Preliminary Report

Prevention of Post Operative Pain after Abdominal Hysterectomy by Single Dose Etoricoxib

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Objective: *To test whether a reduction in post operative morphine consumption could be achieved by a single-dose of etoricoxib before induction of anesthesia.*
Design: *Randomized, double-blind, placebo-controlled study.*
Material and Method: *Two hours before surgery, patients undergoing transabdominal hysterectomy (under general anesthesia) were randomized to a single oral dose of: 1) etoricoxib 120 mg (n = 17), 2) etoricoxib 180 mg (n = 17), or 3) placebo (n = 15). Intravenous morphine was given for patient-controlled analgesia (PCA) device. Morphine consumption, pain scores both at rest and on coughing, and side-effects were recorded at 1, 2, 4, 8 and 24 h after surgery. Patients' global evaluation of study medication was assessed at the end of the present study.*
Results: *Etoricoxib provided greater clinical benefit than the placebo in terms of mean morphine in milligram at 24 hour consumption (stardard deviation): a) 26.4 mg (SD of 11.2) for etoricoxib 120 mg; b) 27.2 mg (SD of 9.9) for etoricoxib 180 mg; and, c) 36.6 mg (SD of 8.9) for the placebo group. At 8 h post surgery, pain both at rest and on coughing in the active drug groups was significantly less than in the placebo, while pain on coughing was significantly less at 24 h. Patients reported better global satisfaction and less somnolence in the etoricoxib groups.*
Conclusion: *Single dose etoricoxib 180 mg given before surgery provides the same analgesic effect as 120 mg for post operative pain after an abdominal hysterectomy.*

Keywords: *Abdominal hysterectomy, Etoricoxib, Morphine consumption, Preventive analgesia*

J Med Assoc Thai 2008; 91 (1): 68-73
Full text. e-Journal: *http://www.medassocthai.org/journal*

Selective COX-2 inhibitors are an alternative management of acute pain because they provide an efficacy similar to that of recommended doses of opioids, but without the opioid-related side effects that hinder post-surgery recovery[1]. Etoricoxib is a potent member of the selective COX-2 class of non-steroidal anti-inflammatory drugs (NSAIDs) and exhibits a reduced risk of gastrointestinal toxicity compared with non-selective NSAIDs[2]. Its clinically important anti-inflammatory and analgesia efficacy, in the treatment of acute and chronic pain, and its favorable safety and tolerability profile as a once-daily dosing regimen, have been shown in numerous diseases and treatment settings[3]. Specifically, etoricoxib has proved effective in the management of acute pain associated with dental surgery, orthopedic surgery, acute gouty arthritis and primary dysmenorrhea[4-7]. In general, the recommended dose for etoricoxib is 120 mg per day. But, in one systematic review, etoricoxib 180 mg demonstrated superior analgesic efficacy than 120 mg (number needed to treat (NNT) for 180 mg = 1.2 with 95%CI 1.1 to 1.4, NNT for 120 mg = 1.5 with 95%CI 1.3 to 1.7),

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respectively[8]. Concerning the adverse effects when increasing the dosage, single dose etoricoxib 180 mg was generally well tolerated[4].

In order to prove the analgesic effect of etoricoxib given before surgery, a single, oral dose of 120 mg is compared with etoricoxib 180 mg in a randomized, double blind, placebo-controlled study.

Material and Method

The present study was conducted at both a university and a regional hospital in Khon Kaen, Thailand, between December 2004 and May 2005. The protocol was approved by each institution's research review board. All patients gave written, informed consent before enrollment.

Patients

Recruited were the American Society of Anesthesiology (ASA) I or II patients, undergoing elective transabdominal hysterectomy under general anesthesia. Excluded from the present study were patients with an allergy to other NSAIDs and patients with asthma.

Randomization and blinding

Randomization was achieved using a computer-generated random list into 3 groups (placebo, etoricoxib 120 mg and etoricoxib 180 mg). Allocation concealment was maintained using a sealed opaque envelope. The research assistant prepared the study drugs for the ward nurses according to the randomization list. Ward nurses, not apprised of the treatment group, gave the study drugs, sealed in a similar package, to the patients in the morning of the operative day.

Patients were given the study drugs 2 hours before induction of anesthesia. Anesthesia was induced with propofol (1-2 mg/kg) after IV pre-medication with 0.05 mg/kg of midazolam and fentanyl 1 µg/kg. Balanced anesthesia was maintained using 70% nitrous oxide in oxygen plus 1-1.5% isoflurane and fentanyl adjusted to maintain an adequate depth of anesthesia.

After surgery, patients were transferred to the post anesthesia care unit (PACU). In the PACU, morphine was available via a patient-controlled analgesia (PCA) pump; programmed to deliver a 2-mg loading, 1-mg bolus with a lockout interval of 5 minutes and a 1-hour maximum use of 10 mg. Twenty-four hours after surgery, the PCA morphine pump was stopped and replaced with an on-demand oral analgesic. Treatment of side effects was provided in response to patient-requests.

Outcomes measurement

Cumulative morphine consumption was recorded at 1, 2, 4, 8 and 24 h after surgery. Assessment of post operative pain at rest and on coughing were made at the same time using a visual analog scale (VAS) 0-10 cm (*i.e.* score 0 = no pain while score 10 = worst pain imaginable). The PACU nurse assessed the outcome at 1 and 2 h then trained ward nurses assessed the remaining outcomes. Patient global assessment in response to therapy (PGART) was assessed at 24 h with a five-point scale (*i.e.* 0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent). The incidence of adverse events (AEs) such as nausea, vomiting, somnolence, dizziness, headache and rash were also evaluated.

Statistical analysis

The sample size calculation was based on a power analysis. In the pilot study (ten patients per group) of post gynecological surgical pain with etoricoxib, the mean 24-hr postoperative morphine consumption was 36, 26 and 16 mg in the placebo, etoricoxib 120, and 180 mg groups, respectively. The pooled standard deviation was 12.15. At a power of 80%, using a significance level of $p < 0.05$, the required sample size was at least 15 subjects per group[9]. The primary efficacy endpoint was morphine consumption in 24 hour.

The primary endpoint and other continuous variables were analyzed using mean, standard deviation (SD) for description and a parametric analysis of the variance model[10] for comparison between groups. Other categorical outcomes were analyzed using the χ^2-test. The patients' global evaluation of the study medication was analyzed using Mann-Whitney *U*-test. A p-value of less than 0.05 was considered significant difference.

Results

A total of 49 patients, between 39 and 52 years of age, were randomized to treatment with etoricoxib 120 mg (n = 17), etoricoxib 180 mg (n = 17), and the placebo (n = 15) and completed the present study. The baseline demographic characteristics were similar among groups (Table 1).

The mean morphine use 24 h post surgery, etoricoxib provided significantly greater clinical benefit than the placebo (p-value = 0.012). There were no significant differences between the etoricoxib groups (Table 2).

Summaries of pain intensity are presented in Table 3. At 8 h post surgery, pain both at rest and on

Table 1. Baseline characteristics of study patients by treatment group

	Etoricoxib 120 mg (n = 17)	Etoricoxib 180 mg (n = 17)	Placebo (n = 15)
Age - y (SD)	41.8 (6.1)	44.9 (6.4)	46.5 (4.5)
Body weight - kg (SD)	57.1(9.0)	58.6 (9.6)	54.7 (5.9)
Duration of surgery - min (SD)	117.7(51.7)	129.1 (45.8)	117.0 (34.1)
Intraoperative fentanyl mean - µg (95%CI)	119.4 (99.2, 139.7)	154.4 (132.9, 175.8)	129.3 (107.5, 151.1)

Table 2. Mean (SD) post-operative morphine consumption over times

Post-operative morphine at anytime	Etoricoxib 120 mg (n = 17), mg (SD)	Etoricoxib 180 mg (n = 17), mg (SD)	Placebo (n = 15), mg (SD)	p-value
1 h	3.2 (2.0)	3.5 (2.2)	3.5 (2.8)	NS
2 h	7.6 (3.7)	7.5 (7.3)	6.9 (3.4)	NS
4 h	11.4 (5.7)	11.5 (5.3)	12.8 (4.6)	NS
8 h	15.3 (7.7)	16.0 (5.7)	20.9 (8.8)	NS
24 h	26.4 (11.2)	27.2 (9.9)	36.6 (8.9)	0.012

Table 3. Mean (95%CI) post-operative pain scores over times

Post-operative pain score at anytime		Etoricoxib 120 mg (n = 17)	Etoricoxib 180 mg (n = 17)	Placebo (n = 15)	p-value
At rest					
	1 h	4.8 (3.1, 6.6)	5.3 (4.1, 6.5)	4.7 (3.2, 6.3)	NS
	2 h	4.8 (3.1, 6.4)	5.5 (4.5, 6.5)	4.9 (2.7, 7.1)	NS
	4 h	5.1 (3.8, 6.3)	5.0 (4.1, 5.9)	6.5 (4.9, 8.2)	NS
	8 h	3.6 (2.5, 4.8)	3.7 (2.7, 4.7)	5.6 (4.2, 6.9)	0.03
	24 h	3.4 (2.2, 4.4)	3.0 (2.1, 3.9)	4.3 (3.2, 5.5)	NS
With activity:					
	1 h	6.5 (5.0, 8.0)	6.7 (5.3, 8.0)	6.2 (4.8, 7.6)	NS
	2 h	6.1 (4.3, 7.8)	6.5 (5.2, 7.8)	6.9 (5.4, 8.5)	NS
	4 h	6.7 (5.2, 8.1)	6.4 (5.1, 7.6)	8.1 (6.8, 9.4)	NS
	8 h	5.9 (4.7, 7.2)	5.4 (4.2, 6.5)	8.4 (7.5, 9.3)	0.001
	24 h	5.3 (3.9, 6.7)	4.5 (3.5, 5.5)	7.0 (5.6, 8.4)	0.020

coughing in the active drug groups was significantly less than in the placebo while pain on coughing was significantly less at 24 h.

In terms of PGART, patients treated with etoricoxib reported a higher score than patients treated with placebo. On the basis of the PGART scores, the percentage of patients who were "responders" (*i.e.* with a good to excellent rating) for, etoricoxib 120 mg, etoricoxib180 mg and placebo were 87.5, 88.3 and 78.5 percent, respectively (Fig. 1).

The overall incidence of clinical adverse events was similar for all treatment groups except for somnolence (Table 4). No serious adverse events occurred in any of the treatment groups.

Table 4. Tolerability data - Clinical adverse experiences in percentage of patients

Variables	Etoricoxib 120 mg (n = 17)	Etoricoxib 180 mg (n = 17)	Placebo (n = 15)
Somnolence	39.82	38.82*	69.34
Dizziness	31.30	23.50	46.70
Headache	18.80	11.80	20.00
Rash	0	5.90	0
Nausea/Vomiting	16.44	10.60	26.68
Rescue antiemetic drug	31.25	17.64	26.67

* Statistical significance between placebo and etoricoxib 180 mg = 0.04 at p-value < 0.05

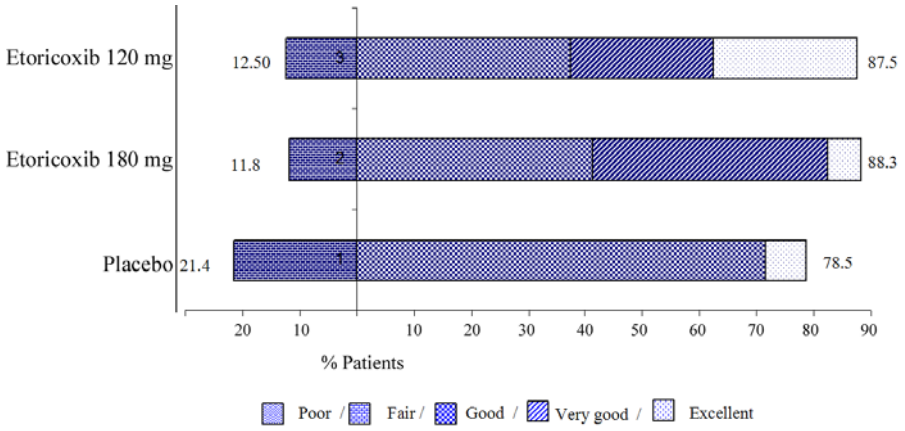

Fig. 1 Patients' global assessment in response to therapy (PGART) at 24-h post-operatively, showing the percentage response to therapy

Discussion

The post operative abdominal gynecological pain model is a well validated and widely accepted model for assessing the efficacy of analgesics for acute pain; because of its reproducibility, high precision, accuracy, and sensitivity in differentiating the efficacy of drugs. In this present study, two doses of etoricoxib totaling 120 or 180 mg were compared with a placebo. All of the etoricoxib doses were significantly superior to the placebo in terms of the mean morphine consumption at 24 hours post-surgery.

The assessment of the proportion of patients reporting a response to treatment of good, very good, or excellent was consistent with the findings of other evaluations, about 88% of the etoricoxib 120- and 180-mg groups reporting such a response, compared with 79% of the placebo group. This result differs from the study of Malmstrom et al[11], wherein there were no poor responses to the treatment in any of the groups, post operatively.

Etoricoxib demonstrated rapid onset and ongoing pain relief over a 24-h period[11]. The present study does not evaluate the onset of analgesia because the time frame of the onset is within the intra-operative period. The long-standing analgesic effect was consistent with the 25- to 27-hour mean elimination half-life of etoricoxib reported elsewhere[12,13].

The commonly reported clinical adverse events were somnolence, nausea, vomiting, and dizziness, which occurred at lower rates in all of the active-treatment groups than the placebo. The higher incidence of nausea and vomiting in the placebo group may have been the result of a more frequent use of morphine. No new adverse events related to the long-term use of etoricoxib in patients with chronic pain (such as from osteoarthritis and rheumatoid

arthritis)[14,15] were identified in this present study.

The present study does not report adverse laboratory events such as elevations in aminotransferases as reported by Malmstorm et al[4]. Only one patient from the etoricoxib 180 mg group developed a skin rash, but required no specific treatment as the rash cleared after 24 hours.

Limitations of the study

An evaluation of analgesic efficacy of etoricoxib in the present study was designed only for 24 hours even though pain after hysterectomy lasted longer. This limitation was due to the NPO state of patients and etoricoxib was available only for oral form. If etoricoxib was given about 2 or 3 days longer, the different pain intensity, especially pain on movement, was expected.

In summary, both etoricoxib 120 and 180 mg single doses significantly provided an overall analgesic effect superior to the placebo, but neither had a comparably significant response. The morphine use and patients' global assessment in response to therapy in both etoricoxib groups were not different. Therefore, etoricoxib 120 mg is the minimum effective dose for post operative pain after an abdominal hysterectomy.

Acknowledgments

The present study was funded by a grant from the Faculty of Medicine, Khon Kaen University. The authors wish to thank Merck & Co., Inc. for drug preparation, Ratana Longtongkul and Punnee Kukiattikool for assistance with study start-up and monitoring, Poonsub Assatroo for coordination of data management and statistical analysis, and Mr. Bryan Roderick Hamman for his assistance with the English-language presentation of the manuscript.

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การใช้ etoricoxib รับประทานครั้งเดียวก่อนผ่าตัดเพื่อลดความปวดหลังผ่าตัดมดลูกทางหน้าท้อง

วราภรณ์ เชื้ออินทร์, สมบูรณ์ เทียนทอง, อักษร พูลนิติพร, วัฒนา ตันทนะเทวินทร์, วิทูรย์ ประเสริฐเจริญสุข, วิมลรัตน์ ศรีราช

วัตถุประสงค์: *เพื่อศึกษาผลการให้ยา etoricoxib ในขนาด 180 และ 120 มิลลิกรัม เทียบกับยาหลอก โดยให้รับประทานครั้งเดียวก่อนมาผ่าตัดมดลูกทางหน้าท้อง ในการระงับปวดและการใช้ยามอร์ฟีนในระยะหลังผ่าตัด*

การออกแบบการศึกษา: *randomized, double-blind, placebo-controlled study*

วัสดุและวิธีการ: *ผู้ป่วยที่มาผ่าตัดมดลูกทางหน้าท้องโดยการวางยาสลบ ถูกแบ่งเป็น 3 กลุ่ม คือ 1) etoricoxib 120 มิลลิกรัม (n = 17) 2) etoricoxib 180 มิลลิกรัม (n = 17) และ 3) ยาหลอก (n = 15) โดยผู้ป่วยแต่ละรายได้รับยา 2 ชั่วโมง ก่อนมาห้องผ่าตัดในระยะหลังผ่าตัดผู้ป่วยได้รับมอร์ฟีนฉีดทางหลอดเลือดดำโดยใช้เครื่องจ่ายยาที่สามารถควบคุมด้วยตนเอง (PCA) บันทึกปริมาณมอร์ฟีนที่ใช้ไปใน 24 ชั่วโมงหลังผ่าตัด ประเมินระดับความปวด ขณะพัก ขณะไอ และอาการแทรกซ้อนที่อาจพบได้ ที่เวลา 1, 2, 4, 8 และ 24 ชั่วโมงหลังผ่าตัด รวมทั้งประเมินระดับ ความพอใจต่อยาระงับปวดที่ได้รับเมื่อครบ 24 ชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *กลุ่มที่ได้รับยา etoricoxib 120 มิลลิกรัม และ 180 มิลลิกรัม มีปริมาณการใช้มอร์ฟีนเฉลี่ย 26.4 (11.2) และ 27.2 (9.9) มิลลิกรัม เมื่อเทียบกับกลุ่มที่ได้ยาหลอกซึ่งใช้ยาไป 36.6 (8.9) มิลลิกรัม ที่เวลา 8 ชั่วโมงหลังผ่าตัดพบว่ากลุ่มที่ได้รับยา etoricoxib มีระดับความปวดทั้งขณะพักและขณะไอน้อยกว่า กลุ่มที่ได้รับยาหลอก เช่นเดียวกับระดับความปวด ขณะไอที่เวลา 24 ชั่วโมงหลังผ่าตัด ผู้ป่วยที่ได้รับยา etoricoxib ประเมินระดับความพอใจต่อยาระงับปวด ที่ได้รับดีกว่ากลุ่มที่ได้รับยาหลอก และในการศึกษานี้ไม่พบอาการ แทรกซ้อนที่เป็นอันตราย*

สรุป: *กลุ่มที่ได้รับยา etoricoxib ขนาด 180 มิลลิกรัม ครั้งเดียวก่อนการผ่าตัดมดลูกทางหน้าท้อง ให้ผลในการระงับปวด ไม่แตกต่างจากกลุ่มที่ได้รับยาขนาด 120 มิลลิกรัม*