Efficacy of Etoricoxib for Pain Relief during Endometrial Biopsy; A Double Blind Randomized Controlled Trial

Chamnan Tanprasertkul MD*,
Densak Pongrojpow MD*

** Department of Obstetrics and Gynecology, Thammasat University, Prathumthani*

Objective: *To compare the efficacy of oral etoricoxib and placebo for pain relief during endometrial biopsy.*
Material and Method: *A double-blind, randomized controlled trial that included 80 women who underwent endometrial biopsy was done at Thammasat University Hospital between 1 September 2005 and 30 June 2006. Forty women were randomly allocated to the etoricoxib group (120 mg, tablet) and 40 to the placebo group. The main outcome was the patient's assessment of intensity of pain measured by visual analog scale (VAS) before speculum insertion, during endometrial biopsy, immediately after endometrial biopsy, and 30 minutes after endometrial biopsy. Satisfactory score was also evaluated.*
Results: *Demographic data including age, BMI, previous vaginal deliveries, previous pelvic surgery and history of curettage were not significantly different between the etoricoxib group and the placebo group. Mean pain score in the etoricoxib group was not significantly lower when compared with the placebo group during endometrial biopsy (5.0 $\pm$ 1.7 versus 5.25 $\pm$ 2.2, p = 0.7) and immediately after endometrial biopsy (2.1 $\pm$ 2.2 versus 2.8 $\pm$ 1.7, p = 0.1) but significantly lower at 30 minutes after endometrial biopsy (0.2 $\pm$ 0.5 versus 0.6 $\pm$ 0.8, p = 0.01). Mean satisfactory score was significantly higher in the etoricoxib group (6.9 $\pm$ 1.8 versus 5.1 $\pm$ 2.3, p = 0.001).*
Conclusion: *A single oral dose of etoricoxib for reduction of pain during endometrial biopsy had not significantly lower the pain score during the procedure compared with the placebo. However mean satisfactory score in the etoricoxib group was higher with statistically significant difference. Also the authors found no serious adverse effects of this drug.*

Keywords: *Pain, Visual analog scale, Etoricoxib, Endometrial biopsy*

J Med Assoc Thai 2008; 91 (1): 13-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

Endometrial biopsy is an office procedure that serves as a useful tool in the work-up of abnormal uterine bleeding. High efficacy and accuracy for the diagnosis of endometrial cancer and endometrial hyperplasia has been reported[1-2]. The technique is fairly easy to learn and may be performed without assistance in an outpatient clinic, however, most women experience some pain and discomfort during the procedure, especially during cervical dilatation and retrieval of the endometrial specimen. Limiting both discomfort and pain will lead to a more acceptable outcome for both patients and providers. While there have already been some studies regarding techniques to reduce pain techniques (such as the use of paracervical block, intrauterine anesthesia and xylocaine sprays) but there is still no single ideal anesthetic technique[3-8].

The COX-2 specific inhibitors possess both the analgesic and anti-inflammatory properties of conventional NSAIDs through COX-2 inhibition, with an improved safety profile achieved by sparing the activity of the COX-1 isozyme. Reports on analgesic efficacy and safety of administered COX-2 specific inhibitors have been demonstrated in clinical studies. Etoricoxib is an oral COX-2 selective agent that has an early onset of action, of about 24-minutes, which achieves peak plasma level at 60 minutes[9]. In primary dysmenorrhea, acute gouty arthritis and post-surgical

Correspondence to : Tanprasertkul C, Department of Obstetrics and Gynecology, Thammasat University, Prathumthani 12120, Thailand. E-mail: chamnandr@msn.com

dental pain, etoricoxib showed a similar pain reduction as conventional NSAIDs, but etoricoxib had lower adverse effects[10-12]. The objective of the present study was to determine the efficacy of oral etoricoxib for pain relief during endometrial biopsy.

Material and Method

This randomized, double-blind study was conducted at the outpatient gynecologic clinic at Thammasat University Hospital. The present study was approved by the Hospital Ethical Committee. Written informed consent was obtained for every patient evaluated. Eligible patients included women 35 years or older who presented with abnormal uterine bleeding, and who required a diagnostic endometrial biopsy. Exclusions included patients with a history of active renal disease, hepatic impairment, congestive heart failure, gastrointestinal ulcer and bleeding, bronchospasm, hemostatic impairment, hypertension, and hypersensitivity to NSAIDs or COX-2 specific inhibitors. Patients with any serious medical conditions, and/or who had a history of NSIADs hypersensitivity were excluded. Patients with uncontrolled bleeding at screening were also excluded.

From a previous study[8], the mean pain scores in the study and placebo group were 5.8 and 7.1, respectively; standard deviation was 2.0. Therefore the sample size obtained by calculation and adding 10% more was 40 patients in each group ($\alpha = 0.05$, $\beta = 0.02$). From 1 September 2005 to 30 June 2006, 80 women who had met the criteria for diagnostic endometrial biopsy were randomly allocated to receive etoricoxib (Arcoxia 120 mg, tablet) or placebo. Patients were randomized according to a computer-generated allocation schedule into two groups of 40 each. The first group received etoricoxib 1 tab (120 milligrams), the second group received a placebo which was the same size and color. Neither group had received other pain relief methods. The drugs were prepared in a sealed opaque envelope and labeled with stickers preprinted with computer generated random numbers. Patients received the drugs at 30-60 minutes before the procedure. The performing gynecologists and the assisting nurses were blinded to the type of drugs used. The technique of biopsy was obtained through the use of the Novak curette, which was inserted through the cervix into the uterine cavity. This type of curette is used with a syringe to apply suction, and a circumferential in-and-out motion is required to obtain a sample.

The pain and satisfaction scores were self-administrated assessment using visual analog scale (VAS; 0 meant no pain or absolutely not satisfied and 10 meant the worst pain imaginable or very satisfied). Each patient had four assessments evaluated for pain. The first one was made before insertion of the speculum. The second one was made during the endometrial biopsy procedure. The third one was made immediately after the procedure and the fourth one was made 30 minutes after the procedure. Satisfactory score was evaluated at the fourth one only. Each patient was offered another potent analgesic drug at any time, if she wanted more pain relief, or otherwise wished to leave the present study. Side effects were monitored throughout the procedure. The random number key was not broken until the data analysis was done.

Data record were analyzed and presented as a percentage (%) and mean $\pm$ SD including age, BMI, previous vaginal parity, a history of pelvic pain, a history of pelvic surgery, a history of prior endometrial biopsy, a history of prior dilatation and curettage, menopausal status, tenaculum use, procedure time, VAS pain score and VAS satisfactory score. The Student t-test was used to compare the continuous variables where appropriate. The Chi-square test was used to compare the discrete variables. A p-value < 0.05 was considered as statistically significant.

Results

Eighty women between the age of 35 and 72 were enrolled during the present study. No patient asked for another potent analgesic drug or left the study. There were no statistically significant differences between groups in age, BMI, or any other demographic characteristics as shown in Table 1. The mean operative time in the etoricoxib group was greater than in the placebo group, but there was no significant difference. Taking etoricoxib before the endometrial biopsy resulted in a reduction of the median VAS pain score, compared with the placebo, but this was not a significant difference at either during or immediately after the procedure. At 30 minutes after the biopsy, there was a significant reduction of the median VAS pain score, compared with the placebo (Fig. 1).

Patients who received etoricoxib had a significantly higher mean satisfaction score, compared to those who received the placebo. No severe adverse effects were found in either group, however two patients in the etoricoxib group reported dizziness, which resolved spontaneously without a need for further medication.

In Table 2, the patients with a history of vaginal parity had a significantly lower proportion of

Table 1. Demographic characteristics and outcomes of the study participants

Characteristics	Etoricoxib (n = 40)	Placebo (n = 40)	p-value
Age (y)	47.05 ± 8.50	44.25 ± 6.93	0.11
BMI (kg/m^2)	25.34 ± 3.76	24.37 ± 4.76	0.31
Previous vaginal parity	75 (30)	85 (34)	0.08
History of pelvic pain	5 (2)	10 (4)	0.34
History of pelvic surgery	5 (2)	15 (6)	0.13
Prior endometrial biopsy	0 (0)	5 (2)	0.15
Prior dilatation and curettage	10 (4)	10 (4)	1.00
Menopause	50 (20)	40 (16)	0.36
Tenaculum use	90 (38)	100 (40)	0.15
Operative procedure time (seconds)	203.70 ± 122.53	164.00 ± 66.32	0.07
VAS Pain score			
1. Before	0 ± 0	0 ± 0	1.00
2. Between	5.08 ± 1.72	5.25 ± 2.22	0.70
3. Immediately after	2.15 ± 2.23	2.85 ± 1.70	0.11
4. After 30 min	0.25 ± 0.54	0.65 ± 0.85	0.01
VAS Satisfactory score	6.90 ± 1.86	5.10 ± 2.37	0.02
Adverse effects	5% (2)	0% (0)	0.15

Data are presented as mean ± standard deviation or % (n)

Table 2. Comparison of VAS pain score in patients with previous vaginal parity

	Previous vaginal parity (n = 64)	No history of vaginal parity (n = 16)	p-value
VAS pain score < 5	46.87% (30/64)	12.5% (2/16)	0.003
Mean VAS pain score	4.81 ± 1.87	6.56 ± 1.75	0.001

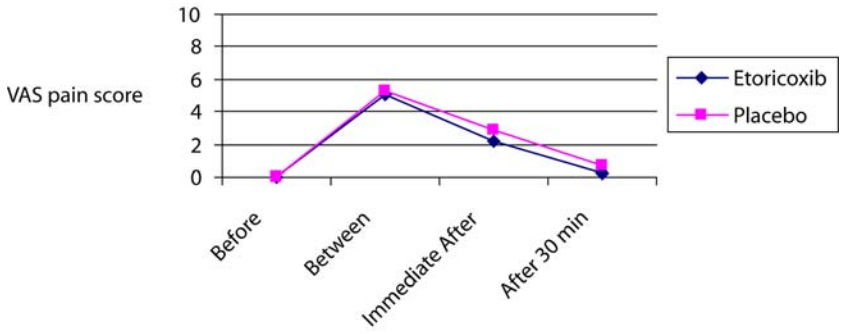

Fig. 1 Mean VAS pain score during endometrial biopsy at four points of time

those who had VAS pain score less than 5 and lower mean VAS pain score when compared with the patients who did not have a history of vaginal parity.

Discussion

Despite endometrial biopsy is a minor surgical procedure and could be done in an outpatient clinic without need of any types of anesthesia, nearly half of the patients experience moderate-to-severe pain during procedure. The discomfort and pain is still the problem and limitation of widely use of this procedure. Mechanism of uterine pain could be described by the

uterine nervous system and prostaglandin pathway[13]. The innervation of the uterus is autonomic arising from the inferior hypogastric plexus (sympathetic) and the pelvic splanchnic nerves (parasympathetic from S2, 3, 4). The afferent fibers travel with sympathetic efferents to T10-12 and L1 spinal cord segments[14]. Previous studies reported intrauterine anesthesia was effective for decreasing pain associated with the endometrial biopsy, and a postulated mechanism of action was an effect of intrauterine administration of an anesthetic drug on the nerve endings within the endometrial mucosa[4-6]. This may not be effective for pain in the lower part of the uterus and cervix when cervical dilatation because it has a different innervation. The sensory innervation of the cervix and lower portion of the uterus is Frankenhauer's plexus or the uterovaginal plexus provides. Paracervical block had been demonstrated that can relieve pain at the lower part of the uterus and cervix without serious complications[3,15].

To the authors' knowledge, this is the first randomized, double-blind, placebo-controlled study comparing the effects of nonsteroidal anti-inflammatory drug for endometrial biopsy. The present study uses COX-2 specific inhibitor, etoricoxib, to reduce the pain because one of the mechanisms is that the uterine wall can produce prostaglandin like other tissues. During endometrial biopsy, disruption of endometrium would cause prostaglandin release leading to the uterine contraction. This mechanism can cause the pain sensation at the upper part of the uterus. In the present study, mean VAS pain score had decreased but it was not statistically significant. This could be explained that blocking only the prostaglandin synthesis mechanism was not sufficient to overcome the pain.

At time point - after 30 minutes, mean VAS pain score showed a significantly decrease but the mean VAS pain score difference was only 0.4 which might not be clinically significant. Mean VAS satisfactory score was statistically, significantly higher in the etoricoxib group compared to the placebo group. However, mean VAS satisfactory scores in both groups were above 5.0 and the score difference was only 1.8 which could imply that the most of the patients more likely prefer this route of anesthesia.

Though COX-2 specific inhibitor might not reduce pain during the procedure, using this drug seems to be safe and not harmful to the patients. The authors noticed that if patients had no history of vaginal parity, VAS pain scores were much more than the patients who had a history of vaginal parity as shown in Table 2. If the procedure needs to be done in the patients without a history of vaginal parity, the anesthetic technique must be carefully applied.

The authors accept that the limitation of the present study is the small sample and might not allow for completely answering this question. In combination with other anesthetic techniques should have an excellent result in reduction the pain through synergistic effects; this question warrants more studies and needs further investigations.

In conclusion, single oral dose of etoricoxib had not significantly lower mean VAS pain score during the endometrial biopsy. However, mean VAS satisfactory score in the etoricoxib group was higher than the placebo group with statistically significant difference. Also the authors found no serious adverse effects of this drug throughout the endometrial biopsy procedure.

References

1. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: a systematic quantitative review. BJOG 2002; 109: 313-21.
2. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia. Acta Obstet Gynecol Scand 2001; 80: 784-93.
3. Cicinelli E, Didonna T, Schonauer LM, Stragapede S, Falco N, Pansini N. Paracervical anesthesia for hysteroscopy and endometrial biopsy in postmenopausal women. A randomized, double-blind, placebo-controlled study. J Reprod Med 1998; 43: 1014-8.
4. Trolice MP, Fishburne C Jr, McGrady S. Anesthetic efficacy of intrauterine lidocaine for endometrial biopsy: a randomized double-masked trial. Obstet Gynecol 2000; 95: 345-7.
5. Zupi E, Luciano AA, Marconi D, Valli E, Patrizi G, Romanini C. The use of topical anesthesia in diagnostic hysteroscopy and endometrial biopsy. J Am Assoc Gynecol Laparosc 1994; 1: 249-52.
6. Cicinelli E, Didonna T, Ambrosi G, Schonauer LM, Fiore G, Matteo MG. Topical anaesthesia for diagnostic hysteroscopy and endometrial biopsy in postmenopausal women: a randomised placebo-controlled double-blind study. Br J Obstet Gynaecol 1997; 104: 316-9.
7. Einarsson JI, Henao G, Young AE. Topical analgesia for endometrial biopsy: a randomized controlled

trial. Obstet Gynecol 2005; 106: 128-30.
8. Dogan E, Celiloglu M, Sarihan E, Demir A. Anesthetic effect of intrauterine lidocaine plus naproxen sodium in endometrial biopsy. Obstet Gynecol 2004; 103: 347-51.
9. Agrawal NG, Porras AG, Matthews CZ, Woolf EJ, Miller JL, Mukhopadhyay S, et al. Dose proportionality of oral etoricoxib, a highly selective cyclooxygenase-2 inhibitor, in healthy volunteers. J Clin Pharmacol 2001; 41: 1106-10.
10. Malmstrom K, Kotey P, Cichanowitz N, Daniels S, Desjardins PJ. Analgesic efficacy of etoricoxib in primary dysmenorrhea: results of a randomized, controlled trial. Gynecol Obstet Invest 2003; 56: 65-9.
11. Malmstrom K, Kotey P, Coughlin H, Desjardins PJ. A randomized, double-blind, parallel-group study comparing the analgesic effect of etoricoxib to placebo, naproxen sodium, and acetaminophen with codeine using the dental impaction pain model. Clin J Pain 2004; 20: 147-55.
12. Schumacher HR Jr, Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, et al. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. BMJ 2002; 324: 1488-92.
13. Rapkin AJ. Neuroanatomy, neurophysiology, and neuropharmacology of pelvic pain. Clin Obstet Gynecol 1990; 33: 119-29.
14. Geiffenstuhl G. Practical pelvic anatomy for the gynecologic surgeon. In: Nichols DH, editor. Gynecologic and obstetric surgery. St. Louis: Mosby Yearbook; 1993:26-71.
15. Phittayawechwiwat W, Thanantaseth C, Ayudhya NI, Prasertsawat P, Kongprasert J. Oral etoricoxib for pain relief during fractional curettage: a randomized controlled trial. J Med Assoc Thai 2007; 90: 1053-7.

ประสิทธิผลของยา etoricoxib ในการลดความเจ็บปวดระหว่างการตรวจหาชิ้นเนื้อจากเยื่อบุโพรงมดลูก

ชำนาญ แท่นประเสริฐกุล, เด่นศักดิ์ พงศ์โรจน์เผ่า

วัตถุประสงค์*: เพื่อศึกษาเปรียบเทียบผลการลดความเจ็บปวดระหว่างกลุ่มที่ได้ยา etoricoxib และกลุ่มที่ได้ยา placebo ในผู้ป่วยที่ถูกตัดเนื้อเยื่อบุโพรงมดลูก*

วัสดุและวิธีการ*: ศึกษาแบบ double-blind, randomized controlled trial ในผู้ป่วยที่ถูกตัดเนื้อเยื่อบุโพรงมดลูก 80 ราย ที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ์ ระหว่าง 1 กันยายน พ.ศ. 2549 – 30 มิถุนายน พ.ศ. 2550 โดยแบ่งผู้ป่วยเป็นสองกลุ่มโดยการสุ่ม กลุ่มที่หนึ่งได้ยา etoricoxib (120 มก.) จำนวน 40 ราย และกลุ่มที่สองได้ยา placebo จำนวน 40 รายก่อนการตัดชิ้นเนื้อ ผู้ป่วยทั้งสองกลุ่มไม่ได้รับยาหรือวิธีการระงับปวดอื่นร่วมด้วย ผู้ป่วยถูกประเมินความเจ็บปวด โดยใช้วิธี visual analog scale (VAS) ประเมิน 4 ช่วงเวลาคือ ก่อนการใส่ speculum, ขณะตัดเนื้อเยื่อบุโพรงมดลูก, ภายหลังการตัดเนื้อเยื่อบุโพรงมดลูกทันที และภายหลังการตัดเนื้อเยื่อบุโพรงมดลูก 30 นาที และได้ประเมินความพึงพอใจด้วยวิธี VAS เช่นกัน*

ผลการศึกษา*: ข้อมูลพื้นฐานผู้ป่วยทั้งสองกลุ่ม เช่น อายุ, ดัชนีมวลกาย,ประวัติคลอดบุตรทางช่องคลอด และประวัติเคยขูดมดลูกหรือผ่าตัดในอุ้งเชิงกราน ไม่มีความแตกต่างกันในทั้งสองกลุ่ม คะแนนเฉลี่ยความเจ็บปวดในกลุ่มที่ได้ยา etoricoxib ต่ำกว่ากลุ่มที่ได้ยา placebo ใน 3 ช่วงเวลา แต่พบว่ามีนัยสำคัญทางสถิติเฉพาะช่วง ภายหลังตัดเนื้อเยื่อบุโพรงมดลูก 30 นาทีเท่านั้น (0.2 $\pm$ 0.5 และ 0.6 $\pm$ 0.8 ตามลำดับ, p = 0.01) และคะแนนเฉลี่ยความพึงพอใจในกลุ่มที่ได้ยา etoricoxib สูงกว่ากลุ่มที่ได้ยา placebo อย่างมีนัยสำคัญทางสถิติ (6.9 $\pm$ 1.8 และ 5.1 $\pm$ 2.3 ตามลำดับ, p = 0.001) โดยไม่พบผลข้างเคียงที่รุนแรงในผู้ป่วยทั้งสองกลุ่ม*

สรุป*: การใช้ยา etoricoxib ในผู้ป่วยที่ถูกตัดเนื้อเยื่อบุโพรงมดลูก ไม่สามารถลดความเจ็บปวดได้อย่างมีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มที่ได้ยา placebo แต่มีคะแนนเฉลี่ยความพึงพอใจในกลุ่มที่ได้ยา etoricoxib สูงกว่าอย่างมีนัยสำคัญทางสถิติ*