7,8,11] They work by reducing mediators that cause inflammation and pain. The combination of NSAIDs and opioids work synergistically in relieving pain. It was hypothesized that the combination of these drugs, celecoxib and tramadol, as premedication will further decrease the pain experienced by patients during prostate biopsy using intrarectal lidocaine as local anesthesia. The objective was to determine whether premedication with oral celecoxib 400mg and tramadol 50mg 2 hours prior to biopsy combined with 10ml 2% lidocaine gel intrarectally would significantly decrease the pain experienced by patients undergoing outpatient TRUS biopsy of the prostate as compared to 2% lidocaine gel alone.

Methods

Patients seen at the Urology Out-Patient clinic of East Avenue Medical Center between April 2011 and September 2011 and eligible for TRUS biopsy of the prostate who provided informed consent were included in the study. They were randomly assigned into 2 groups. The experimental group received premedications of celecoxib 400mg/tablet plus tramadol 50mg/capsule 2 hours before biopsy and 10ml 2% lidocaine gel intrarectally 10 minutes prior to biopsy. The control received 10ml 2% lidocaine alone 10 minutes prior to biopsy. Pre-treatment evaluations included medical history, physical examination, ultrasound of prostate and total prostate specific antigen (PSA). Anticoagulation or aspirin therapy regimens were discontinued seven days before the biopsy procedure. The indication for TRUS guided needle biopsy of the prostate was PSA greater than 4ng/dl and/or abnormal (hard, nodular) digital rectal examination results.

Patients with known allergies to either or both tramadol or celecoxib, history of epilepsy or seizure disorders, or assessed to have acute or chronic prostatitis, were excluded. Patients who had received selective serotonin reuptake inhibitors, tricyclic antidepressants or other tricyclic compounds, opioids, NSAID, monoamine oxidase inhibitors or neuroleptics within the previous 3 months, those with compromised hepatic or renal function, bleeding diathesis, anticoagulation treatment, active anal and rectal conditions (eg. hemorrhoids, anal fissures were likewise excluded.

Premedication and Biopsy Technique

Each patient in both groups self-administered ciprofoxacin 500mg/tablet, 1 tablet 2 times a day as prophylactic antibiotic therapy which was started on the night prior to biopsy and continued for 5 days. On the morning of biopsy, all patients self-administered the Fleet Enema® 3 hours to 5 hours before the scheduled time of biopsy. Patients in the experimental group were to self-administer celecoxib 400mg and tramadol 50mg 2 hours before biopsy so that the peak serum drug level (celecoxib = 2 hours, tramadol = 1 hour) would be attained by the time that the biopsy procedure was underway.[11]

The patients were placed in the lateral decubitus position on the biopsy table. Both treatment arms were given 10ml 2% lidocaine gel (Cathjell®) intrarectally and waited for 10 minutes. A well lubricated 7.5 MHz transrectal probe was inserted into the rectum to visualize the prostate. Sagittal and transverse views of the prostate were obtained and ultrasonographic abnormalities and gland dimensions were noted. Three-dimensional volume was calculated by multiplying gland height, width and depth in centimeters and multiplying the product by 0.52.

Biopsy was performed with the patient in the left lateral decubitus position during longitudinal scanning using an automated biopsy gun with an 18 gauge biopsy needle. All biopsies were performed through a systematic approach with a total of 12 specimens taken from the

base, mid gland and apex of the right and left sides of the lateral and far lateral peripheral zone.

Data Collection and Analysis

The patients were presented with 2 visual pain scale after 5 minutes upon completion of the biopsy and were asked to rate the pain. The scale was linear, 10-point visual analog pain scale and a standard 6-point face pain scale with the following corresponding number of 0 - no pain, 1 – 2 slight, 3 – 4 mild, 5 – 6 moderate, 7 – 8 severe, 8 – 10 worst pain. All patients were monitored for possible complications during and after the procedure, including any instance of post-procedural fever, urinary retention, or persistent bleeding. Patients were instructed to call or visit the clinic whenever any of these problems were noted. Data gathered were encoded and analyzed using Epi Info(TM) 3.5.1 software of the Center for Disease Control and Prevention (CDC).

Results

There were 31 patients included in the study, 16 in the experimental and 15 in the control group. The 2 groups were similar in characteristics in terms of age, prostate size and PSA level (Table 1). Ages ranged from 50 to 76 years old in the control group and 56 to 78 years old in the experimental group with a mean age (± SD) of 65.1 +/- 4.5 and 65.4 +/- 6.1 for control and experimental groups, respectively, which showed similarities on chi-square test (P = 0.78). The prostate size in grams ranged from 21.7 to 122.4 with a mean size of 61.1 +/ - 19.0 for control and 54.1 +/- 16.7 for the experimental group with *P* value of 0.84. Prostate specific antigen (PSA) values on the other hand, ranged from 5.1 to 120ng/dl with a mean of 31.85 +/- 35.8 in the treatment group and 7.6 to 500 ng/dl with a mean of 49.75 +/- 125 in the control group showing *P* value of 0.94. Digital rectal examinations were abnormal in 37.5 percent in the experimental group and 26.7 percent in the control group. The biopsy result revealed adenocarcinoma in 10 of the 31 patients studied, 5 (31.3%) in experimental and 5 (33.3%) in control group. There was no significant morbidity observed in the study, two developed fever, one in each group, which noted the following day after biopsy lasted less than 24 hours. No significant hematuria, persistent rectal bleeding, or urinary retention was noted. There were 2 patients who reported tolerable light-headedness in the treatment arm group.

The pain score recorded on visual analog scale (VAS) ranged from 1 to 9 for the control group and 2 to 8 for the treatment group. The overall mean pain score (± SD) were 4.1 +/- 1.7 in the experimental group and

Table 1. Patient characteristics.

Characteristics	Experiment	Control	P value
No. of Patients	16	15	
Age (Mean/SD/Range)	65.4 +/- 6.1 (56 - 78)	65.1 +/- 4.5 (56 - 73)	0.78
Prostate Size (g) (Mean/SD/Range)	54.1 +/- 16.7 (21.7 - 79.4)	61.1+/-19.0 (41.2 - 122.4)	0.84
PSA (ng/dl) (Mean/SD/Range)	31.85 +/- 35.8 (5.1 - 120)	49.75+/- 125.0 (7.6- 500)	0.94
DRE			
Normal	10 (62.5%)	11 (73.3%)	
Abnormal	6 (37.5%)	4 (26.7%)	
Biopsy Result			
Positive	5 (31.3%)	5 (33.3%)	
Negative	11 (68.8%)	10 (66.7%)	

5.5+/- 1.9 in the control group with *P* value of 0.034 using chi-square test which was significant (Table 2). There was a mean pain score decrease of 1.5 from the scale of 1 to 10 in the experimental group.

Table 2. Pain recorded on visual analog scale.

Pain Score	Experiment	Control	P Value
Mean/SD	4.1 +/- 1.7	5.5 +/- 1.9	0.034
Range	2-8	1-9	

Discussion

Patients undergoing TRUS guided needle biopsy of the prostate for diagnosing prostate cancer routinely report pain and discomfort during the procedure which can be slight to worst pain possible. This study showed that the average pain experienced by patients undergoing TRUS biopsy of the prostate in both study groups were mild to moderate, with VAS score as high as 6 and 9 in the experimental and control groups, respectively. The premedication of celecoxib and tramadol in combination with intrarectal lidocaine gel significantly reduced the pain experienced by patients as compared to lidocaine alone. Ideally, the pain felt by patients undergoing biopsy with any form of anesthesia should be less than 3 on VAS to be effective.[4] However, in this study, the average pain scores were 4 in the treatment group and 5.5 in the control group. Nevertheless, the premedication of celecoxib and tramadol in addition to intrarectal lidocaine still significantly showed a decrease of 1.5 in pain score in the control group. The efficacy of intrarectal lidocaine could further be improved by addition of celecoxib and tramadol as premedication for pain control in patients during prostate biopsy.

The efficacy of the premedications could be attributed to the actions of celecoxib which were to minimize the release of inflammatory mediators and desensitize pain receptors. On the other hand, tramadol worked by blocking pain receptors centrally thereby decreasing pain further.

Conclusion

This study showed that pain control using intrarectal lidocaine during transrectal ultrasound guided prostate biopsy can be improved by adding premedications providing alternative options for pain management. The addition of oral celecoxib 400mg and tramadol 50mg 2 hours before intrarectal 10ml 2% lidocaine gel significantly reduced the pain experienced by patients during ultrasound guided prostate biopsy.

References

1. Irani J, Fournier F, Bon D, Gremmo E, Dore B and Aubert G. Patient tolerance of transrectal ultrasound guided biopsy of the prostate. Br J Urol 1997; 79: 608.
2. Collins GN, Lloyd SN, Hehir M and McKelvie GB. Multiple transrectal ultrasound-guided prostatic biopsies: true morbidity and patient acceptance. Br J Urol 1993; 71: 460.
3. Issa MM, Bux S, Chun T, Petros JA, Labadia A J, Anastasia K, et al. A randomized prospective trial of intrarectal lidocaine for pain control during transrectal prostate biopsy: the Emory University experience. J Urol 2000; 164: 397.
4. Autorino R, De Sio M, Di Lorenzo G, Damiano R, Perdonà 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.
5. Scott LJ and Perry CM. Tramadol: a review of its use in perioperative pain. Drugs 2000; 60: 139.
6. Lewis KS and Han NH. Tramadol: a new centrally acting analgesic. Am J Health Syst Pharm 1997; 54: 643.
7. Issioui T, Klein K, et al. The efficacy of premedication with celecoxib and acetaminophen in preventing pain after otolaryngologic surgery. Anesth Analg 2002; 94: 1188-1193.
8. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001; 345: 433–442.
9. Pendleton J, Costa J, et al. 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: 1372-1375.
10. Obek C, Ozkan B, Tunc B, Can G, Yalcin V, Solok V. Comparison of 3 different methods of anesthesia before transrectal prostate biopsy: a prospective randomized trial. J Urol 2004; 172: 502.
11. Brunton L, Lazo J, Parker K. Goodman and Gilman's The Pharmacological Basis of Therapeutics, Eleventh Edition. 2006: Ch 26. MacGraw-Hill.