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Comparison efficacy of pain relief for post-breast surgery pain between rofecoxib and valdecoxib

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Objective : *To campare the efficacy of pain relief for post-breast surgery pain between rofecoxib and valdecoxib*

Study design : *Randomized, compare 2 actives trial*

Materials and Methods : *Subjects were 18 –65 year-old-female with ASA status 1-2 who underwent breast surgery. Every recruited patient was required to provide their written informed consents before enrollment. Randomization was taken to divide the subjects into 2 groups: rofecoxib and valdecoxib groups. All subjects received two tablets of either rofecoxib (25 mg) or valdecoxib (20 mg) at 1 hour before induction of anesthesia and 12 hours after the first administration. General anesthesia was applied to all subjects using the anesthetics as in the set-up protocol. Postoperative pain was treated with intravenous meperidine 0.5 mg kg^{-1} on request. The total consumption of meperidine in 24 hours and the number of patients who request meperidine were recorded. The 0-10 visual numeric pain (VNS) and visual numeric satisfaction scores were self-assessed at 2, 6 and 24 hours. Side effects such as headache, dizziness and peripheral edema were also observed.*

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Results : *There were 52 and 54 patients categorized to receive rofecoxib and valdecoxib respectively. One patient in the rofecoxib group who had hematoma and needed a reoperation was excluded. There were 30 and 36 patients who requested for postoperative meperidine and the mean consumption of meperidine were 25.87 ± 26.30 and 23.52 ± 20.27 mg of rofecoxib and valdecoxib groups consecutively. These differences show no statistical significance. Pain and satisfaction scores at 2, 6 and 24 hours were not of significant difference between the two groups.*

Conclusion : *The efficacy for pain relief after breast surgery of rofecoxib and valdecoxib were not of significant difference.*

Keywords : *NSAIDs: COX-2 inhibitor, Breast surgery.*

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ปิ่น ศรีประจิตติชัย, วัชริน สินธวานนท์, ปกรณ์ อุรุโสภณ, ศุภลักษณ์ วสันต์ธนารักษ์. การศึกษาเปรียบเทียบประสิทธิผลการแก้ปวดของยาโรฟีคอกซิบและยาวาลดิคอกซิบภายหลังการผ่าตัดบริเวณเต้านม. จุฬาลงกรณ์เวชสาร 2548 พ.ค; 49(5): 281 – 8

วัตถุประสงค์ : *เพื่อเปรียบเทียบผลการแก้ปวดจากการผ่าตัดบริเวณเต้านมของยาโรฟีคอกซิบ (rofecoxib) และยาวาลดิคอกซิบ (valdecoxib)*

รูปแบบการศึกษา : *การศึกษาแบบทดลอง มีการควบคุมและสุ่มตัวอย่าง*

วัสดุและวิธีการ : *การศึกษานี้ทำในกลุ่มตัวอย่างเพศหญิงที่เข้ารับการผ่าตัดบริเวณเต้านม 107 คน อายุระหว่าง 18 - 65 ปี และ physical status 1-2 ได้ลงนามในใบยินยอมร่วมมือในการศึกษา กลุ่มตัวอย่างได้รับการแบ่งโดยการสุ่มให้ได้รับยาโรฟีคอกซิบ ขนาด 25 มิลลิกรัม 2 เม็ด หรือยาวาลดิคอกซิบ ขนาด 20 มิลลิกรัม 2 เม็ด อย่างใดอย่างหนึ่ง โดยผู้ป่วยได้รับประทานยาครั้งแรกก่อนเริ่มผ่าตัด 1 ชั่วโมง และ 12 ชั่วโมงภายหลังได้รับประทานยาครั้งแรก ผู้ป่วยทุกรายได้รับการระงับความรู้สึกแบบทั่วไปด้วยชนิดและขนาดยาระงับความรู้สึกที่คำนวณตามน้ำหนักตัวตามที่กำหนดไว้ ระงับปวดภายหลังการผ่าตัดใน 24 ชั่วโมงด้วยยา meperidine ขนาด 0.5 ม.ก. ต่อก.ก. ทางหลอดเลือดดำ ทุก 4 ชั่วโมง หากผู้ป่วยร้องขอ บันทึกขนาดยา meperidine ที่ผู้ป่วยแต่ละคนได้รับทั้งสิ้นภายใน 24 ชั่วโมง จำนวนผู้ป่วยที่ร้องขอยาแก้ปวด และความรุนแรงของความปวดด้วย 0-10 Visual numeric pain score (VNS) ที่ 2, 6 และ 24 ชั่วโมงภายหลังผ่าตัดเสร็จ ทำการบันทึกความพึงพอใจด้วย 0-10 Visual numeric satisfaction score และผลข้างเคียงของยา เช่น ปวดศีรษะ เวียนศีรษะ และแขนหรือขาบวม*

ผลการศึกษา : *ผู้ป่วยที่ได้รับยาโรฟีคอกซิบ และยาวาลดิคอกซิบมีจำนวน 52 และ 54 รายตามลำดับ ผู้ป่วย 1 รายต้องออกจากการศึกษาเนื่องจากได้รับการผ่าตัดอีกครั้งจากมีก้อนเลือดที่แผลผ่าตัด จำนวนผู้ป่วยที่ได้รับยา meperidine ในกลุ่มที่ได้รับยาโรฟีคอกซิบและยาวาลดิคอกซิบเท่ากับ 30 และ 36 รายตามลำดับ ขนาดยา meperidine เฉลี่ยของกลุ่มที่ได้รับยาโรฟีคอกซิบ และยาวาลดิคอกซิบเท่ากับ 25.87 $\pm$ 26.30 และ 23.52 $\pm$ 20.27 มิลลิกรัมตามลำดับ ซึ่งไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ ค่าความรุนแรงของความปวดที่ 2, 6 และ 24 ชั่วโมง ระหว่างสองกลุ่ม ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติเช่นกัน*

สรุป : *ประสิทธิผลการแก้ปวดภายหลังการผ่าตัดบริเวณเต้านมระหว่างยาโรฟีคอกซิบ และยาวาลดิคอกซิบไม่ต่างกันอย่างมีนัยสำคัญ*

คำสำคัญ : *ยาแก้ปวดที่ไม่ใช่สเตียรอยด์, การผ่าตัดบริเวณเต้านม*

Since the advent of selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors), there have been widely used both for acute and chronic pain control because of their advantages over cyclo-oxygenase-1 inhibitors (COX-1 inhibitors) and traditional NSAIDs that they have less effect on platelet function and less gastrointestinal irritation.[1,2] However, there seems to be unreasonable to use of COX-2 inhibitors for acute pain control such as postoperative pain because of the short period of administration that might not be useful for the mentioned advantages. Besides, the rationales for treatment of postoperative pain there have been reported. The first reason is derived from pain mechanism, which composes of peripheral and central sensitizations.[3] The action of NSAIDs on peripheral sensitization is to cut off or reduce prostaglandin that mediates central pain pathway and also reduction of inflammation.[4,5] These ideas lead to the concept of preemptive analgesia. Consequently, COX-2 inhibitors can reduce pain and should be administered before surgery since it has less effect on platelet dysfunction.[3] Secondly, patients who underwent operation usually were on NPO for at least 6-8 hours before and a bit after the surgery. Thus, the GI mucosa might be less injuried by COX-2 than COX-1 inhibitors.[6] Finally, postoperative consumptions of opioids were reduced in case that it was used with NSAIDs, which caused less nausea or vomit, dizziness, ileus and respiratory depression.[7,8] Recently, there have been several studies on the use of COX-2 inhibitors for postoperative pain control; the results of which indicated satisfactory pain reduction.[9-10]

The COX-2 inhibitors are continuously developed until the second generation of COX-2 inhibitors, which has highly selective action on COX-2 enzyme. These newest drugs- valdecoxib, parecoxib, etoricoxib and lumiracoxib are claimed to have less effects on platelet and GI.[11] Moreover, there has been a claim for its better pain control than the first generation in oral surgery.[12] Normally, the newer drug produced means the more expensive cost of the drug. There are still a few studies comparing the first and the second generation of COX-2 inhibitors. Additionally, breast surgery is probably appropriate for using oral form of COX-2 inhibitors, which there has not been any study on COX-2 inhibitor in breast surgery. Thus, the objective of this study was to compare the efficacy of postoperative pain control between the first generation of rofecoxib and the second generation of valdecoxib in breast surgery.

Material and Methods

This study was a prospective, randomized, compare 2 actives, double-blinded study, which was run at King Chulalongkorn Memorial Hospital. The Ethics Committee of the Faculty of Medicine approved the methodology and written informed consent was obtained from each recruited subject. One hundred and seven, 18-65 years-old, female patients with ASA status I-II who were scheduled for breast mass biopsy, excision and mastectomy were recruited into this study. Exclusion criteria were: allergy to meperidine, NSAIDs or sulfa, pregnancy, having renal insufficiency, asthma, peptic ulcer or bleeding tendency. Computer-generated randomization was done into 2 groups; rofecoxib (R) and valdecoxib (V) groups. No premedication was allowed. The study drugs were prepared with code numbers and given to the patient by nurses who were not involved in this

study. Patients in the rofecoxib group received two tablets of rofecoxib 25 mg and the valdecoxib group received two tablets of valdecoxib 20 mg at 1 hour before induction of anesthesia and at 12th hour after the first administration.

Anesthesia was induced with propofol 2 mg kg^{-1} and was maintained with 50 % O2/N2O, 1-3 % isoflurane and fentanyl 0.1 microgram kg^{-1}. Intubation was facilitated by vecuronium 0.1 mg kg^{-1} and maintained with 0.1 mg kg^{-1}per hour. At the end of surgery, residual neuromuscular blockade was antagonized with neostigmine. Postoperative pain control was intravenous meperidine 0.5 mg kg^{-1} and oral paracetamol 1 gm every 4 hours on request.

Patients' age, body weight and height were recorded. The size of the excised mass was categorized by dimension: that was less than 1 cm, under 3 cm and over $\geq$ 3 cm. Dosage of fentanyl, duration of anesthesia was also recorded. The final operation that classified by needle guide biopsy, excision and mastectomy and the final pathological result that categorized by benign and malignant were collected. The primary outcome was the meperidine consumption in the first 24 hours and the number of patient who received meperidine. Numeric pain score 0-10 (VNS: 0= no pain; 10= worst imaginable pain) and numerical satisfaction score 0-10 (Satisfaction score: 0= unsatisfied at all; 10= very satisfied) were self-assessment and collected by data collectors at 2, 6 and 24 hours. All data collectors did not know which drug was given to the patient. Sample size was calculated from the mean difference of meperidine consumption (3.7 mg) and the standard deviations (10.63 and 10.44 mg), which derived from our pilot study. The calculated sample size was 154 subjects per each group (α=0.05 and β=0.2).

Demographic continuous data with normal distribution were tested with student-t test. The categorical and numerical data were tested with chi-square. In case of the expected cell less than 5, the fisher's exact test was used. The amount of meperidine, VNS and satisfaction score used Mann Whitney U test for comparison between two groups. A p-value less than 0.05 indicated statistical significance.

Results

There were 52 and 54 patients randomized into Group R and V respectively. One patient in Group R was excluded due to her re-operation to remove hematoma at 10th hour postoperatively so that the sequence of evaluation was disturbed. Age, weight and height were not of significant difference (Table 1). The size of mass, type of operation, dosage of fentanyl, the final pathological diagnosis and duration of anesthesia were not of significance (Table 2).

Table 1. Demographic data.

	Group R (n= 52)	Group V (n= 54)	P-value
Age (Year)	43.48 ± 12.17	43.09 ± 12.30	0.87
Height (Cm)	157.01 ± 17.46	154.45 ± 8.71	0.35
Body weight (Kg)	56.05 ± 10.93	56.29 ± 10.78	0.92

Table 2. Perioperative conditions.

	Group R (n= 52)	Group V (n= 54)	p-value
Size of mass (n)			0. 45
< 1 cm	3	5	
1-3 cm	30	31	
> 3 cm	20	18	
Type of operation (n)			0.21
Mastectomy	18	15	
Excision	33	34	
Biopsy	1	5	
Total fentanyl (mcg)	75.58 + 29.15	70.83 + 31.62	0.42
Final pathology (n)			0.72
Benign	29	32	
Malignant	23	22	
Duration of anesthesia (Minutes)	102.52 + 52.14	96.30 + 55.54	0.55

The means of accumulated postoperative-24-hour meperidine consumptions were 25.87 + 26.30 mg (95 % CI = 18.72-33.02) in Group R and 23.52 + 20.27 mg (95 % CI = 18.11-28.93) in Group V respectively. Kolmogorov Smirnov tests showed that the accumulated meperidine consumptions in both groups were not normal distribution. There was no significant difference of the accumulated meperidine between the two groups (95 % CI of the mean difference = 6.65-11.35). The number of patients who received meperidine were 30 (57.69 %) in Group R and 36 (66.67 %) in Group V consecutively. There were no statistical significant differences in both the mean accumulated meperidine and the patients received meperidine (p-values = 0.61 and 0.34 respectively). The number of patients who request for paracetamol in 24 hours were 4 in Group R and 7 in Group V respectively (p-value = 0.37).

Table 3. The median scores of VNS and satisfaction scores between two groups.

Scores/ Group	Pain score at			Satisfaction score at		
	2 h	6 h	24 h	2 h	6 h	24 h
Median						
Group R	3	2	0	9	10	10
Group V	3	2	0.5	10	10	10

Note: No statistical significance

The pain scores (VNS) at 2, 6 and 24 hours were not different between the two groups (p- values= 0.85, 0.22 and 0.36 respectively). The satisfaction scores at 2, 6 and 24 hours were not different between the two groups (p-values = 0.38, 0.97 and 0.50 respectively). The median scores of pain and satisfaction scores showed in Table 3.

Discussion

The result showed no statistical difference in the amount of the rescue drug and the numbers of patients who received meperidine within postoperative 24 hours. That probably means this study could not show any difference in efficacy of pain relief of the COX-2 inhibitor, i.e.the first generation of rofecoxib and the second generation of valdecoxib. The result was no surprise, although the first generation of rofecoxib was proved to have the same range of COX-2 selectivity as those of second-generation COX-2 inhibitors, but valdecoxib has earlier onset of action for pain relief. [11] Systematic reviews of COX-2 inhibitors showed rather the same magnitude of NNT (number need to treat), which were 2-3 for both rofecoxib and valdecoxib compared to placebo.[13-14] However, there was another report for a better pain relief score at early post administration (0.5- 1.5 h) of valdecoxib than rofecoxib in oral surgery- (molar extractions), but the time-weighted sum of pain relief within 6 hours post administration were not significant. The onset of action could not be detected in this study because the timing of drug administration, which we administered drugs orally 1 hour before the operation, but 1-4 hours after administration for that study. Also, there was no general anesthesia for molar extractions, in which, the effect of general anesthesia probably caused unreliable pain evaluation at the early postoperative period. It is not surprising that they found valdecoxib has earlier onset of pain relief. However, there was similar magnitude of pain relief within 6 hours after operation for both rofecoxib and valdecoxib. [15] These results supported our findings. So, it is a high probability that rofecoxib and valdecoxib can relief pain of the same range 24-hour postoperatively.

Regarding the number of the subjects, we actually planned for the sample size of 154 per each group. Unluckily, rofecoxib was withdrawn due to a pharmaceutical report of its cardiovascular adverse effect. Consequently, this study had to be undesirably end at 107 patients. These might affect the reliability of the study result due to the low power (power =0.12 calculated from 107 samples).

Regarding of the adverse effects, it was found that a patient in the rofecoxib had hematoma after mastectomy and she needed a reoperation. In this case, there were normal results of coagulation, platelet number and function tests. We could not therefore conclude whether that was caused by rofecoxib since the sample size of the subjects was small. Perhaps, it happened by chance. Also regarding peripheral edema, we could not observe the difference between the two groups due to the small sample size. However, valdecoxib caused salt and water retention to the same magnitude as rofecoxib for the long-term inhibition of renal COX-2. [11]

We therefore conclude that this study could not show the difference in efficacy of post-breast surgery pain relief of rofecoxib and valdecoxib.

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