Oral Etoricoxib for Pain Relief during Fractional Curettage: A Ramdomized Controlled Trial

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Objective: *To compare the efficacy of oral etoricoxib and placebo combined with paracervical block for pain relief during fractional curettage*
Material and Method: *A double-blind, randomized controlled trial that included 220 women who underwent fractional curettage and received paracervical block for pain relief was done at Ramathibodi Hospital between September 2005 and June 2006. One hundred and ten women were randomly allocated to the etoricoxib group (90 mg, tablet) and 110 to the placebo group. The main outcome was the patient's assessment of intensity of pain measured by verbal rating scales after speculum insertion, during fractional curettage, immediately after curettage, and 30 minutes after curettage.*
Results: *Demographic data including age, previous vaginal deliveries, and history of curettage were not significantly different between etoricoxib group and placebo group. Most common indication for fractional curettage was menometrorrhagia in both groups. Pain score in etoricoxib group was significant lower during fractional curettage (5 vs. 6, p = 0.04), immediately after curettage (2 vs. 3, p = 0.009), and 30 minutes after curettage (0 vs. 1, p = 0.003). Comparing the number of patients with mild pain (score 0-3), there were significant higher number of mild pain patient at the time during curettage (39 vs. 20 cases), immediate after curettage (78 vs. 60 cases), and 30 minutes after curettage(107 vs. 100 cases) in etoricoxib group.*
Conclusion: *Combination of etoricoxib with paracervical block for reduction of pain during fractional curettage had statistically significant lower pain scale when compared with placebo with paracervical block. However, the difference was small and may have questionable clinical significance.*

Keywords: *Verbal rating scale, Etoricoxib, Fractional curettage, Paracervical block*

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The fractional curettage is commonly used for diagnosis and treatment in gynecology. The use of paracervical block in fractional curettage had a significant analgesic effect but some studies suggested that the level of pain relief were still moderate pain[1]. Although the use of general anesthesia is effective as the standard method for pain relief, it carries a higher mortality risk than the local anesthesia.

The COX-2 specific inhibitors possess 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. The safety and tolerability of post operative administered COX-2 specific inhibitors have been demonstrated in numerous clinical studies. In comparing etoricoxib, placebo, naproxen sodium for primary dysmenorrhea, atoricoxib once a day was more effective than placebo and similarly effective to naproxen sodium[2]. In post surgical dental pain, oral etoricoxib was significantly superior for total pain relief in molar extraction over 8 hours compared with placebo or acetaminophen/codeine treatment and

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similar pain relief compared to naproxen[3]. In comparing etoricoxib and indomethacin in acute gouty arthritis, visual analog pain score (VAS) was no different but etoricoxib has a lower adverse effect[4].

Etoricoxib is an oral COX-2 selectivity that has early onset of action about 24-minutes and peak plasma level at 60 minutes[5]. It is being investigated as a perioperative treatment for surgical pain relief[6,7]. The objective of the present study was to determine the efficacy of oral etoricoxib for pain relief during fractional curettage.

Material and Method

The present study was a double-blind, randomized controlled trial comparing etoricoxib with placebo for pain relief during fractional curettage under paracervical block. The present study was approved by the Ramathibodi Hospital Ethical Committee, and informed consent was obtained from all participants. From September 2005 to June 2006, 220 women who had fractional curettage done under paracervical block were randomly allocated to receive etoricoxib (Arcoxia®) (90 mg, tablet) or placebo (folic acid 5 mg/tablet). They were evaluated and excluded from the present study in cases of active renal disease, history of hepatic impairment, previous congestive heart failure, gastrointestinal ulcer and bleeding, bronchospasm, hemostatic impairment, hypertension, and hypersensitivity to lidocaine, NSAID or COX-2 specific inhibitors. The randomized sequence was generated by computer. The drugs were prepared in a sealed opaque envelope, labeled with stickers preprinted with computer-generated random numbers. They received the drug at 30-60 minutes before the procedure. The performing gynecologists and the assisting nurses were blinded to the type of drugs used. The patients were treated according to the departmental routine. The random-number key was not broken until the data analysis was done.

The patients used a verbal rating scale to indicate intensity of pain. They were asked to identify how much pain they had by choosing a number from 0 to 10, 0 means no pain and 10 means the worst pain. The authors defined the degree of pain, 0-3 = mild pain, 4-7 = moderate pain, 8-10 = severe pain[8]. Each patient was asked for four assessments. The first one was made immediately for intensity of pain during insertion of the speculum. The second was made during curettage. The third was made immediately after curettage and the fourth one was made 30 minutes after curettage. Each patient was advised to ask for another potent analgesic drug at any time if she wanted more pain relief or otherwise wished to leave the present study.

The paracervical block in the present study was standardized, by injecting 1% lidocaine with a 23-gauze spinal needle at 3 and 9 o'clock of cervicovaginal reflection, 10 ml at each site. Intermittent aspiration was performed before and during injection to avoid paracervical blood vessel puncture. Oxygen and vasopressor were always available. The standard procedure for fractional curettage was performed after waiting 2 minutes for the onset of lidocaine. The cervical canal was curetted first followed by the endometrial curettage.

Data record were analyzed and presented as number (%), mean $\pm$ SD and median included age, previous vaginal delivery, history of curettage, indications for fractional curettage, uterine sound, operative time, and the procedure difficulty which was rated by a surgeon (1 = not difficult, 4 = extremely difficult). The Student *t*-test and Mann-Whitney *U*-test were used to compare the continuous variables where appropriate. The Chi-square test was used to compare the discrete variables. $p < 0.05$ was considered as statistically significant.

Results

During the present study, no patient asked for another potent analgesic drug or left the present study. Both groups had no significant differences of demographic data and had menometrorrhagia being the most common indication for curettage (Table 1). Comparing the uterine sound and the procedure difficulty in performing curettage, there were no significant differences between both groups. However, the operative time had a significant difference (Table 2).

There was no significant difference of verbal pain rating scale after speculum insertion in both groups. The verbal pain rating scale for etoricoxib group was significantly lower at the time during curettage, immediately after curettage and 30 minutes after curettage than the placebo group. The pain increased from speculum insertion through fractional curettage and then decreased to nearly no pain at 30 minutes after curettage (Table 3). Comparing the number of patients with mild pain (pain score 0-3), there was a significant difference between both groups. The etoricoxib group had a significantly higher proportion of mild pain than the placebo group at the time during curettage, immediately after curettage and 30 minutes after curettage (Table 4). No severe adverse effect was found in both groups.

Table 1. Baseline characteristics between etoricoxib group and placebo group

	Etoricoxib (n = 110)	Placebo (n = 110)	p-value
Age (y)	47.2 ± 6.3	48.5 ± 6.1	0.12
Previous vaginal delivery	72 (65.5)	76 (69.1)	0.56
History of curettage	51 (46.4)	49 (44.5)	0.78
Indications for fractional curettage			
Menometrorrhagia	64 (58.2)	62 (56.3)	0.5
Postmenopausal bleeding	21 (19.1)	29 (26.4)	
Perimenopausal bleeding	14 (12.7)	12 (10.9)	
Endometrial hyperplasia	11 (10.0)	7 (6.4)	

Data presented as mean ± SD and n (%)

Table 2. Procedure characteristics between etoricoxib and placebo group

	Etoricoxib (n = 110)	Placebo (n =110)	p-value
Interval of drug taking time (min)	45.90 ± 4.29	46.15 ± 3.76	0.77
Uterine sound (cm)	5.74 ± 0.80	4.58 ± 0.79	0.74
Operative time (min)	11.40 ± 1.33	11.10 ± 1.28	0.04*
Procedure difficulty	1 (1, 2)	1 (1, 2)	0.41

Data presented as mean ± SD and median (25^{th} Percentile, 75^{th} Percentile)
* Significant difference between two groups

Table 3. Visual rating pain score during and after fractional curettage between etoricoxib and placebo group

Time	Etoricoxib	Placebo	p-value
After speculum insertion	1 (0, 2)	1 (0, 2)	0.43
During curettage	5 (3, 8)	6 (5, 8)	0.04*
Immediate after curettage	2 (1, 4)	3 (1, 5)	0.009*
30 min after curettage	0 (0, 2)	1 (0, 2)	0.003*

Data presented as median (25^{th} Percentile , 75^{th} Percentile)
* Significant difference between two groups

Table 4. Number and percentage of patients with verbal pain rating scale in mild pain (VAS = 0-3)

Time	Etoricoxib	Placebo	p-value
After speculum insertion	110 (100)	108 (98.2)	0.50
During curettage	39 (35.5)	20 (18.2)	0.01*
Immediate after curettage	78 (70.9)	60 (54.5)	0.04*
30 min after curettage	107 (97.3)	100 (90.9)	0.04*

Data presented as n (%)
* Significant difference between two groups

Discussion

The various procedures used during fractional curettage such as placement of the long Allis for traction of the cervix and dilation of the cervical os as well as curettage itself can cause pain sensation. Pain sensation transmits by sensory and sympathetic pathways from the posterolateral aspect of the cervix to the lateral spinothalamic tracts of the spinal cord. The paracervical block is a convenient, safe, simple, and effective anesthetic for curettage. Although it is widely used, the previous study from Ramathibodi Hospital suggests that the level of pain relief is still moderate pain (VAS = 4-7)[1].

Because paracervical block can relieve pain at 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 in the upper part of the uterus because it has a different innervation. Although the use of general anesthesia provides a significant analgesic effect, this method can be limited by the risk of adverse effects.

The uterine wall can produce prostaglandin like many other tissues. During fractional curettage, 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. Etoricoxib is a highly specific oral COX-2 inhibitor that reduces prostaglandin synthesis[5]. It is the analgesic drug commonly used for pain relief because it has a rapid onset and is safe.

Therefore, oral etoricoxib was considered to combine with paracervical block for effective pain relief during fractional curettage. This provided another anesthetic method that could avoid general anesthesia and reduce the cost of the procedure. The result of the present study showed that the combination of paracervical block and etoricoxib was more effective than paracervical block alone. The pain score in etoricoxib group seemed to be significantly lower during and after fractional curettage and the number of patients with verbal pain rating scale lower than 4 was significantly higher in this group. It could be explained that etoricoxib can reduce prostaglandin synthesis thus, might reduce uterine contraction and pain sensation. The addition of oral etoricoxib does not increase any adverse effect. However, the lower pain score in the etoricoxib group was nearly the same level of pain compared to the placebo group. The difference of median pain score of the three assessment points of measurement were only 1 score, so there may be no clinical significance to improve pain in the present study.

Therefore, more research should be conducted to evaluate efficacy of etoricoxib such as the interval of drug taking and the optimum doses to make more clinical significance. The present study provides a new concept of drug used for reducing pain intensity in the common gynecological procedure. Moreover, the oral analgesic drug can be applied before curettage, which is proper for outpatient cases. Eventually, it can be concluded that combination of paracervical block and etoricoxib for reducing pain during fractional curettage was statistically significant when compared with paracervical block alone. However, as the difference of pain scores was nearly at the same level, there may be no clinical significance.

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การใช้ยา Etoricoxib รับประทานเพื่อลดความเจ็บปวดระหว่างการขูดมดลูกแบบแยกส่วน: การศึกษาชนิดสุ่ม

วิไลพร พิทยาเวชวิวัฒน์, เฉลิมศรี ธนันตเศรษฐ, ณัฐพงศ์ อิศรางกูร ณ อยุธยา, ประทักษ์ โอประเสริฐสวัสดิ์, จิตรดา คงประเสริฐ

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบผลการลดความเจ็บปวดระหว่างกลุ่มที่ได้ยา etoricoxib และกลุ่มที่ได้ยา placebo ร่วมกับการทำ paracervical block ในผู้ป่วยที่ทำการขูดมดลูกแบบแยกส่วน*

วัสดุและวิธีการ: *ศึกษาแบบ double-blind, randomized controlled trial ในผู้ป่วยที่ทำการขูดมดลูกแบบแยกส่วน 220 ราย ที่โรงพยาบาลรามาธิบดี ระหว่างเดือนกันยายน พ.ศ. 2548 – มิถุนายน พ.ศ. 2549 โดยแบ่งผู้ป่วยเป็นสองกลุ่มโดยการสุ่ม โดยกลุ่มที่หนึ่งได้ยา etoricoxib (90mg) จำนวน 110 ราย และกลุ่มที่สองได้ยา placebo จำนวน 110 ราย ผู้ป่วยทั้งสองกลุ่มได้รับ paracervical block เพื่อระงับปวดร่วมด้วย ผู้ป่วยประเมินความเจ็บปวด โดยใช้ verbal pain rating scale ประเมิน 4 ช่วงเวลา ภายหลังการใส่ speculum, ขณะขูดมดลูก, ภายหลังการขูดมดลูกทันที และภายหลังการขูดมดลูก 30 นาที*

ผลการศึกษา: *ข้อมูลผู้ป่วยทั้งสองกลุ่มที่เกี่ยวกับอายุ, ประวัติคลอดบุตรทางช่องคลอด และประวัติเคยขูดมดลูกมาก่อน ไม่มีความแตกต่างกันในทั้งสองกลุ่ม สำหรับข้อบ่งชี้ในการขูดมดลูกที่พบมากที่สุดในทั้งสองกลุ่มได้แก่ menometrorrhagia คะแนนความเจ็บปวด ในกลุ่มที่ได้ยา etoricoxib ต่ำกว่า กลุ่มที่ได้ยา placebo อย่างมีนัยสำคัญทางสถิติระหว่างการขูดมดลูก (5 และ6, p = 0.04), ทันทีภายหลังขูดมดลูก (2และ3, p = 0.009) และ 30 นาทีภายหลังขูดมดลูก (0และ1, p = 0.003) และพบจำนวนผู้ป่วยที่ระดับความเจ็บปวดอยู่ใน mild pain (score 0-3) ในกลุ่มที่ได้รับยา etoricoxib มากกว่ากลุ่ม placeboในช่วงเวลา ระหว่างการขูดมดลูก(39,20 ราย), ทันทีภายหลังขูดมดลูก (78,60ราย) และ 30 นาทีภายหลังขูดมดลูก (107,100 ราย) อย่างมีนัยสำคัญ*

สรุป: *การใช้ยา etoricoxib ร่วมกับ paracervical block ในผู้ป่วยที่ทำการขูดมดลูกแบบแยกส่วน สามารถลด ความเจ็บปวดได้อย่าง มีนัยสำคัญทางสถิติเมื่อเทียบกับกลุ่มที่ได้ยา placebo ร่วมกับ paracervical block โดยระดับความเจ็บปวดอยู่ในระดับไม่แตกต่างกันมากนัก ซึ่งอาจจะไม่มีความแตกต่างกันในทางคลินิก*