Perioperative Administration of Pregabalin in Patients Undergoing Arthroscopic Anterior Cruciate Ligament Reconstruction: Does It Help to Relieve Postoperative Pain?

Sasikaan Nimmaanrat MD*, Boonsin Tangtrakulwanish MD**,
Prapakorn Klabklay MD**, Tanarat Boonriong MD**

** Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhl, Thailand*
*** Department of Orthopaedic Surgery and Physical Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Objective: *To evaluate the analgesic effect of perioperative administration of pregabalin in patients undergoing arthroscopic anterior cruciate ligament reconstruction.*
Material and Method: *Fifty-six patients were randomly assigned to receive either pregabalin 75 mg or a matching placebo, one hour prior to spinal anesthesia, with the second dose repeated 12 hours after the first dose in this comparative study. The means of postoperative pain intensity measured by a verbal rating scale (VRS) of 0 to 10, sedation score of 0 to 3, requirement for morphine using a patient-controlled analgesia (PCA) device, and the median respiratory rate, as well as adverse effect were recorded every four-hour, up to 24 hours.*
Results: *Twenty-seven patients received pregabalin, and 29 cases got placebo. Characteristics were not significantly different between the two groups, except for the ages of 29.3 years in the pregabalin group, and 33.8 years in the placebo group. The means of postoperative pain severity, sedation score, consumption of PCA morphine, median respiratory rate, and adverse effects were not significantly different between the two groups.*
Conclusion: *Perioperative administration of pregabalin was not superior to placebo in terms of reducing postoperative pain intensity and PCA morphine requirement in patients undergoing arthroscopic anterior cruciate ligament reconstruction.*

Keywords: *Pregabalin, Arthroscopic, Anterior cruciate ligament, Reconstruction, Postoperative pain*

J Med Assoc Thai 2012; 95 (10): 1297-301
Full text. e-Journal: *http://jmat.mat.or.th*

Pregabalin [(S)-(+)-3-(aminomethyl)-5-methylhexanoic acid] is pharmacologically similar to alkylated Gamma Amino Butyric Acid (GABA) analogue[1] but has no action in the GABAergic neuronal system[2]. Pregabalin was developed and approved for use many years after gabapentin. Both are anticonvulsants with clinically demonstrated efficacy for various kinds of neuropathic pain[1]. They act on the alpha-2-delta subunit of the voltage-gated calcium channel inhibiting calcium influx and hence decrease the release and transmission of excitatory neurotransmitters[2-4], which may possibly lead to reduction of postoperative pain. It has been found that perioperative administration of gabapentin provides analgesia. It also has an opioid sparing effect[5-8].

Correspondence to:
Nimmaanrat S, Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Phone: 088-790-7842
E-mail: snimmaanrat@yahoo.com.au

Pregabalin has been studied in some kinds of postoperative pain and the results seem to be promising[9-18] but with more adverse effects including dizziness, blurred vision, and headache[10]. Furthermore, pregabalin has been shown to have a lower incidence of neuropathic pain, less opioid requirement, improved range of motion during the first 30 days[19], less pain severity, and better functional outcomes at three months[20]. On the other hand, other studies reveal negative results[14,21-24].

To further evaluate pregabalin's efficacy and safety in terms of postoperative pain relief, a comparative study was conducted in patients undergoing arthroscopic anterior cruciate ligament reconstruction.

Material and Method

The present study was approved by the Ethics Committee, Faculty of Medicine, Prince of Songkla University. Based on data from an earlier study[11],

25 patients were included for each of two trial groups, to result in a final power of 80% and type I error of 0.05. Using computer-generated block randomization, the enrolled patients were randomly assigned into two groups, one receiving pregabalin, and the other got placebo.

Eligible patients were those aged 18 to 65 years, American Society of Anesthesiologists physical status I and II, and body mass index (BMI) of 16 to 35. The exclusion criteria were patients who had a known allergy to pregabalin, impaired hepatic or renal functions, a history of alcohol or substance abuse, chronic pain other than in the knee joint, uncontrolled medical diseases, or who were already taking daily analgesics or were unable to operate a patient-controlled analgesia (PCA) device.

After signing an informed consent form, the enrolled patients were divided into two groups. All subjects were preoperatively instructed regarding how to measure pain intensity by using a verbal rating scale (VRS); 0 = no pain, 10 = the worst pain imaginable). All of them were reviewed by an anesthesiologist one day prior to the set date. Spinal anesthesia was carried out in all patients, using 0.5% hyperbaric bupivacaine.

One hour prior to spinal anesthesia, either one capsule of pregabalin 75 mg, or one identical capsule containing only placebo was given to each patient. Each patient then accordingly received a repeated dose of the pregabalin, or the placebo 12 hours subsequent to the first dose. Postoperative pain was managed with PCA morphine with the following setting, no continuous infusion, bolus 1 mg, lockout interval 5-minutes and 4-hour limit of 40 mg. No other analgesics were allowed to the study population.

Patients' maximum VRS were measured at baseline (before surgery) and at 4, 8, 12, 16, 20, and 24 hours from the initiation of spinal anesthesia. Respiratory rate and adverse effects including sedation as well as postoperative nausea and vomiting (PONV) were also evaluated every four-hour for the first 24 hours. Sedation score was graded as 0 = none (awake), 1 = drowsy, 2 = asleep, rousable, and 3 = asleep, unrousable. PONV was ranked as 0 = no PONV, 1 = mild nausea (no contraction of abdominal and respiratory muscles), 2 = moderate nausea/retching (with contraction of abdominal or respiratory muscles), and 3 = severe nausea or vomiting. The rescue antiemetic ondansetron 8 mg was administered intravenously to patients with PONV score 2 or more.

In the first 24 hours after spinal anesthesia, other adverse events including dizziness, headache, and blurred vision were also assessed. Total PCA morphine consumption was recorded at different time intervals as previously mentioned. Other patient evaluations were assessed at 24 hours, notably global pain relief (poor, fair, good or excellent), satisfaction of pain relief (none, minimum, moderate, maximum), limitation of mobilization due to pain (none, minimum, moderate, maximum), disturbance of sleep by pain (yes, no), and preference for stronger analgesic (yes, no).

Data analysis was based on the "per protocol" principle. All statistical calculation was performed utilizing Program R version 2.10.1. Either Fisher's exact test or Chi-square test was employed for analysis of categorical data. Continuous data with/without normal distribution were analyzed with student t-test or Mann-Whitney U test, respectively.

Results

Fifty-six patients completed the study covering the first 24 hours after spinal anesthesia. The baseline characteristics of the pregabalin/control group were not statistical significance of gender (male of 88.9/89.7%), mean age (29.3/33.8 years), BMI (23.4/23.7 kg/m^2), and mean duration of surgery (100.7/92.6 hours).

Postoperative pain severity was low in both groups at four-hour, while was lower in the pregabalin group at later periods, but no statistical significance, as well as sedative score. The requirement for PCA morphine in the first 24 hours, sedation score, and respiratory rate was also not statistically significantly different as demonstrated in Table 1.

The adverse effects had no statistical significances between pregabalin/control groups, postoperative nausea and vomiting of 10/14 (37/48.2%), dizziness of 7/14 (25.9/48.3%), headache 6/7 (22.4/24.1%), and blurred vision of 2/3 (7.4/10/3%). In addition, limitation of activity from pain, sleep disturbance by pain, patient's global evaluation of pain relief, patient's satisfaction, and preference for stronger analgesia had no statistical significances.

Discussion

The present study is a continued investigation of the previous study[25]. The results revealed that perioperative administration of pregabalin 75 mg did not reduce postoperative pain severity more than the control. In comparison with another orthopedic surgery, total knee arthoplasty, the long scheme of pregabalin of 300 mg before surgery and 100 mg for 14 days after

Table 1. Postoperative pain severity, sedation score, PCA morphine consumption, and median respiratory rate of the pregabalin and control at different time intervals

Postoperative at 4/8/12/16/20/24 hours	Pregabalin (n = 27)	Control (n = 29)
Mean pain severity at	1.1/5.4/4.9/4.3/4.4/4.6	0.97/5.5/5.6/5.2/4.6/4.6
Mean PCA morphine consumption	0.96/7.6/13.9/18.8/22.3/26.3	0.8/6.8/12.8/16.7/21.3/24.1
Mean sedative score at	0/0/0/0/0/0	0/0/0/0/0/0
Median respiratory rate	20/20/18/20/20/20	20/20/20/20/20/20

* Statistical significance, $p < 0.05$

surgery showed less oral opioid requirement while hospitalized ($p = 0.005$) and sedative effect[19].

In fact, pregabalin is rapidly absorbed following oral administration, with peak plasma concentrations occurring between 0.7 and 1.3 hours, and pregabalin elimination half-life is approximately 6 hours and steady state is achieved within 1 to 2 days of repeated administration[26]. Nevertheless, preoperative pregabalin of 300 mg results in anxiolytic effect in minor orthopedic surgery[27], but not major surgery[28].

In conclusion, perioperative administration of pregabalin was not superior to placebo in terms of reducing postoperative pain intensity and PCA morphine requirement in patients undergoing arthroscopic anterior cruciate ligament reconstruction.

References

1. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol 2007; 20: 456-72.
2. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet 2010; 49: 661-9.
3. Guindon J, Walczak JS, Beaulieu P. Recent advances in the pharmacological management of pain. Drugs 2007; 67: 2121-33.
4. Golembiewski JA. Postoperative pain management – is there a role for gabapentin or pregabalin? J Perianesth Nurs 2007; 22: 136-8.
5. Seib RK, Paul JE. Preoperative gabapentin for postoperative analgesia: a meta-analysis. Can J Anaesth 2006; 53: 461-9.
6. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med 2006; 31: 237-47.
7. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain – a systematic review of randomized controlled trials. Pain 2006; 126: 91-101.
8. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007; 104: 1545-56.
9. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004; 48: 1130-6.
10. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008; 134: 106-12.
11. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh PK, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaesth 2008; 101: 700-4.
12. Mathiesen O, Jacobsen LS, Holm HE, Randall S, Adamiec-Malmstroem L, Graungaard BK, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008; 101: 535-41.
13. Trabulsi EJ, Patel J, Viscusi ER, Gomella LG, Lallas CD. Preemptive multimodal pain regimen reduces opioid analgesia for patients undergoing robotic-assisted laparoscopic radical prostatectomy. Urology 2010; 76: 1122-4.
14. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008; 100: 834-40.
15. Kim SY, Jeong JJ, Chung WY, Kim HJ, Nam KH,

Shim YH. Perioperative administration of pregabalin for pain after robot-assisted endoscopic thyroidectomy: a randomized clinical trial. Surg Endosc 2010; 24: 2776-81.
16. Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: a randomized, double-blind trial. J Med Assoc Thai 2009; 92: 1318-23.
17. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obes Surg 2010; 20: 1678-81.
18. Freedman BM, O'Hara E. Pregabalin has opioid-sparing effects following augmentation mammaplasty. Aesthet Surg J 2008; 28: 421-4.
19. Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. Anesth Analg 2010; 110: 199-207.
20. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg 2010; 110: 1180-5.
21. Paech MJ, Goy R, Chua S, Scott K, Christmas T, Doherty DA. A randomized, placebo-controlled trial of preoperative oral pregabalin for post-operative pain relief after minor gynecological surgery. Anesth Analg 2007; 105: 1449-53.
22. Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, et al. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 2009; 53: 227-35.
23. Chang SH, Lee HW, Kim HK, Kim SH, Kim DK. An evaluation of perioperative pregabalin for prevention and attenuation of postoperative shoulder pain after laparoscopic cholecystectomy. Anesth Analg 2009; 109: 1284-6.
24. Peng PW, Li C, Farcas E, Haley A, Wong W, Bender J, et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. Br J Anaesth 2010; 105: 155-61.
25. Nimmaanrat S, Tangtrakulwanich B, Wanasuwannakul T, Boonriong T. Expectations, experiences and attitudes of orthopedic patients undergoing arthroscopic cruciate ligament reconstruction toward postoperative pain and its management. J Med Assoc Thai 2010; 93: 1268-73.
26. Bockbrader HN, Radulovic LL, Posvar EL, Strand JC, Alvey CW, Busch JA, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 2010; 50: 941-50.
27. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. J Psychopharmacol 2011; 25: 249-53.
28. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: a dose-ranging study. Anesth Analg 2009; 108: 1140-5.

การให้ยาพรีกาบาลินในผู้ป่วยก่อนและหลังการผ่าตัดสร้างเอ็นไขว้หน้าข้อเข่าโดยการส่องกล้อง: ลดความปวดหลังการผ่าตัดได้หรือไม่?

ศศิกานต์ นิมมานรัชต์, บุญสิน ตั้งตระกูลวนิช, ประภากร กลับกลาย, ธนะรัตน์ บุญเรือง

วัตถุประสงค์: *เพื่อประเมินผลระงับปวดของยาพรีกาบาลินที่ให้ก่อนและหลังผ่าตัดในผู้ป่วยผ่าตัดสร้างเอ็นไขว้หน้าข้อเข่าโดยการส่องกล้อง*

วัสดุและวิธีการ: *สุ่มผู้ป่วย 56 ราย เพื่อได้รับยาพรีกาบาลิน 75 มิลลิกรัม หรือ ยาไร้สารขนานแรก 1 ชั่วโมงก่อนการฉีดยาระงับความรู้สึกเข้าช่องน้ำไขสันหลัง และขนานที่สอง 12 ชั่วโมงหลังขนานแรก ความปวดหลังผ่าตัดเฉลี่ยการวัดแบบระดับขั้นด้วยวาจา (0 ถึง 10) คะแนนความสงบ (0 ถึง 3) ความต้องการยามอร์ฟีนโดยใช้เครื่องควบคุมการบริหารยาด้วยตนเอง ค่ากลางอัตราการหายใจ และผลข้างเคียง ตรวจวัดทุก 4 ชั่วโมง เป็นเวลา 24 ชั่วโมง*

ผลการศึกษา: *ผู้ป่วย 27 ราย ได้รับยาพรีกาบาลิน และ 29 ราย ได้รับยาไร้สาร ผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญเกี่ยวกับลักษณะผู้ป่วย ยกเว้นผู้ป่วยได้รับยาพรีกาบาลินอายุ 29.3 ปี ผู้ป่วยได้รับยาไร้สารอายุ 33.8 ปี ผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญเกี่ยวกับค่าเฉลี่ยคะแนนความปวด คะแนนความสงบ ความต้องการใช้ยามอร์ฟีน ค่ากลางอัตราการหายใจ และผลข้างเคียง*

สรุป: *การให้ยาพรีกาบาลินแก่ผู้ป่วยก่อนและหลังการผ่าตัดสร้างเอ็นไขว้หน้าข้อเข่าโดยการส่องกล้อง ไม่มีผลลดคะแนนความปวดและความต้องการใช้ยามอร์ฟีน*