Pain Control in Laparoscopic Gynecologic Surgery with/without Preoperative (Preemptive) Parecoxib Sodium Injection: A Randomized Study

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Objective: *To determine the effectiveness of preoperative parecoxib sodium injection for pain relief after laparoscopic gynecologic surgery.*

Material and Method: *A prospective double-blind, randomized study was conducted in 268 patients who underwent laparoscopic gynecologic surgery at Vajira Hospital between November 1, 2010 and March 31, 2011. The patients were randomly allocated into two groups to receive either single intravenous 40 mg parecoxib (treatment group; n = 133) or normal saline (control group; n = 135) 30 min before surgery. The degree of postoperative pain was assessed every 2 h in the first 8 h postoperation, then every 4 h until completion of 24 h by using a verbal rating scale. Total consumption of meperidine over a 24-h period and the adverse events relevant to parecoxib sodium were also recorded.*

Results: *Mean pain scores at all measured times in the treatment group were insignificantly lower than those in the control group (p = 0.106). The mean 24-h postoperative meperidine consumption in the treatment group was significantly lower compared to that in the control group (26.3 $\pm$ 28.1 mg and 39.1 $\pm$ 34.6 mg, respectively, p = 0.001). The proportion of patients requiring meperidine in the treatment group was significantly lower than that in the control group (58.6% and 70.3%, respectively, p = 0.045). No serious adverse events were observed in both groups.*

Conclusion: *Preoperative parecoxib sodium significantly reduced postoperative meperidine requirement and consumption, while insignificantly declined the pain scores. Serious adverse events were not encountered.*

Keywords: *Preemptive analgesia, Parecoxib sodium, Laparoscopic gynecologic surgery*

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Not only no complication, but also well-controlled pain improves the patients' satisfaction and recovery after any surgeries. Nowadays, the mainstay conventional postoperative pain control is still using opioid administration[1]. However, respiratory depression is its common adverse effect[1]. With the evidence about pain pathway, surgical trauma induces the expression of cyclooxygenase-2 (COX-2) leading to the release of prostaglandins (PGs), which sensitize peripheral nociceptors and produce localized hyperalgesia (peripheral sensitization)[1-4]. Besides, tissue injury induces COX-2 expression in spinal cord neurons, which in turn increases neuronal excitability causing secondary hyperalgesia (central sensitization)[1,3]. For these reasons, non-steriodal anti-inflammatory drugs (NSAIDs) may be an alternative choice for postoperative pain control[1,3].

For overcoming the adverse effects of conventional NSAIDs such as interference of platelet function, gastrointestinal and renal side effects etc, selective COX-2 inhibitor has been developed and widely used[4-6]. Parecoxib sodium, an only injectable selective COX-2 inhibitor, is biotransformed in the liver to active form, valdecoxib, which has rapid onset within 30 min and lasts for 8 h[6]. One systematic study[7] concluded that its use of 40 mg dosage is effective and safe during postoperative orthopedic surgery.

Over the past years, preoperative analgesia has been proposed to use in conjunction with the

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conventional postoperative analgesia in several means of surgery including general intraabdominal surgery[8], orthopedics[9-11] and dental surgery[12] with the aim of improving pain management. However, ideal regimen should be capable of limiting sensitization of the nervous system throughout the entire perioperative period, have fewer side effects and be convenient to administer. Therefore, for preoperative fasting patients, parenteral analgesia plays an important role[10-13].

To date, although, laparoscopic surgery has been accepted as a standard procedure for gynecologic diseases because of less postoperative pain and shorter recovery period compared to laparotomy, the patients still have some degree of postoperative pain especially in the first 24 h. Since there have been no available data regarding the role of preoperative COX-2 inhibitor on postoperative outcome in this kind of surgery, the aim of the present study was to determine the effectiveness of preoperative parecoxib sodium injection for pain relief after laparoscopic gynecologic surgery.

Material and Method

This prospective double-blind, randomized study was conducted after approval of the Bangkok Metropolitan Administration Ethics Committee for Researches Involving Human Subjects.

The patients who underwent laparoscopic gynecologic surgery at the Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital between November 1, 2010 and March 31, 2011 were recruited into the present study. The enrolled subjects were those aged 18 to 65 years who had a diagnosis of benign gynecologic diseases. Exclusion criteria were participants who had any underlying diseases contraindicated for COX-2 inhibitor including peptic or duodenal ulcers, cardiovascular and renal diseases, hypersensitivity to sulfonamides or NSAIDs, poor verbal communication in the Thai language, malignancy found in operative finding, and the surgery converted to laparotomy. Informed consent was obtained from all patients included in the present study prior to the surgery.

All participants were randomly allocated into one of the two groups by using a block of four. The treatment group received single intravenous (IV) 40 mg parecoxib sodium 30 min before surgery while the control group received single IV 2 ml normal saline. For ensuring allocation concealment, the sequential random number code was enclosed in a sealed envelope. All patients underwent laparoscopic gynecologic surgery under a standard general anesthesia. The patients and the researchers were blinded to the allocation.

All patients were instructed how to assess pain, at 2-h, 4-h, 6-h, 8-h, 12-h, 16-h, 20-h, and 24-h postoperative, using a verbal rating scale (VRS) ranging from 0 (no pain) to 10 (the worst possible pain)[14]. Attending nurses who had been well trained by the researchers and were unaware that the treatment allocation would assess the patients' pain score. The patients were not awakened for assessment during sleep. Intramuscular (IM) meperidine was used as an analgesic agent for all participants during the first 24 h postoperation. A dosage of 50 mg was administered to the patients when a pain score over 7, 25 mg for those with a score of 4 to 7, and no medication when a score under 4. Patients who scored below 4 and requested analgesia were re-evaluated. If the score remained under 4, the patients would be reassured without further analgesic treatment. After 24 h, the patients would then receive oral analgesics instead. The patients' characteristics, operative details, pain scores and consumption of meperidine during the first 24 h, as well as side effects of parecoxib were recorded.

The primary outcome of interest was post-operative meperidine consumption within 24 hours. Secondary outcome measures included proportion of patients requiring meperidine, pain scores during the first 24 h postoperation, and the adverse events.

Sample size was calculated based on data of the primary outcome from a preceding pilot study in the other 60 patients. With a power of 80% at a significant level of 0.05, 127 patients were needed for each group. After adding 10% for possible missing data, 280 patients were required.

Statistical analysis was performed with the SPSS software package version 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean and standard deviation (SD), and categorical variables as number (%). Differences between outcomes of the two groups were evaluated using Chi-square test or unpaired t-test as appropriate. Pain scores in both groups at each postoperative time point were compared using repeated measures ANOVA. All outcomes were considered significant only if the p-value < 0.05.

Results

Out of 280 patients who presented for benign gynecologic diseases, 268 were eligible for the present study. Twelve patients were excluded due to the criteria.

Among 268 enrolled subjects, there were 133 participants in the treatment group and 135 in the control group. The mean ages of patients in the treatment and control groups were 37.8 ± 8.2 and 37.5 ± 8.3 years, respectively (p = 0.746). Mean body mass index in the treatment group was 22.0 ± 3.5 kg/m^2 compared to 22.9 ± 4.1 kg/m^2 in the control group (p = 0.068). Both groups had similar operative characteristics, indication for surgery, operative procedures, mean operative time, and blood loss (Table 1).

During the first 24 h post surgery, the proportion of patients requiring meperidine in the treatment group (58.6%) was significantly lower than that in the control group (70.3%), (p = 0.045). Likewise, a statistically significant lower in mean 24-h consumption of meperidine was observed in the treatment group (26.3 ± 28.1 mg) compared to the control group (39.1 ± 34.6 mg), (p = 0.001) (Table 2).

The mean (standard deviation) VRS of treatment/control group were 2.5 (1.7)/2.6 (2.0), 2.7 (1.2)/2.8 (1.4), 2.6 (1.0)/2.8 (1.2), 2.7 (1.3)/2.9 (1.6), 2.8 (1.3)/2.9 (1.1), 2.7 (1.0)/3.1 (1.3), 2.6 (0.7)/2.9 (0.9), 2.6 (0.7)/2.8 (0.6) at 2-h, 4-h, 6-h, 8-h, 12-h, 16-h, 20-h, and 24-h, respectively (p = 0.106).

Serious adverse events were not encountered; however the minorities of the subjects in treatment/control group was reported 13 (9.8%)/14 (10.4%), (p > 0.05). Those included mild nausea or vomiting 8/13 cases, and stomachache 5/1 cases.

Discussion

The present study demonstrated a significant impact of preoperative parecoxib on lower meperidine requirement and consumption after laparoscopic gynecologic surgery. It revealed insignificantly lower mean pain scores at all measured times. There were comparable adverse events in both groups.

In patients undergoing total abdominal hysterectomy, Ng et al reported a reduction of mean analgesic consumption of 26% in those receiving preoperative 40 mg parecoxib compared to the placebo

Table 1. Patient characteristics and surgical data

Characteristics	Treatment group (n = 133)	Control group (n = 135)	p-value
Indication for surgery, No. (%)			0.490*
Pelvic endometriosis	17 (12.8)	13 (9.6)	
Myoma uteri or adenomyosis	61 (45.9)	71 (52.6)	
Adnexal pathology	55 (41.3)	51 (37.8)	
Operative procedure, No. (%)			0.926*
Adhesiolysis	17 (12.8)	14 (10.3)	
Adnexal surgery	51 (38.3)	53 (39.3)	
Myomectomy	13 (9.8)	15 (11.1)	
Hysterectomy	52 (39.1)	53 (39.3)	
Operative time (min), mean ± SD	152.2 ± 60.5	150.4 ± 66.0	0.821**
Blood loss (ml), mean ± SD	122.8 ± 172.2	141.7 ± 169.0	0.365**

* Chi-square test
** Unpaired t-test

Table 2. Postoperative meperidine requirement and consumption

Postoperative meperidine requirement	Treatment group (n = 133)	Control group (n = 135)	p-value
Postoperative meperidine requirement, No. (%)	78 (58.6)	95 (70.3)	0.045*
Average meperidine consumption for pain control (mg), mean ± SD	26.3 ± 28.1	39.1 ± 34.6	0.001**

* Chi-square test
** Unpaired t-test

group[15]. This reduction was somewhat less than that of 32% in the authors' laparoscopic cases. One randomized study conducted in patients undergoing lumbar spine surgery found a significant decrease in morphine requirement and mean pain scores over the first 48 h after surgery in those receiving preoperative 40 mg parecoxib compared to those in the placebo group[11]. On the contrary, Akaraviputh et al observed no difference in analgesic consumption and mean pain scores after laparoscopic cholecystectomy between the two groups who received either preoperative 20 mg parecoxib or normal saline[13].

The different outcomes among the present and previous studies might lie on varieties of studied populations, sample sizes, surgical procedures, dosages of parecoxib, and different practice guidelines for postoperative pain management. In the present study, single 40 mg parecoxib was used preoperatively for patients undergoing laparoscopic gynecologic surgery. With its action that lasts for 8 h, therefore the present study period of 24 h might be beyond its analgesic effect. Aside from incisional pain in laparotomy, the pain after laparoscopic surgery also results from other factors *e.g.* the stretching of intraabdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity[16-18]. Contrasts to incisional pain, these three types of pain are not exclusively mediated by COX-2 induction[19]. Moreover, the present study consisted of non-homogeneous operative procedures that produced various degree of tissue trauma and made difference in pain response. These reasons might explain the result of an insignificant decline in pain score.

The adverse events observed in the present study were comparable in both groups. This result was compatible with the other studies[11]. Furthermore, some symptoms, *i.e.*, nausea and vomiting could be directly related to surgery or anesthesia; therefore, it was possible that the side effects encountered in the presented patients were multifactorial rather than the results of parecoxib alone.

This is the first study that determines the effectiveness of preoperative parecoxib for pain relief after laparoscopic gynecologic surgery with a large number of patients. The limitation in our study was non-homogeneity of operative procedures. Additionally, titration of meperidine dosage upon pain level in the present study instead of using patient-controlled analgesia (PCA) might affect the accuracy of meperidine dosage needed by patients. Therefore, further studies with specific surgical procedure and proper post-operative analgesic modality are warranted to confirm the findings.

In conclusion, preoperative parecoxib significantly reduced meperidine requirement and consumption, while insignificantly declined the pain scores. Serious adverse events were not encountered.

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Potential conflict of interest

None.

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การควบคุมความปวดในการผ่าตัดผ่านกล้องส่องช่องท้องทางนรีเวชโดยใช้/ไม่ใช้ยาฉีดพารีคอกซิบโซเดียมก่อนการผ่าตัด: การศึกษาแบบสุ่มอิสระ

สาวินี รัชชานนท์, ชาดากานต์ ผโลประการ, ขนิษฐา ไตรปักษ์

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของการบริหารยาฉีดพารีคอกซิบโซเดียม ก่อนการผ่าตัดเพื่อลดปวดภายหลังการผ่าตัดผ่านกล้องส่องช่องท้องทางนรีเวช*

วัสดุและวิธีการ: *การศึกษาไปข้างหน้าสุ่มอิสระปิดบังสองทางในผู้ป่วยที่เข้ารับการผ่าตัดผ่านกล้องส่องช่องท้องทางนรีเวช 268 ราย ระหว่างวันที่ 1 พฤศจิกายน พ.ศ. 2553 ถึง 31 มีนาคม พ.ศ. 2554 ถูกสุ่มอิสระแบ่งออกเป็น 2 กลุ่ม เป็นกลุ่มที่ได้รับยาพารีคอกซิบโซเดียม 40 มิลลิกรัม (กลุ่มศึกษา 133 ราย) หรือกลุ่มที่ได้รับน้ำเกลือ (กลุ่มควบคุม 135 ราย) ทางหลอดเลือดดำเป็นเวลา 30 นาทีก่อนการผ่าตัดผู้ป่วยได้รับการประเมินคะแนนความปวดทุก 2 ชั่วโมงใน 8 ชั่วโมงแรก และทุก 4 ชั่วโมงจนครบ 24 ชั่วโมง ด้วยการระบุระดับคะแนนด้วยวาจา (verbal rating scale) บันทึกปริมาณยามีพีริดีนทั้งหมดที่ได้รับภายใน 24 ชั่วโมง และผลข้างเคียงที่ตรงประเด็นกับยาพารีคอกซิบ*

ผลการศึกษา: *ค่าเฉลี่ยคะแนนความปวดในทุกช่วงเวลาประเมินในกลุ่มศึกษา ต่ำกว่ากลุ่มเปรียบเทียบอย่างไม่มีนัยสำคัญ ($p = 0.106$) ค่าเฉลี่ยปริมาณยามีพีริดีนที่ได้รับภายใน 24 ชั่วโมง หลังผ่าตัดในกลุ่มศึกษาน้อยกว่าในกลุ่มเปรียบเทียบอย่างมีนัยสำคัญ (26.3 ± 28.1 และ 39.1 ± 34.6 มิลลิกรัม ตามลำดับ $p = 0.001$) สัดส่วนของผู้ที่ต้องการยามีพีริดีนในกลุ่มศึกษาน้อยกว่าในกลุ่มเปรียบเทียบอย่างมีนัยสำคัญ (58.6% และ 70.3% ตามลำดับ $p = 0.045$) ไม่พบผลข้างเคียงร้ายแรงในทั้งสองกลุ่ม*

สรุป: *การบริหารยาฉีดพารีคอกซิบโซเดียมก่อนการผ่าตัดช่วยลดความต้องการ และปริมาณของยามีพีริดีนภายหลังการผ่าตัดอย่างมีนัยสำคัญ ในขณะที่คะแนนความปวดลดลงอย่างไม่มีนัยสำคัญ ไม่พบผลข้างเคียงที่ร้ายแรง*