# Postoperative Pain Relief in Major Gynaecological Surgery by Perioperative Parecoxib Administration: Thammasat University Hospital Study

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***Objective:*** *To study postoperative pain relief in major gynaecological surgery by perioperative parecoxib administration in Thammasat University Hospital.*
***Material and Method:*** *This double-blind randomized controlled clinical trial was conducted in Thammasat University Hospital, Pathumthani, Thailand from October 2013 to May 2014. One hundred and twenty patients who underwent elective gynaecological surgery were randomized assigned to study and control groups. Study group (n = 60) received 40 mg parecoxib and control group (n = 60) received placebo at 1 hour before surgery. The postoperative visual analog scale (VAS) at 3, 6, 12 and 24 hours, frequency of meperidine consumption in 24 hours and side effects of parecoxib were recorded.*
***Results:*** *VAS of study group after operation at 3, 6, 12 and 24 hours was significantly lower than control group. Meperidine consumption in placebo group was significantly higher than study group (27.50±19.36 and 48.75±28.15 mg, respectively; p<0.001). There was no side effect from parecoxib in this study.*
***Conclusion:*** *Intravenous postoperative parecoxib injection could relief pain and reduced meperidine consumption. Parecoxib could be safely used in gynaecological surgery for postoperative pain relief.*

***Keywords:*** *Parecoxib, Meperidine, Pain relief, Gynaecological surgery*

***J Med Assoc Thai 2015; 98 (7): 636-42***
***Full text. e-Journal:*** *http://www.jmatonline.com*

Management of postoperative pain is one of the most challenging issues in surgery, including in gynaecological practice. Uncontrolled pain may cause several postoperative complications. The concept of preemptive analgesia is based on the hypothesis that the most effective way to reduce postoperative pain is to prevent nociceptive input from afferent stimuli to the central nervous system so that central nervous system hyperexcitability does not occur[1]. Several preemptive analgesic regimens had been utilized namely local anesthetic infiltration, nerve block and intravenous opioid or nonsteroidal anti-inflammatory drugs (NSAIDs) administration[2].

Several studies had demonstrated that opioids were excellent analgesic agent for postoperative pain management[1-3]. The use of opioids resulted in many adverse effects namely nausea, vomiting, sedation, bladder dysfunction, respiratory depression and delayed recovery[3]. Cyclooxygenase enzyme (COX) is involved in prostaglandin synthesis. Nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibited COX enzymes had been established as useful adjuncts in the pain management[4]. Non-selective NSAIDs block both COX-1 and COX-2 receptors. Cyclooxygenase 2 activation induced proinflammatory prostanoid production, whereas COX-1 activation induced homeostatic prostanoid synthesis. Non-selective COX-1 inhibitors may alter platelet function and increase perioperative bleeding[5]. Clinicians are reluctant to use NSAIDs in perioperative period because of the potential gastrointestinal and operational wound bleeding. Since 1988, many COX-2 selective inhibitors were introduced namely valdecoxib, rofecoxib, celecoxib and parecoxib. These drugs work preferentially and have less side effects on gastro-intestinal bleeding and platelet dysfunction. New COX-2 selective inhibitor may overcome NSAIDs limitations and gain safety usages that were proved from previous study[6]. Parecoxib is a water-soluble pro-drug that undergoes complete and rapid biotransformation to valdecoxib. It is a suitable drug

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for postoperative patients who have contraindication for oral analgesia. Parecoxib NSAIDs with well-documented efficacy had been recommended in many studies[5-7]. Parecoxib is the first highly selective COX-2 inhibitor. It had excellent efficacy, less side effects on platelet aggregation and gastrointestinal function to non-specific NSAIDs[7]. The aim of this study was to determine the efficacy of perioperative parecoxib injection on post operative pain relief after exploratory laparotomy for gynaecological surgery.

**Material and Method**

This prospective double-blind randomized controlled trial was approved by the Ethic Committee, Faculty of Medicine, Thammasat University. This study was conducted in Thammasat University Hospital. Subjects aged between 20-60 years old who underwent elective exploratory laparotomy for gynaecological surgery between October 2013 and May 2014 were recruited. Written inform consent was signed after patients understood the protocol well from a thorough counselling. Exclusion criteria were the present of cardiovascular, renal or hepatic diseases, bleeding disorder and hypersensitivity to NSAIDs. Patients were randomly assigned using a computer-generated table of random number to one of two groups. Group's allocation was concealed in sealed opaque envelopes that were opened in the operating room. The study group received 40 mg parecoxib infusion 1 hour before induction of anesthesia and the control group received normal saline infusion as a placebo in the same manner. All patients underwent exploratory laparotomy for gynaecological surgery via standard treatment. The degree of postoperative pain was assessed at 3, 6, 12 and 24 hours after surgery by using visual analog scale (VAS) (0 = no pain, 10 = worst possible pain). The nurse staff that assessed the VAS was blinded to the preoperative intervention. Postoperative pain control was administered to all patients via standard protocol. Intravenous meperidine (0.5-1 mg/kg/dose) was given when the pain score was equal or greater to 5 every 4 hours during the first 24 hours after the operation. After 24 hours, the use of meperidine could be switched to oral analgesia. The consumption of analgesic agent was also recorded.

Data were analyzed by using the SPSS 13.0 for the statistical analysis (SPSS Inc., Chicago, USA). Continuous data between two groups were compared using mean or median and unpaired t-tests were applied. Fisher's exact and Chi-square tests were used in categorical data. Level of statistical significance was set at $p \leq 0.05$.

**Results**

There were 120 patients in the present study. All of them were divided into two groups: study and control group. Each group consisted of sixty patients. Study and control group received preoperative parecoxib and placebo, respectively. There was no dropout case from the study. Demographic characteristics of both groups were presented in Table 1. Both groups showed no statistical different of demographic data.

Type of incision and operative procedure were presented in Table 2. There were no statistical different of incision type, procedure and operative time between both groups. Seventy and 73.3 percent of placebo and parecoxib cases underwent hysterectomy. Mean operative time of parecoxib and placebo groups were the same at one and a half hour. Mean of total meperidine need in placebo group was more than that of parecoxib group (48.7 and 27.5 mg, respectively; $p<0.001$).

VAS was applied at 3, 6, 12 and 24 hours postoperatively to both groups as shown in Table 3. VAS of parecoxib group was significantly better than that of placebo group at any time of postoperative periods.

There was no dyspepsia, chest pain and gastrointestinal bleeding in both group.

**Discussion**

Parecoxib, an injectable COX-2 inhibitor, is widely used in postoperative pain control. It had excellent pain relief and opioid consumption reduction. Preoperative administration of parecoxib was more effective than postoperative administration in elective general surgical procedures such as appendectomy, cholecystectomy and hernioplasty[8,9]. Intramuscular or intravenous injected use of parecoxib can be seleted[10].

This is the first study of parecoxib in perioperative major gynaecological surgery in Thailand. Main route of parecoxib administration in this study was intravenous injection in 5 minutes. Intravenous or intramuscular injection of parecoxib had the same postoperative pain relief from Lloyd et al report in 2009[11]. Intravenous administration was the convenient and satisfactory route for surgical patients especially all surgical patients, who had already received intravenous fluid catheter. Parecoxib injection via intravenous catheter was a more preferred route

**Table 1.** Demographic characteristics of the studied women; parecoxib and placebo groups

| | Parecoxib (n = 60) | Placebo (n = 60) | *p*-value |
|---|---|---|---|
| Age (year)* | | | 0.70 |
| Pre-menopausal | 41 (68.3) | 39 (65.0) | |
| Post-menopausal | 19 (31.7) | 21 (35.0) | |
| Weight (kg)** | 53.33±15.82 | 59.53±13.24 | 0.21 |
| Height (cm)** | 154.90±4.425 | 155.30±5.845 | 0.63 |
| BMI (kg/m$^2$)** | 23.26±3.93 | 24.66±4.78 | 0.08 |
| Occupational* | | | |
| Government | 27 (45.0) | 18 (30.0) | |
| Employee | 12 (20.0) | 13 (21.7) | |
| Self employed | 9 (15.0) | 20 (33.3) | |
| Housewife | 12 (20.0) | 9 (15.0) | |
| Education* | | | |
| No | 3 (5.0) | 2 (3.3) | |
| Primary school | 9 (15.0) | 17 (28.3) | |
| High school | 15 (25.0) | 19 (31.7) | |
| Bachelor degree | 33 (55.0) | 22 (36.7) | |
| Underlying* | | | |
| No | 45 (75.0) | 42 (70.0) | |
| DM | 0 | 4 (6.7) | |
| HT | 6 (10.0) | 7 (11.7) | |
| DLP | 9 (15.0) | 4 (6.7) | |
| Other | 0 | 3 (5.0) | |
| History gynecologic surgery* | | | |
| No | 57 (95.0) | 54 (90.0) | |
| Yes | 3 (55.0) | 6 (10.0) | |
| Parity* | | | |
| Nulliparous | 27 (45.0) | 26 (43.3) | |
| Multiparous | 33 (55.0) | 34 (56.7) | |
| Abortion* | | | |
| No | 45 (75.0) | 50 (83.3) | |
| Yes | 15 (25.0) | 10 (16.7) | |

BMI = body mass index; DM = diabetes mellitus; HT = hypertension; DLP = dyslipidemia
* n (%), ** Mean ± standard deviation

**Table 2.** Type of incisions, procedures, operative time and meperidine dosage between parecoxib and placebo groups

| | Parecoxib (n = 60) | Placebo (n = 60) | *p*-value |
|---|---|---|---|
| Incision* | | | 0.140 |
| Midline | 30 (50.0) | 21 (35.0) | |
| Transverse | 30 (50.0) | 39 (65.0) | |
| Procedure* | | | 0.840 |
| Hysterectomy | 44 (73.3) | 42 (70.0) | |
| Conservative | 16 (26.7) | 18 (30.0) | |
| Operation time** | 97.75±34.73 | 93.25±40.01 | 0.820 |
| Meperidine (mg)** | 27.50±19.36 | 48.75±28.15 | <0.001$^+$ |

* n (%), ** Mean ± standard deviation, $^+$ Statistical significance

than the intramuscular route. It allowed a better blood collection route and patients reported lower pain score than patients with intramuscular route[11].

Bunyavejchevin et al's work in 2012[12] conducted diagnostic laparoscopy cases where patients received intraoperative parecoxib. Mean

**Table 3.** Postoperative pain assessed as visual analogue score between parecoxib and placebo groups

| | Parecoxib (n = 60) | Placebo (n = 60) | *p*-value |
|---|---|---|---|
| Pain score** | | | |
| 3 hours | 4.30±1.49 | 6.95±1.66 | <0.001+ |
| 6 hours | 4.95±1.73 | 6.25±1.65 | <0.001+ |
| 12 hours | 3.90±1.05 | 4.81±1.93 | 0.002+ |
| 24 hours | 2.85±1.24 | 3.41±1.27 | 0.010+ |

** Mean ± standard deviation, + Statistical significance

**Table 4.** Comparison of parecoxib and gynaecological surgery

| Author | Barton et al.[16] | Ng et al.[15] | Bikhazi et al.[17] | Ratchanon et al.[18] | Bunyavejchein et al.[12] | Nong et al.[13] | Present study |
|---|---|---|---|---|---|---|---|
| Year | 2002 | 2003 | 2004 | 2011 | 2012 | 2013 | 2014 |
| Country | USA | UK | USA | Thailand | Thailand | China | Thailand |
| Type | Open | Open | Open | Open | Scope | Open | Open |
| Age (year) | 41.5 | 43 | 43 | 37.6 | 33.5 | 42.8 | 375 |
| Case (n) | 202 | 36 | 208 | 268 | 60 | 79 | 120 |
| Time (minute) | - | | 122 | 151 | 27.15 | 140 | 95.3 |
| Hysterectomy (%) | 99 | 100 | 73.6 | 39 | 0 | 100 | 77.6 |
| Analgesia | | Morphine | | Meperidine | Acetaminophen | Morphine | Meperidine |
| Dose (mg)** | | | | 26.3/39.1* | | 41/49* | 27.5/48.7* |
| VAS (hour)*** | | | | | | | |
| 1 | | 7.0/7.9* | | | | | |
| 2 | | 5.9/7.4* | | | 2.9/4.3* | 4.3/4.9* | |
| 3 | | | | | | | 4.3/6.9* |
| 4 | | | | | 3.0/1.9 | | |
| 6 | | | | | 2.7/4.5* | 3.5/4.5* | 4.9/6.2* |
| 8 | | 5.3/6.8* | | | | | |
| 12 | | 4.3/7.0* | | | 2.3/1.9 | 3.0/3.6* | 3.9/4.8* |
| 24 | | 4.7/5.6* | | | | 2.0/3.0* | 2.8/3.4* |
| TRM (hour) | 6.3 | | 15.3 | | | | |

TRM = time to rescue medication; Open = exploratory laparotomy; scope = laparoscopic surgery
* Significant difference ($p<0.05$), ** Study/control, *** VAS: mean visual analog scale (range 1-10); study/control

VAS at 24 hours after surgery were 2.3 and 2.85 in Bunyavejchevin's and this work respectively. Pain score value in this study was slightly higher than Bunyavejchevin's work. However, their laparoscopic wound was much smaller than the normal surgical wound in our study (0.5 and 10 cm average, respectively). Thus, postoperative relief parecoxib was shown to be suitable for conservative gynaecological surgery.

The use of parecoxib prior to operation reduced the need of opioid drug in our investigation. Nong et al[13] had reported the used of 40 mg parecoxib preoperative with good VAS reduction in gynecological tumor operation. In our investigation, pre-operative of 40 mg parecoxib required only 27 mg meperidine for VAS control, compared to 41 mg morphine from Nong's work. It is well known that meperidine is 10 time less potent than morphine[14]. The use of less meperidine despite the lesser analgesic potency than morphine in our preoperative administration of parecoxib demonstrated that preoperative administration of parecoxib was a very effective method of pain management.

Ng et al's work in 2003 was congruent with our study[15]. They compared hysterectomy patients who received 40 mg of parecoxib preoperatively compared to the placebo group. Parecoxib recipients had significantly reduced morphine consumption compared to the placebo group at 54 and 72 mg in 24 hours, respectively.

The present study had similar result with Barton et al's and Bikhazi et al's work in 2002 and 2004[16,17]. Their works compared hysterectomy patient who received 40 mg of parecoxib preoperatively to placebo group. Parecoxib recipients had significantly prolonged time to rescue medication (TRM) than the placebo group with statistical significant.

Ratchanon et al's work in 2011[18] reported the excellent result of preoperative used of parecoxib in exploratory laparotomy patients. Ratchanon's work had hysterectomy in 39% of their report while nearly 77.6% of the patient underwent in our case. The comparison of the parecoxib study both case presented in Table 4.

In the study, there were no adverse side effects of parecoxib such as dyspepsia, chest pain and gastrointestinal bleeding.

**Conclusion**

The present study demonstrated that intravenous of preoperative parecoxib injection produced reduction of visual analog scale pain score in 24 hours as well as postoperative meperidine consumption with no serious side effect. Parecoxib could be safely used in gynecological surgery for post operative pain control.

**What is already known on this topic?**

Several preemptive analgesic regimens had been used including local anesthetic infiltration, nerve block, intravenous opioid or NSAIDs administration. Several studies had demonstrated that opioids were excellent analgesic agent for postoperative pain management. The use of opioids resulted in many adverse effects namely nausea, vomiting, sedation, bladder dysfunction, respiratory depression and delayed recovery[3]. Cyclooxygenase enzyme (COX) is involved in prostaglandin synthesis. Non-selective NSAIDs block both COX-1 and COX-2 receptors. COX-2 activation induced proinflammatory prostanoid production, whereas COX-1 activation induced homeostatic prostanoid synthesis. Non-selective COX-1 inhibitors may alter platelet function and increase perioperative bleeding[5]. Clinicians are reluctant to use NSAIDs in perioperative period because of the potential gastrointestinal and operational wound bleeding. Since 1988 COX-2 selective inhibitors were introduced namely valdecoxib, rofecoxib, celecoxib and parecoxib. These drugs work preferentially and have fewer side effects on gastrointestinal bleeding and platelet dysfunction.

**What this study adds?**

Intravenous postoperative parecoxib injection could relief pain and reduced meperidine consumption. Parecoxib could be safely used in gynaecological surgery for postoperative pain relief.

**Acknowledgement**

The study was funding supported by Faculty of Medicine, Thammasat University, Thailand.

**Ethical approval**

The study was approved by Ethical Committee, Faculty of Medicine, Thammasat University, study protocol numbers MTU-EC-OB-2-095/56. Study ID from Thai Clinical Trials Registry (TCTR) was TCTR 20140523001 (http://www.clinicaltrials.in.th/).

**Potential conflicts of interest**

None.

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## *ผลการระงับปวดหลังการผ่าตัดใหญ่ทางนรีเวชวิทยาโดยการบริหารยาพาริค็อกซิบก่อนรับการผ่าตัด: การศึกษาในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ*

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***วัตถุประสงค์:*** *ศึกษาประสิทธิผลของการฉีดยาพาริค็อกซิบก่อนรับการผ่าตัดเปิดหน้าท้องทางนรีเวชต่อการระงับปวดหลังการผ่าตัด*

***วัสดุและวิธีการ:*** *เป็นการศึกษาชนิดควบคุมและสุ่มตัวอย่างชนิดปิดในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ ระหว่างเดือนตุลาคม พ.ศ. 2556 ถึง พฤษภาคม พ.ศ. 2557 โดยมีจำนวนผู้ป่วยที่รับการรักษาทางนรีเวช 120 ราย ที่มารับการผ่าตัดรักษาโดยแบ่งเป็น 2 กลุ่ม กลุ่มละ 60 ราย โดยกลุ่มแรกเป็นกลุ่มศึกษาจะได้รับยาพาริค็อกซิบ 40 มิลลิกรัม ในเวลา 1 ชั่วโมง ก่อนรับการผ่าตัดเปิดหน้าท้อง กลุ่มที่สองเป็นกลุ่มควบคุมได้รับยาหลอก ก่อนรับการผ่าตัด 1 ชั่วโมง บันทึกระดับความเจ็บปวดที่ได้รับการประเมินโดยใช้ visual analog scale (VAS) ที่ 3, 6, 12 และ 24 ชั่วโมง หลังการผ่าตัดตามลำดับ ความถี่ของการใช้ยาเมเพอริดีนหลังผ่าตัด 24 ชั่วโมง ตลอดจนฤทธิ์ข้างเคียงของยาพาริค็อกซิบ*

***ผลการศึกษา:*** *ผลของการวัดระดับความเจ็บปวดหลังผ่าตัดชั่วโมงที่ 3, 6, 12 และ 24 ในกลุ่มศึกษามีค่าน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ การใช้ยาเมเพอริดีนในกลุ่มควบคุมมีปริมาณมากกว่ากลุ่มศึกษาอย่างมีนัยสำคัญทางสถิติ (27.5±19.36 และ 48.75±28.15 มิลลิกรัม ตามลำดับ) ไม่พบข้อแทรกซ้อนของยาพาริค็อกซิบในการศึกษานี้*

***สรุป:*** *การฉีดยาพาริค็อกซิบเข้าหลอดเลือดดำก่อนรับการผ่าตัดสามารถลดความเจ็บปวดและลดการใช้ยาเมเพอริดีนลง โดยสามารถใช้ยาพาริค็อกซิบเพื่อระงับความเจ็บปวดภายหลังผ่าตัดทางนรีเวชได้อย่างปลอดภัย*