การศึกษาการเปรียบเทียบการใช้ยา Etoricoxib กับยาหลอกเพื่อลดความเจ็บปวดในผู้ป่วยที่ได้รับการขูดมดลูกร่วมกับการฉีดยาชาด้านข้างของปากมดลูก

Prospective randomized,double-blinded,placebo-controlled trial of preoperative etoricoxib for pain relief in uterine fractional curettage under paracervical block

Anant Mungcharoensantikul M.D.* **อนันต์ มุ่งเจริญสันติกุล พ.บ.***

ABSTRACT

Objective : To evaluate the analgesic efficacy of preoperative etoricoxib combined with paracervical block in patients who underwent uterine fractional curettage.

Study design : This double-blinded, randomized, placebo-controlled trial included 80 women outpatients aged 35-60 years were abnormal uterine bleeding who underwent uterine fractional curettage under paracervical block. Forty women were randomly assigned to etoricoxib 120 mg and 40 women to the placebo. The main outcome measure was the intensity of pain measured using the visual analog pain score during and after the procedure.This study was approved by Ethics Committee of Buriram Hospital. Student's t-test, Mann-Whitney U-test, and Chi-squared test were used for statistical analysis.

Results : The intensity of pain during operative procedure in the etoricoxib group was lower than in the placebo group (median visual analog pain score (interquartile range) 48 (43-64) vs. 61 (57-72), p = 0.001) The amount of postoperative acetaminophen used in the etoricoxib proup was also lower than in the placebo group (2.2±1.7 vs. 3.2 ± 1.7 tablets, p = 0.011). We found no significant adverse effects in this study.

Conclusion : The operative administration of 120 mg oral etoricoxib can slightly reduce pain during fractional curettage under paracervical block. However, the degree of pain reduction by this treatment has no clinical importance.

Key words : COX-2; Etoricoxib; Fractional curettage; Visaul analog score

นายแพทย์ชำนาญการพิเศษ กลุ่มงานสูติ-นรีเวชกรรม โรงพยาบาลบุรีรัมย์

บทคัดย่อ

วัตถุประสงค์ : เพื่อศึกษาผลการลดความเจ็บปวดของยา Etoricoxib ร่วมกับการฉีดยาชาด้านข้างของปากมดลูกในผู้ป่วยที่ได้รับการขูดมดลูก

รูปแบบการวิจัย : Double-blinded, randomized, placebo-controlled trial

วิธีการศึกษา : กลุ่มผู้ป่วยนอกจำนวน 80 คนได้รับการวินิจฉัยว่ามีภาวะเลือดออกผิดปกติจากโพรงมดลูก อายุ 35-60 ปี ที่ต้องได้รับการขูดมดลูกโดยวิธีการฉีดยาชาด้านข้างของปากมดลูก (Paracervical block) โดยแบ่งผู้ป่วยเป็น 2 กลุ่ม 40 คนแรกได้รับยา Etoricoxib 120 mg. และ 40 คนต่อมาได้รับยาหลอก ประเมินผลโดยการวัดความเจ็บปวดหลังจากขูดมดลูกโดยใช้ visual analog pain score โดยการวิจัยนี้ได้รับอนุญาตจากคณะกรรมการจริยธรรม โรงพยาบาลบุรีรัมย์

สถิติ : Student's t-test, Mann-Whitney U-test, and Chi-squared test

ผลการศึกษา : ความรุนแรงของความเจ็บปวดหลังจากการขูดมดลูกในผู้ป่วยที่ได้รับยา Etoricoxib ต่ำกว่าในกลุ่มที่ได้รับยาหลอก (median visual analog pain score 48 ต่อ 61, P = 0.001) จำนวนผู้ป่วยที่ต้องได้รับยาพาราเซตตามอลในกลุ่มที่ได้รับยา Etoricoxib น้อยกว่ากลุ่มที่ได้รับยาหลอก (2.2 ±1.7 ต่อ 3.2 ± 1.7 เม็ด P = 0.011) และไม่พบผลข้างเคียงจากการศึกษานี้

สรุป : การให้ยา Etoricoxib 120 mg. ร่วมกับการฉีดยาชาด้านข้างของปากมดลูก (paracervical block) สามารถลดความเจ็บปวดระหว่างการขูดมดลูกได้ อย่างไรก็ตามความแรงของความเจ็บปวดที่ลดลงได้ไม่ได้มีความสำคัญในทางปฏิบัติมากนัก

คำสำคัญ : COX-2, Etoricoxib, การขูดมดลูก, visual analog score

Introduction

Uterine fractional curettage has been regularly performed on an outpatient basis, most often of investigating causes of abnormal uterine bleeding. It is usually performed under local anesthesia such as paracervical block.[1] Paracervical block can be performed by the operating gynecologists. Although paracervical block with either lidocaine or saline seems to be safe, inexpensive, and easy to perform, it provides an inadequate and a variable analgesic effect.[2] The reason that paracervical block cannot totally alleviate the pain during fractional curettage can be partly explained by the neuroanatomy of the uterus and cervix. The paracervical block relieves pain in the lower part of the uterus and cervix by blocking nerve impulses that are conveyed through the uterovaginal plexus. It may not be effective for pain originating in the upper part of the uterus, which has a different innervation.[3] Therefore, various methods such as intrauterine anesthesia[4] , intravenous sedation[5] , and an adjunctive administration of oral analgesic drugs : opioids or nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for alleviating the pain during fractional curettage under paracervical block[3,6 - 8], However, the results are inconsistent.

The central mechanism of pain reduction with NSAIDs is through the inhibition of prostaglandin synthesis by the cyclooxygenase (COX) enzyme [9]. COX enzyme is composed of two isoforms, COX-1 and COX-2, with mediate distinct biologic processes. The inhibition of COX-2 produces an analgesic effect, whereas COX – 1 inhibition results in toxicity[9]. Therefore, selective Cox – 2 inhibitiors have recently been introduced as alternatives to the nonselective NSAIDs in the management of pain Etoricoxib (Arcoxia, Merck & Co. Inc.,New Jersey, USA) is a second – generation COX -2 inhibitor with 100 – fold increase in selectivity for COX-2 over COX-1. Its rapid onset time (20 min) and long duration of action (half-life of approximately 25 h) allows convenient once-daily dosing [10]. This has been demonstrated in the management of chronic pain and in the acute management of patients with dysmenorrhoea or those undergoing dental procedures.[11,12] The recommended dose for acute pain management is 120 mg.

The aim of this study was to evaluate the analgesic efficacy of pre-operative administration of etoricoxib 120 mg. when compared with placebo in patients undergoing uterine fractional curettage under paracervical block.

Materials and methods

This study was approved by Ethics Committee of Buriram Hospital, Buriram, Thailand. The written informed consent was obtained from patients. From March through December 2010, 80 healthy. Inclusion criterion were abnormal uterine bleeding, outpatients aged 35-60 years at the Department of Obstetrics and Gynecology, Buriram Hospital were enrolled in the study. They agreed to return for follow-up and complete a diary chart of side effects and the amount of acetaminophen used. Exclusion criterion were allergic reactions or contra-indications to NSAIDs , renal insufficiency, liver disease, asthma , coagulopathy, peptic ulcer or a previous history of gastrointestinal bleeding, and currently on drugs that have an interaction with etoricoxib (angiotensin converting enzyme inhibitor, aspirin, warfarin, lithium, methotrexate, rifampicin , or cimetidine).

A randomized, double-blinded, placebo-controlled study was used. The patients were randomized with a block of four techniques into two groups to receive either 120 mg. of etoricoxib or a placebo about 30 min before the procedures. The active tablets and the corresponding placebo tablets were packed in opaque sealed envelopes and the envelopes were labeled sequentially with the subject number in the center (1-80). Each envelope was then distributed in sequential numeriacal order to ensure randomization and double-blindness to treatment. The investigator generated the allocation sequence, and nurse assistants enrolled participants and assigned participants to their groups. The patiens, gynecologist performing the procedure and nurse assistants were blinded to the contents of the oral medication. The code was not broken until the study was completed. Uterine fractional curettage was performed by gynecologist under paracervical block with 1% lidocaine without other premedications such as diazepam, morphine, or pethidine. The lidocaine was injected as 5 ml each at 3 and 9 O' clock position of cervicovaginal reflection as standard technique at an estimated depth of 1 cm with using a 22-gauge spinal needle. Intermittent aspiration was performed before and during injection to ensure that paracervical blood vessels were not punctured. The standard uterine fractional curettage was performed after a lidocaine injection for 5 min to ensure the onset of action. The cervical canal was dilated, if necessary , to 8 mm using a Hegar dilator.

The primary outcome was the pain during curettage. To indicate intensity of pain, patients used a visual analog scale,

marking an "X" on a 100-min line (0 mm = no pain, 100 mm = intolerable pain). Using the visual analog scale, each patient made four assessments of the intensity of pain including before and during uterine fractional curettage as well as immediately and 30 min after uterine fractional curettage. Patient satisfaction was assessed at the end of the procedure. Data recorded included age, body weight, education level, income, history of vaginal delivery, miscarriage and uterine curettage, depth of uterine cavity, difficulty of uterine fractional curettage assessed by need for cervical dilatation, estimated blood loss, operative time and complications. Women were also requested to return for follow-up 1 week after curettage. Follow-up of these women included interviewing for adverse effects, total of acetaminophen used, and satisfaction. The diary chart was also carefully reviewed in detail.

Before this study was instituted, a power analysis was performed with respect to visual analog pain score during uterine curettage. A pilot study (10 patients in each group) showed that mean ± standard deviation were 39.8 ± 8.6 and 48.5 ± 14.8 in the etoricoxib group and in the placebo group, respectively. With an alpha of 0.05, a power of 90%, a two-side analysis required 40 patients per group. Analyses of the outcomes were based on intention-to-treat. Statistical analyses were performed with SPSS 12.0 for windows(SPSS Inc., Chicago, IL). The Student's t-test, and the Mann-Whitney U-test were used to compare continuous variables, and the Chi square test was used to analyze proportion. $P < 0.05$ (two-tailed test) was considered significant.

Results

From March through December 2010, a total of 80 patients were randomized to treatment : 40 received etoricoxib and 40 received placebo(fig.1). All of them were included in the analysis. The demographical characteristics of the two groups were similar, and there were no significant difference with respect to age, body weight, education level, income, history of vaginal delivery, history Of miscarriage, history of previous curettage, and depth of uterine cavity (Table 1). There was also no difference in the operative time, difficulty levels of the procedure, and estimated blood loss (Table 1).

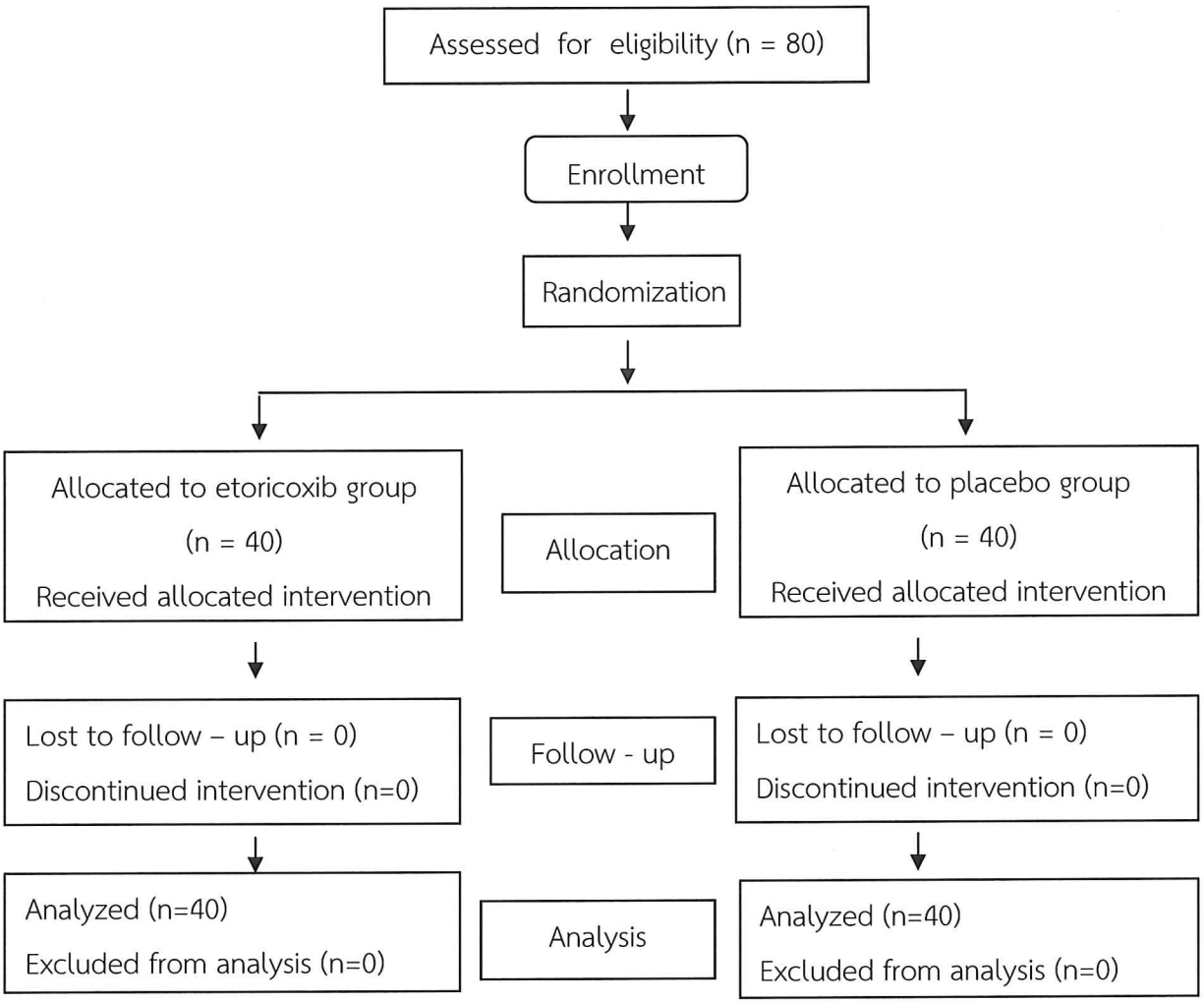

Fig. 1 Profile of patient recruitment and follow-up following randomization to either etoricoxib or placebo group.

Table 1

Characteristics of women undergoing fractional curettage

	Etoricoxib group (n = 40)	Placebo group (n = 40)
Age (years)	43.6 ± 11.2	42.6 ± 15.3
Body weight(kg)	62.2 ± 6.9	62.0 ± 8.6
Education level		
Primary and secondary school	20 (50%)	20 (50%)
College	12 (30%)	8 (20%)
University	8 (20%)	12(30%)
Income		
<1000 US $/month	35 (87.5%)	37 (92.5%)
≥1000 US $/month	5 (12.5%)	3 (7.5%)
≥1 prior vaginal delivery	32 (80%)	30 (75%)
≥1 prior abortion	15 (37.5%)	18 (45%)
≥1 prior curettage	10 (25%)	16 (40%)
Depth of uterine cavity (cm)	8.4 ± 0.8	8.2 ± 0.7
Operative time (min)	14.7 ± 2.5	14.7 ± 3.1
Difficulty level of the procedure		
Yes	20 (50%)	24 (60%)
Estimated blood loss(ml)	12.0 ± 3.7	11.0 ± 3.3

Data presented as mean ± standard or n (%). P > 0.05 for all comparisons.

The visual analog score for the etoricoxib group was significantly lower during operative procedure (median visual analog pain scores (interquartile range) 48 (43-64) vs. 61 (57-72), P = 0.001) and 30 min postoperative procedure (median (interquartile range) 4 (0-10) vs. 10 (3-22), P = 0.016) (Fig.2).

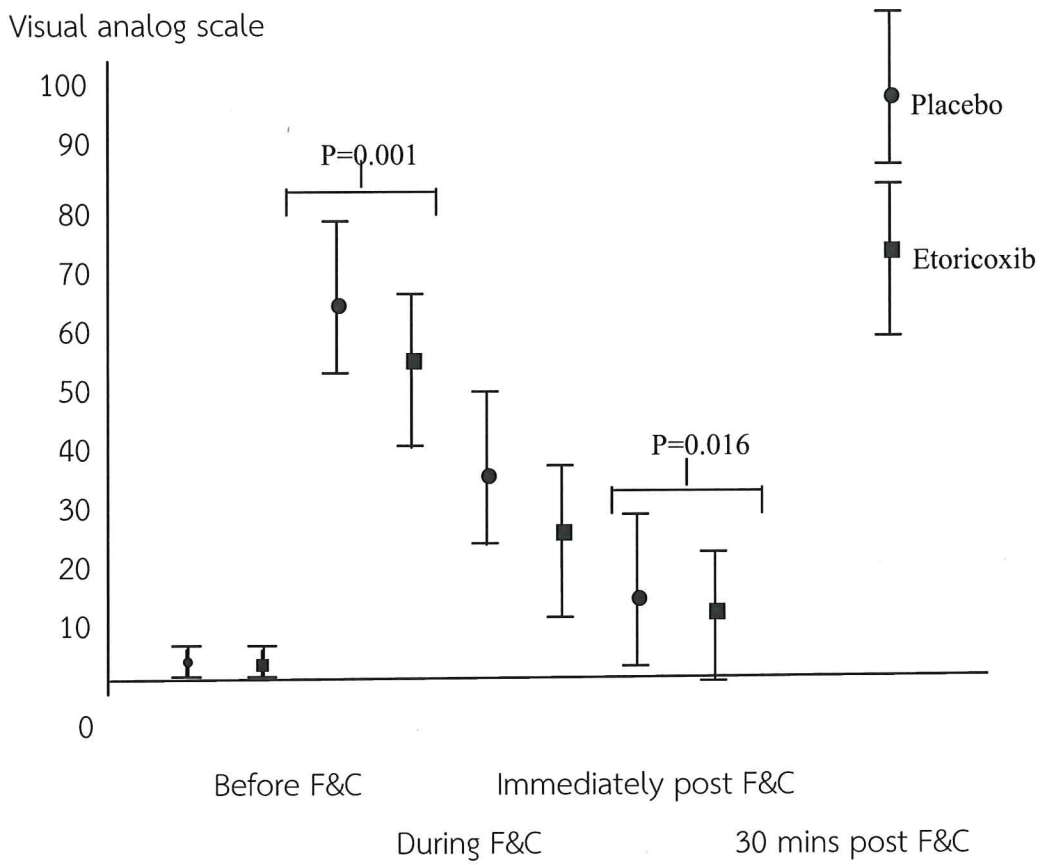

Fig. 2. Visual analog scale scores during the fractional curettage (FC). Median and interquartile ranges are presented.

There was also a significant difference in visual analog scores within each group ($P < 0.001$), which supports the validity of the assessment that pain increases during fractional curettage. Patients' satisfaction was not different between two groups. The amount of postoperative acetaminophen used in the etoricoxib group was significant lower than in the placebo group (Table 2). There was no serious complication from the procedure and no adverse effects of drugs. During the study no patient requested another analgesic drug or left the study.

Table 2

Patient satisfaction and amount of postoperative acetaminophen used

	Etoricoxib group (n = 40)	Placebo group (n = 40)	P - value
Satisfaction			
Yes	36 (90%)	38 (95%)	0.675
Amount of postoperative acetaminophen used (500 mg tablet)	2.2 ± 1.7	3.2 ± 1.7	0.011

Results are shown as mean ± standard deviation or n (%).

Discussion

In this randomized, placebo–controlled clinical trial, the COX – 2 specific inhibitor, oral etoricoxib, was more effective than placebo for pain relief during and 30 min after uterine fractional curettage under paracervical block. Etoricoxib can decrease pain during and 30 min after fractional curettage in this study. Because etoricoxib is a second – generation COX -2 inhibitor with 100 – fold increase in selectivity for COX -2 over COX-1, it can reduce prostaglandin synthesis. Pain during fractional curettage occurs from the direct stimulation to the uterine wall and disruption of endometrium during the procedure. This can cause prostaglandin release leading to uterine contraction and pain sensation in the upper part of the Uterus.The result of this study contracdicts a previous study[3], which indicated that rofecoxib failed to relieve pain during and after uterine curettage. This may be explained by the more selective COX-2 inhibition of etoricoxib than rofecoxib and different study populations. Abnormal uterine bleeding and abortion were included in the previous study, but only abnormal uterine bleeding was included in the present study. This finding is similar to a previous study showing that etoricoxib can provide effective analgesia after uterine evacuation[13]. Patients in the previous study received general anesthesia while patients in the present study received paracervical block. Our results are similar to the previous study showing that etoricoxib can provide effective a nalgesia after fractional curettage under paracervical block[7]. Differences from the previous study include the conventional

dose of etoricoxib (120 mg) and the evaluation of acetaminophen used after procedure in the present study. The strengths of this study included utilizing a validated method of pain measurement in fractional curettage and gynecologist performed fractional curettage which could decrease interpersonal variation. The weakness of the study is that we cannot control the individual nature of pain perception, a biopsychosocial experience influenced by many factors. In conclusion, the preoperative administration of 120 mg oral etoricoxib can slightly reduce pain during fractional curettage under paracrevical block. However, the degree of pain reduction by this treatment has no clinical importance.

References

1. Aimakhu VE, Ogunbode O. Paracervical block anesthesia for minor gynecologic surgery. Int J Gynaecol Obstet 1972 ; 10 : 66 -71.
2. Chanrachakul B, Likittanasombut P, O – prasertsawat P, Herabutya Y. Lidocaine versus plain saline for pain relief in fractionak curettage : a randomized controlled trial. Obset Gynecol 2001 ; 98 : 592-5.
3. Poomtavorn Y, Phupong V. Prospective randomized, double – blinded, placebo – controlled trial of preoperative rofecoxib for pain relief in uterine curettage. Arch Gynecol Obstet 2005 ; 23 : 115 – 8.
4. Rattanachaiyanont M, Leerasiri P, Indhavivadhana S. Effectiveness of intrauterine anesthesia for pain relief during fractional curettage. Obstet Gynecol 2005;106 : 533 -9.
5. Allen RH, Kumar D, Fitzmaurice G, Lifford KL, Gokdberg AB. Pain management of first-trimester surgical abortion : effects of selection of local anesthesia with and without lorazepam or intravenous sedation. Contraception 2006; 74:407 – 13.
6. Owolabi OT, Moodley J. A randomized trial of pain relief in termination of pregnancy in South Africa. Trop Doct 2005;35:136 – 9.
7. Phitayawechwiwat W, Thanantaseth C, Ayudhya NI, Prasertsawat P, Kongprasert J. Oral etoricoxib for pain relief during fractional curettage : a randomized controkked trial. J Med Assoc Thai 2007 ; 90:1053 – 7.
8. Buppasiri P, Tangmanowutikul S, Yoosuk W. Randomized controlled trial of mefenamic acid vs paracervical block for relief of pain for outpatient uterine curettage. J Med Assoc Thai 2005; 88:881 – 5.

9. Hawkey CJ. COX – 1 and COX -2 inhibitors. Best Pract Res Clin Gastro-enterol 2001 ; 15 :801 -20.
10. Gottesdiener K, Schnitzer T, Fisher C, et al. Results of a randomized, dose – ranging trial of etoricoxib in patients with ostearthritis. Rheumatology (Oxford) 2002; 41:1052 – 61.
11. Riendeau D, Percival MD, Brideau C, et al. Etoricoxib (MK -0663) : preclinical profile and comparison with other agents that selectively inhibit cyclo-oxygenase-2. J Pharmacol Exp Ther 2001; 296:558-66.
12. Malmstrom K, Kotey P, Cichanowitz N, Daniels S, Desjardins PJ. Analgesic efficacy of etoricoxib in primany dysmenorrheal : results of a randomized, controlled trial. Gynecol Obstet Invest 2003; 56:65 – 9.
13. Liu W, Loo CC, Chiu JW, Tan HM, Ren HZ, Lim Y. Analgesic efficacy of pre-oper-ative etoricoxib for termination of pregnancy in an ambulatory centre. Singapore Med J 2005; 46:397-400.