The Preemptive Analgesic Effect of Celecoxib for Day-Case Diagnostic Laparoscopy

PITCHA PHINCHANTRA, MD*
SUVIT BUNYAVEHCHEVIN, MD, MHS*,
SOMCHAI SUWAJANAKORN, MD*,
WIRACH WISAWASUKMONGCHOL, MD*

Abstract

In a randomized trial, the preemptive analgesic effect of celecoxib in 110 infertile women undergoing day-case diagnostic laparoscopy was studied at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The patients randomly received either 200 mg celecoxib or placebo orally 2 hours before diagnostic laparoscopy. The post-operative shoulder pain and wound pain were self assessed and recorded, using Visual Analogue Scores (VAS) at 1, 2, 4, 12, and 24 hours. Total post-operative analgesic requirements were recorded at 24 hours. The mean Visual Analogue Scores (VAS) of shoulder pain in celecoxib group was statistically lower than those of the placebo group ($p = 0.04$). Nevertheless, the mean VAS of wound pain and the total post-operative analgesic requirements were not significantly different. It was concluded that the preemptive celecoxib in day-case diagnostic laparoscopy might have the advantage of decreasing post laparoscopic shoulder pain.

Key word : Celecoxib, Diagnostic Laparoscopy, Analgesic Effect

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Experimental studies with animal pain models have demonstrated that brief anoxious stimuli may result in long-lasting neuronal sensitization. Moreover, clinical evidence suggests that surgical trauma may induce prolonged changes in both the peripheral and central nervous system (CNS), which together amplify post-operative pain[1]. The prevention of pain is better management strategy than treating the pain once it has occurred[2]. Preemptive analgesia is the administration of analgesia before painful stimuli. This prevents the establishment of hypersensitized state and, thus, the amplification of post-operative pain.

* Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Pre-operative administration of nonsteroidal anti-inflammatory drugs (NSAIDs) in day-case diagnostic laparoscopy has a beneficial effect on post-operative morbidity[3,4]. NSAIDs reduce pain and inflammation by inhibiting the synthesis of prostaglandin. However, NSAIDs inhibit both cyclooxygenase enzymes (COX-1 and COX-2) to varying degree[5, 6]. COX-1 is constitutively expressed and is responsible for several "housekeeping" physiologic functions such as GI mucosal protection, platelet function and regulation of renal haemodynamics and electrolyte balance. In contrast, COX-2 is an inducible isoenzyme and is involved in the production of prostaglandins that mediate pain and inflammatory processes[7-9]. The inhibition of COX by NSAIDs produces both clinical benefits and toxicity[10-12].

The COX-2 specific inhibitor was developed to provide significant anti-inflammatory action and anti-pain, as seen with conventional NSAIDs, but without the toxicity associated with COX-1 inhibition. Celecoxib is the first COX-2 specific inhibitors. Celecoxib demonstrated 375-fold selectivity for COX-2 over COX-1. After oral administration of a single 200 mg dose, celecoxib is 97 per cent bound to plasma proteins. Time to maximal plasma concentration is 2 to 4 hours[13]. The drug undergoes extensive hepatic metabolism *via* cytochrome P450 (CYP)2C9, forming inactive metabolites. Approximately 27 per cent of the administered dose is eliminated in the urine and 58 per cent in the feces. A mean effective half-life is 11.2 hours[14].

The effect of preemptive COX-2 specific inhibitor on pain prevention following the day-case diagnostic laparoscopy has not been reported. Therefore, the authors designed a study to test the efficacy of preemptive analgesic effects of 200 mg oral celecoxib in day-case diagnostic laparoscopy.

MATERIAL AND METHOD

The study design was double-blind, placebo-controlled, and randomized. This study was approved by the hospital ethics committee, and informed written consent was obtained from each participant. The trial medication was supplied by Pharmacia Inc. (New York, USA) as identical appearing capsules containing either 200 mg celecoxib or placebo. One hundred and ten healthy women (American Society of Anesthesiologists class I) were scheduled to undergo elective diagnostic laparoscopy and chromopertubation with methylene blue for evaluation of infertility. The patients with a known history of adverse reaction to NSAIDs sulfonamide and celecoxib, history of peptic ulcer disease, asthma, chronic liver disease, chronic renal disease, preexisting coagulation disease, previous abdominal surgery, pregnancy, and lactation were excluded from the study. The patients were enrolled and randomized according to a block of eight randomization.

Prior to the operation, each patient was familiarized with the 11 point Visual Analogue Scores (VAS), with 0 on the left side indicating no pain and 10 on the right side indicating the worst imaginable pain[15].

Two hours before surgery, the patients received a capsule containing either 200 mg celecoxib (n = 55) or placebo (n = 55). For anesthesia, the patients received IV sedation with midazolam (0.1 mg/kg), meperidine (1 mg/kg) and a local anesthetic (1% xylocaine) injection at the trocar insertion site. Breathing was maintained by 100 per cent O2 mask with bag. Vital signs and O2 saturation were monitored.

After injection of 10 ml 1 per cent xylocaine at the trocar insertion site (infraumbilicus), laparoscopy was performed by the one-puncture technique (diameter 10 mm) with carbon dioxide-induced pneumoperitoneum. Chromopertubation with methylene blue was performed in all cases. Data was completed on all the patients detailing name, medical record number, age, weight, height, dose of sedation, duration of surgery, diagnosis and any ill effects post-operatively.

Post-operatively, 1,000 mg acetaminophen was provided on patient request. Visual Analogue Scales of shoulder and wound pain were self assessed and recorded at 1, 2, 4, 12, and 24 hours after the completion of surgery. When the patients were oriented to time, place and had stable vital signs, they were discharged from the hospital with a self assessing questionnaire (VAS, post-operative analgesic requirement and adverse side effects) and twenty 500 mg acetaminophen tablets. The questionnaire was sent to the investigator by mail.

A formal sample size calculation was performed. From the pilot study, the standard deviation of wound pain (VAS) scores was approximately 1.3 cm and a specified mean difference of 9 mm. A two-sided significant level of 0.05 and a power of 90 per cent were used. The calculated sample size was 55 patients in each group. The age, weight, height, duration of surgery, and dose of sedative drugs were analyzed using the student's *t*-test. The means of Visual Analogue Scores (VAS) between the groups were analyzed

using the repeated measure. Significance was assumed at the 5 per cent level.

RESULTS

A total of 110 patients were randomized to receive medicine (55 in each group). There was no significant difference between the placebo and celecoxib groups with respect to age, height, duration of surgery or the dose of sedative drugs (Table 1). One hundred and three (93.6%) out of 110 took home the questionnaires, 51/55 (92.7%) in the placebo group and 52/55 (94.5%) in celecoxib group, were returned.

Repeated measure Analysis revealed that patients who received celecoxib had significantly less shoulder pain in the 24 hours after surgery than those in the placebo group (Fig. 1). There was a significant difference with respect to shoulder pain scores at 12 hours ($p = 0.04$) (Table 2). In contrast, there was no significant difference between the two groups with wound pain scores (Fig. 2). VAS of wound pain scores were consistently lower in the celecoxib group.

There were no significant differences between the groups in the mean dosages of post-operative analgesic requirement in 24 hours (Table 1). In addition, 10/51 (19.6%) of patients who had received placebo required no acetaminophen in 24 hours after surgery compared with 15/52 (28.8%) of those who had received celecoxib, but there was no significant difference.

DISCUSSION

Day-case diagnostic laparoscopy for evaluation of infertility was considered to be a minor surgical procedure. However, previous data by the authors showed that there was high VAS pain scores and post-operative analgesia requirement. The efficacy of post-

Table 1. Patient characteristics, procedure data and analgesic requirements.

Variable	Celecoxib	Placebo	P
Number (n)	52	51	
Age (years)	32.7 ± 4.0	32.4 ± 4.0	NS
Weight (kg)	51.4 ± 5.9	51.4 ± 8.6	NS
Height (cm)	156.8 ± 4.6	156 ± 5.5	NS
Meperidine (mg)	73 ± 6.7	75 ± 8.7	NS
Midazolam (mg)	5.3 ± 1.5	5.5 ± 1.0	NS
Duration of surgery (min)	20.6 ± 7.3	21.2 ± 7.0	NS
Acetaminophen (mg)	1,550 ± 1,370	1,890 ± 1,455	NS

Mean ± SD
NS = no significant difference

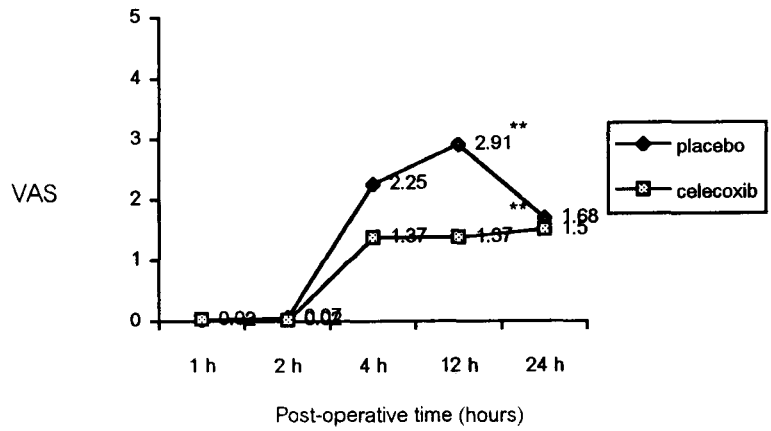

Fig. 1. Mean shoulder pain (VAS) overtime significant difference between the groups ($p = 0.04$). ** significant difference ($p = 0.004$).

Table 2. Visual analogue scores of shoulder pain. Results are expressed as mean.

Post-operative time (hours)	Celecoxib	Placebo	P-value
1	0.03	0.02	0.880
2	0.02	0.07	0.124
4	1.37	2.25	0.123
12	1.37	2.91	0.004**
24	1.50	1.68	0.736

** significant difference ($p < 0.05$)

operative pain control was essential because the patients required early discharge.

The ideal analgesic for day-case surgery should be effective with rapid onset, minimal side effects and a long elimination half-life. NSAIDs are the most promising group of analgesics. They inhibit the two recognized forms of cyclooxygenase enzymes. The mechanism of NSAIDs (COX-2 inhibitor) are usually thought to produce effects by inhibiting the production of eicosanoids from arachidonic acid, which would decrease peripheral sensitization, the activation of nociceptors[16] and the sensory inflow from the periphery to the central nervous system. NSAIDs may act in the spinal cord directly on some of the mechanisms that maintain or induce central sensitization[17]. However, the adverse effect of NSAIDs (COX-1 inhibitor) was demonstrated.

Celecoxib, specific COX-2 inhibitor, inhibit COX-2 over COX-1. This action leads to reduced eicosanoids production and post-operative pain, as seen with conventional NSAIDs but it does not interfere with physiological function such as platelet function, and GI mucosal protection from COX-1 sparing effect. Celecoxib is useful for decreasing pain in several conditions namely osteoarthritis, rheumatoid arthritis, and acute pain. For the acute pain, available data suggest that celecoxib has an analgesic effect in patients with post surgical dental pain from the removal of the molar teeth. Celecoxib (200 mg) was significantly more effective than placebo in all measures of efficacy including, total pain relief and time to the use of rescue medication[18].

The preemptive effects of celecoxib have not been reported for day-case diagnostic laparoscopy. The present study demonstrated that preemptive celecoxib significantly reduced the VAS of the shoulder pain but not the wound pain or analgesic requirement in day-case diagnostic laparoscopy.

Direct irritation of the diaphragm due to the residual CO2 pneumoperitoneum, excessive traction of the triangular ligament and overstretching of the diaphragmatic muscle fibers are the cause of shoulder pain. In addition, the peritoneal inflammation is also the origin of the shoulder pain[19]. The distension of the peritoneum may be associated with tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. A previous report demonstrated that peritoneal biopsy after laparoscopy showed peritoneal inflammation and neuronal rupture [19]. The present study showed that there was significant reduction in the shoulder pain in patients who received preemptive celecoxib and acetaminophen for

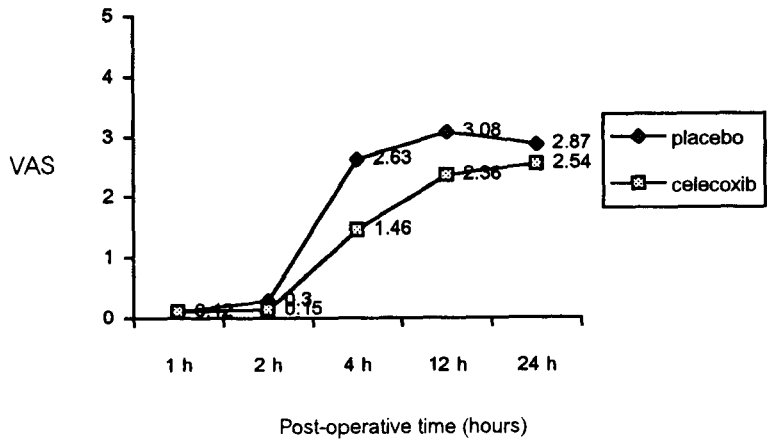

Fig. 2. Mean would pain (VAS) overtime no significant difference between groups (p = 0.109).

post-operative analgesia. Probably, the inflammatory processes from these causes were extremely reduced by celecoxib.

The inflammation process obtained from direct injury at trocar insertion site was involved in the cause of the wound pain. Since the operative time of day-case diagnostic laparoscopy was usually short, combined with a small abdominal incision, and little manipulation, the inflammatory process should be minimal. In addition, the acetaminophen for post-operative analgesic and the preemptive effect of local analgesic infiltration may affect the pain. From the previous data, the preemptive administration of local analgesic infiltration before diagnostic laparoscopy resulted in significantly lower pain scores than that of the control group[20]. The combination of the two analgesic methods may adequately control the pain from a small incision, so the preemptive effect of celecoxib was not obvious.

Notably, the higher pain scores of both groups at 4 hours after surgery may be explained by the decreasing intra-operative analgesic drugs level and the beginning of the patient's activity.

In conclusion, the preemptive celecoxib in day-case diagnostic laparoscopy might have an advantage in decreasing post laparoscopic shoulder pain.

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การใช้ยา celecoxib ก่อนการผ่าตัดเพื่อลดอาการปวดในการผ่าตัดผ่านกล้องเพื่อการวินิจฉัย

พิชชา ปิ่นจันทร์, พบ, สุวิทย์ บุณยะเวชชีวิน, พบ, MHS*, สมชาย สุวจนกรณ์, พบ*, วิรัช วิศวสุขมงคล, พบ**

บทความนี้เป็นรายงานการศึกษาผลการระงับความเจ็บปวดของการใช้ยา celecoxib ก่อนการผ่าตัดเพื่อการวินิจฉัยในสตรีที่มีภาวะมีบุตรยาก 110 ราย ที่มารับการผ่าตัดผ่านกล้องเพื่อการวินิจฉัยที่โรงพยาบาลจุฬาลงกรณ์ ผู้ป่วยจะได้รับการสุ่มรับประทานยา celecoxib 200 มิลลิกรัม หรือยาหลอกก่อนการผ่าตัดเป็นเวลา 2 ชั่วโมง ความเจ็บปวดหลังการผ่าตัดบริเวณไหล่และแผลถูกประเมินและบันทึกโดยใช้ Visual Analogue Scores (VAS) ปริมาณยาบรรเทาปวดหลังการผ่าตัดทั้งหมดถูกบันทึกที่ 24 ชั่วโมง พบว่าค่าเฉลี่ยความเจ็บปวดที่บริเวณไหล่ในกลุ่ม celecoxib ต่ำกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติ ($p = 0.04$) แต่ค่าเฉลี่ยความเจ็บปวดที่บริเวณแผล และปริมาณยาบรรเทาปวดหลังการผ่าตัด ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ การใช้ยา celecoxib ก่อนการผ่าตัดผ่านกล้องเพื่อการวินิจฉัยมีข้อดีในการลดอาการปวดบริเวณไหล่หลังการผ่าตัด

คำสำคัญ : Celecoxib, การผ่าตัดผ่านกล้องเพื่อการวินิจฉัย, ผลการระงับความเจ็บปวด

พิชชา ปิ่นจันทร์, สุวิทย์ บุณยะเวชชีวิน, สมชาย สุวจนกรณ์, วิรัช วิศวสุขมงคล
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* ภาควิชาสูติศาสตร์-นรีเวชวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330