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Cost-effectiveness of Rofecoxib versus Celecoxib for pain management after thyroid surgery

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Objectives : *To compare the cost and the effectiveness of pain relief between Rofecoxib and Celecoxib in thyroid surgery.*

Design : *Randomized, double-blind, controlled trial study.*

Setting : *King Chulalongkorn Memorial Hospital*

Subjects : *Forty-five patients undergoing elective thyroid surgery were randomly assigned to receive two tablets of either vitamin C 100 mg (placebo group; n=14), Rofecoxib 25 mg (group R; n=15) or Celecoxib 200 mg (group C; n=16).*

Methods : *The assigned drugs were administered orally 1-2 hr before conventional thyroid surgery and general anesthesia. Total 24-hr pethidine consumption, pain, nausea/vomiting scores were recorded at 0, 1, 2, 4, 6, 8, 12 and 24 hr after surgery. Kruskal-Wallis and Chi-square tests were used as appropriate. The effectiveness of pain relief was set at the numerical pain score < 3. The incremental costs for the active comparators, rescued pethidine, and antiemetics were analyzed. Presumably, those were the similar costs of anesthetics, surgical expenses and nursing costs among three groups. The costs for achieving 100 % effectiveness were compared among the three groups.*

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Results : *There were no significant difference in total 24-hr pethidine consumption. Peak pain scores were not significantly different between Rofecoxib and Celecoxib groups but significantly lower than placebo group ($p<0.05$). Percentages of patients achieved the numerical pain score <3 were significantly higher in Rofecoxib and Celecoxib groups at only 2 hr postoperatively. The incremental costs of treatment were 991, 1735 and 1587.20 baht and the averaged costs to achieve 100 % effectiveness were 141.52, 115.67 and 122.09 baht per person in placebo, Rofecoxib and Celecoxib groups, respectively.*

Conclusions : *The administration of Rofecoxib for post-thyroidectomy pain control was more cost-effective than Celecoxib and placebo.*

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

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ปกรณ์ อุรุโสภณ, วัชริน สินธวานนท์, ปิ่น ศรีประจิตติชัย, สุรัญชนา สรเสนา. การศึกษาต้นทุน–ประสิทธิผลของยา Rofecoxib และ Celecoxib สำหรับอาการปวดหลังการผ่าตัดต่อมธัยรอยด์. จุฬาลงกรณ์เวชสาร 2548 ก.ย; 49(9): 509 – 18

เหตุผลของการทำวิจัย : *เนื่องจากมีการใช้ยา Rofecoxib และ Celecoxib กันแพร่หลายในการรักษาอาการปวดแผล หลังการผ่าตัดซึ่งได้ผลค่อนข้างดี แต่ยังไม่มีการศึกษาเปรียบเทียบในแง่ของความคุ้มทุน ผู้วิจัยจึงทำการศึกษาถึงต้นทุนและประสิทธิผลของการใช้ยาดังกล่าว*

วัตถุประสงค์ : *เปรียบเทียบราคาต้นทุนและประสิทธิผลของการใช้ยา Rofecoxib และ Celecoxib ในการผ่าตัดต่อมธัยรอยด์*

รูปแบบการวิจัย : *การศึกษาไปข้างหน้าแบบสุ่มมีกลุ่มเปรียบเทียบ*

สถานที่ทำการศึกษา : *โรงพยาบาลจุฬาลงกรณ์*

วิธีการศึกษา : *ผู้ป่วย 45 รายที่มารับการผ่าตัดต่อมธัยรอยด์ แบ่งออกเป็น 3 กลุ่มโดยตารางสุ่ม ผู้ป่วยจะได้รับยาก่อนการผ่าตัด 1-2 ชั่งโมง โดยกลุ่มควบคุมได้รับ vitamin C 200 มก., กลุ่ม R ได้รับยา Rofecoxib 50 มก. และกลุ่ม C ได้รับยา Celecoxib 400 มก. หลังจากการผ่าตัดจะได้รับการบันทึกอาการปวด โดย verbal numeric score ที่เวลา 0,1,2,4,6, 8, 12 และ 24 ชั่วโมง บันทึกปริมาณ pethidine ที่ได้รับและการรักษาอาการข้างเคียงที่เกิดขึ้น ศึกษาประสิทธิผลของยาที่ทำให้ VNS < 3 และต้นทุนที่เพิ่มขึ้นจากการใช้ยาแก้ปวด ยาแก้อาการข้างเคียงที่เกิดขึ้น จากนั้นเปรียบเทียบต้นทุนที่ทำให้ได้ประสิทธิผล 100 %*

ผลการศึกษา : *พบว่าไม่มีความแตกต่างในปริมาณของยา pethidine ที่ใช้และอาการข้างเคียงที่เกิดขึ้น กลุ่มควบคุมจะมี VNS สูงกว่าอีก 2 กลุ่ม แต่ไม่ต่างกันระหว่างกลุ่ม R และกลุ่ม C จำนวนของผู้ป่วยที่มี VNS < 3 ในกลุ่ม R และ C จะมีปริมาณสูงกว่าอย่างมีนัยสำคัญที่เวลา 2 ชั่วโมง ต้นทุนที่เพิ่มขึ้นในกลุ่มควบคุม, กลุ่ม R และกลุ่ม C คือ 991, 1735 และ 1587.20 บาท และต้นทุนที่ทำให้มีประสิทธิผล 100 % เฉลี่ยต่อคนคือ 141.52, 115.67 และ 122.09 บาทตามลำดับ*

สรุป : *การให้ยา Rofecoxib ร่วมไปด้วยเพื่อรักษาอาการปวดหลังการผ่าตัดต่อมธัยรอยด์จะมีความคุ้มทุนกว่าการใช้ยา Celecoxib และการใช้ยา pethidine อย่างเดียว*

คำสำคัญ : *NSAIDs: COX-2 inhibitor, การผ่าตัดต่อมธัยรอยด์*

Understanding of pain mechanisms has encouraged the development of new strategies for pain control based on multimodal analgesic technique. Non-steroidal anti-inflammatory drugs (NSAIDs) gain more important role, especially Rofecoxib and Celecoxib. They offer pain-relieving benefits similar to conventional NSAIDs [1-3] with fewer gastrointestinal effects [4-7] and no interference with coagulation system. [8] Many clinical trials demonstrated the efficacy and safety of Rofecoxib and Celecoxib for postoperative pain, including in orthopedic surgery, [9,10] urologic surgery [11] and ear, nose and throat surgery. [8, 12] Also, there was a study indicating a better pain relief of Rofecoxib than Celecoxib in thyroid surgery. [13] However, there is still no clinical trial comparing the cost-effectiveness of these drugs. Thus, this study is aimed to reveal and compare the effectiveness for pain relief regarding to the incremental costs among Rofecoxib, Celecoxib and conventional analgesics in thyroid surgery.

Materials and Methods

This study was a prospective, randomized, controlled, double-blind study, which was conducted at King Chulalongkorn Memorial Hospital. The Ethics Committee of the Faculty of Medicine, Chulalongkorn University has approved the methodology. Written informed consent was obtained from each patients. Patients undergoing elective thyroid surgery with American Society of Anesthesiologists Physical Status I-II and body weight > 45 kg were eligible for enrollment. Exclusion criteria included allergy to NSAIDs, sulfa or pethidine, history of gastrointestinal ulcer, bleeding diathesis, renal insufficiency, asthma or pregnancy. They were assigned to one of three groups: placebo (P), Rofecoxib (R), and Celecoxib (C), according to a computer-generated table of random numbers. Patients in P, R and C groups were given either 2 tablets of vitamin C 100 mg, Rofecoxib 25 mg or Celecoxib 200 mg, consecutively. The assigned drugs were prepared by code number and administered orally 1-2 hr before surgery by nurses who were not involved in the study.

General anesthesia was induced with propofol 2 $mg.kg^{-1}$ and fentanyl 1 $mcg.kg^{-1}$. Tracheal intubation was facilitated with vecuronium 0.1 $mg.kg^{-1}$. Anesthesia was maintained with 1-3 % isoflurane in 50 % oxygen/nitrous oxide. At the end of the surgery, residual neuromuscular blockade was antagonized with 2.5 mg of neostigmine and 1.2 mg of atropine intravenously.

Numerical pain score 0-10 (VNS: 0 = no pain, 10 = worst pain imaginable) was evaluated after 15 minutes in post anesthetic care unit (PACU). If pain VNS $\geq$ 3, pethidine 0.5 $mg.kg^{-1}$ was given intravenously every 15 min until the pain VNS < 3. The VNS was recorded at 1, 2, 4, 6, 8, 12 and 24 hr. At surgical ward, pethidine 0.5 $mg.kg^{-1}$ was ordered as a rescue drug when the pain VNS $\geq$3. Nausea and vomiting were evaluated by using numerical score 0-3 (nausea/vomiting score: 0 = no symptom, 1 = mild nausea, 2 = severe nausea and 3 = vomit). Ondansetron 4 mg was administered intravenously once nausea/vomiting score >0. Numerical satisfaction score 0 - 10 (satisfaction score: 0 = unsatisfied at all; 10 = very satisfied) was evaluated at 24 hr. All data were obtained by registered nurses on duty who did not know the study drugs.

Patients' age, body weight and height were recorded. The size of thyroid glands was categorized

by diameter $\leq$ 5 cm and over 5 cm. The total 24 hr pethidine consumption, peak pain score and the number of patients having pain VNS < 3 were assessed. Peak nausea/vomiting score and the number of nausea or vomiting treatment were recorded. The continuous data with normal distribution were tested with ANOVA and post Hoc tests. The categorical and numerical data were tested with Kruskal-Wallis test and Mann-Whitney U test for inter-group comparison. A p-value of less than 0.05 indicated statistical significance.

Cost analysis was measured by an incremental variable cost which composed of cost of the study drug, the pain rescue drug, the antiemetic drug and syringe with needles (multiply with number of treatment). The effectiveness of pain control was set at the pain VNS < 3. Percentages of patients who had the pain VNS < 3 were processed to cost-effectiveness analysis.

Results

There were 14, 15 and 16 patients in placebo, Rofecoxib and Celecoxib groups respectively. There was no significant difference among three groups in age, weight, height, gender, thyroid mass size and duration of surgery and anesthesia (Table 1).

The pain scores at 1,4,6,8,12 and 24 hr were not significantly different among three groups. Only the peak pain score at 2 hr in placebo group was significantly higher than others, but there was no significant difference between Rofecoxib and Celecoxib groups (Table 2). Percentages of patients achieved the pain VNS < 3 were significantly higher in both Rofecoxib and Celecoxib groups only at 2 hr after surgery (Figure 1). There was no significant difference among three groups in the total 24 hr pethidine consumptions, peak nausea/vomiting scores and number of nausea/vomiting treatment. Peak satisfaction score also showed no statistical difference (Table 2).

Table 1. Demographic data.

	Placebo (n = 14)	Rofecoxib (n = 15)	Celecoxib (n = 16)	p-value
Age (yr)	39.57 $\pm$ 9.85	38.60 $\pm$ 10.70	40.62 $\pm$ 11.30	0.91
Weight (kg)	60.52 $\pm$ 12.93	56.10 $\pm$ 7.21	62.43 $\pm$ 13.34	1.00
Height (cm)	156.0 $\pm$ 4.69	157.76 $\pm$ 4.19	159.24 $\pm$ 6.36	0.16
Gender (M/F)(n)	1/13	0/15	3/13	0.88
Surgery time (min)	113.93 $\pm$ 62.89	90.60 $\pm$ 35.55	104.12 $\pm$ 19.61	0.81
Anesthesia time (min)	135.0 $\pm$ 66.32	113.37 $\pm$ 37.00	133.44 $\pm$ 23.41	0.81
Intraoperative fluid administration (mL)	1264.29 $\pm$ 890.0	893.31 $\pm$ 486.22	1109.16 $\pm$ 432.91	0.52

Note: Values are mean $\pm$ SD and numbers (n).
No statistical significance

Table 2. Peak pain, nausea/vomiting and satisfaction scores, total 24-hr pethidine consumption and the number of treatment.

	Placebo (n = 14)	Rofecoxib (n = 15)	Celecoxib (n = 16)	p-value
Peak pain score (0 -10)	6.5 (4 -10)	5 (1-8)*	5 (2-10)*	0.09
Total 24- hr of pethidine consumption (mg)	72	40	65	0.54
Patients received pain treatment (number)	12	7	8	0.32
Peak nausea score (0 -3)	1 (0-3)	0 (0-3)	1 (0-3)	0.66
Patient received N/V treatment (number)	6	4	2	0.47
Satisfaction score (0 -10)	8 (5-9)	9 (6-10)	9 (6-10)	0.76

Note: Values are mean, median (with interquartile ranges) for the scores.

*$P < 0.05$ versus placebo group.

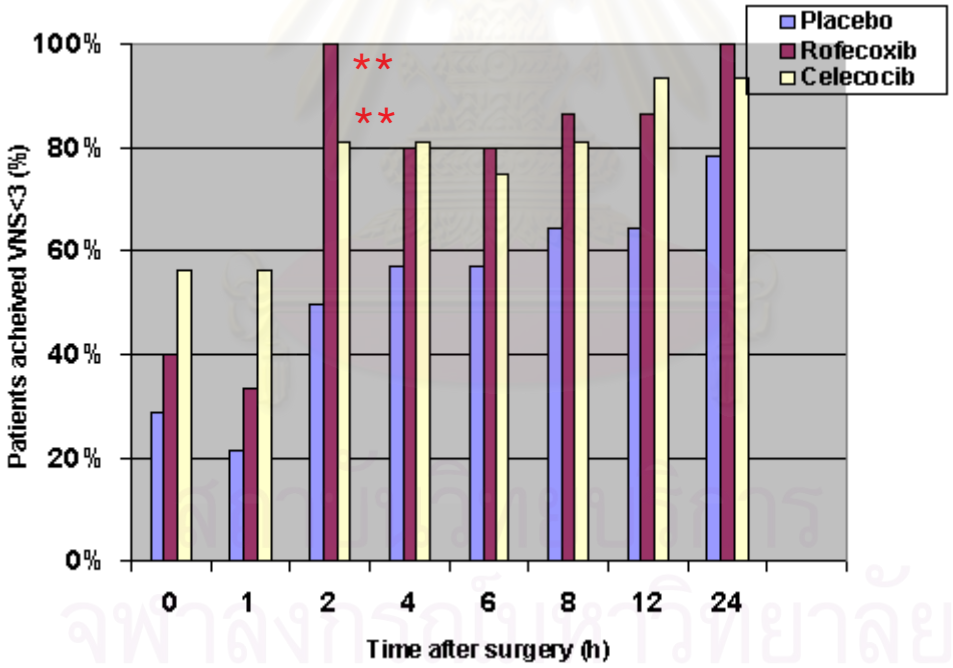

Figure 1. Percentage of patients achieved pain VNS <3 at postoperative period.

Note: ** P <0.05 compared to placebo

The cost analysis revealed the additional costs of P, R and C groups were 991, 1735 and 1587.2 baht, respectively. Effectiveness of pain relief (the pain VNS < 3) at 2 hr were 50,100 and 81.25 %. The total costs to achieved 100 % effectiveness were; 1982, 1735 and 1953.48 baht in P, R and C groups respectively. And the cost-effective ratio were 141.52, 115.67 and 122.09 baht per person (Table 3).

Table 3. The incremental cost of treatment and cost-effectiveness analysis.

	Placebo (n = 14)	Rofecoxib (n = 15)	Celecoxib (n = 16)
Cost of study drugs (baht)	2	1068	851.20
Cost of rescued pethidine (baht)	828	529	667
Cost of antiemetic drug (baht)	161	138	69
Total incremental cost (baht)	991	1735	1587.20
Effectiveness (%)	50	100	81.25
The averaged cost per person (baht) / cost-effective ratio	141.52	115.67	122.09

Discussion

The study showed that both Rofecoxib and Celecoxib provided better pain relief for post-thyroid surgery than placebo. This finding was similar to previous reports, which were conducted in dental surgery, orthopedic surgery, urologic surgery and also ENT surgery. [1, 2, 8-12] However this study could not reveal the significant difference of pain relief between Rofecoxib and Celecoxib as stated in a previous study. [13] This might be explained by the difference in dosage of Celecoxib. We designed to compare 50 mg of Rofecoxib with 400 mg of Celecoxib instead of 200 mg as in previous study since they were equipotent analgesic dosage of these two drugs. [19]

Unsurprisingly, we could not detect difference of the pain scores at any time among three groups because the rescued pethidine was administered once the VNS pain score >3. Thus, the maximal pain score at any time (the peak pain score) should be used for a comparison since we frequently evaluated pain score. We found that percentages of patients achieved pain VNS < 3 were significantly higher in both Rofecoxib and Celecoxib than placebo at 2 hr after surgery. These could be easily explained by the pharmacokinetics of both drugs that they will reach maximal plasma concentrations about 2-4 hr after oral administration. [19] The higher percentages of patients achieved pain VNS < 3 of both Rofecoxib and Celecoxib at the other postoperative evaluation times could be noticed (Figure 1). But this study could not demonstrate any statistical difference which could possibly caused by the small sample size. At the beginning, we planed to have the sample size of 30 in each group since it was the smallest sample size for non normal distribution data such as pain score and pethidine requirement in comparison test. Moreover, because this study aimed to analyze the expenditure, the reasonably large sample size would provide more accuracy in cost analysis. Unfortunately, Rofecoxib was withdrawn from the market due to a pharmaceutical report of adverse cardiovascular events. Consequently, this study had undesirably ended at the total of 45 patients. However there had been a significant pain relief at 2 hr postoperatively in active comparators in spite of the small sample size. Also there was a study of

cost-efficacy of Rofecoxib comparing with placebo demonstrated the number of patients who needed rescued analgesics were 7 in 37 and 23 in 36. Base on that study, the calculated sample size should be 14 for each group, which was similar to our sample size.[20]

The incremental cost of pain treatment was able to be used for cost analysis since we assumed that the expense of anesthesia, surgery, admission and labor costs were similar for those who underwent uncomplicated thyroidectomy. The incremental variable cost of pain treatment was supposed to be the summation of all costs for pain killer drugs and the treatment for their side effects. Placebo group had the lowest and Rofecoxib group had the highest incremental costs because the price of Rofecoxib 25 mg is higher than of Celecoxib 200 mg. However, Rofecoxib provides much more pain relief than the others as there was no patient having the pain VNS $\geq$ 3 at 2 hr postoperatively. Thus, if the consideration was taken with the effectiveness of pain relief, the expense of Rofecoxib group was lower than the others. Similarly, the average cost per person in Rofecoxib group confirmed that it was more cost-saving than Celecoxib and both were lower than traditional opioid treatment group. Despite the result of Rofecoxib, preoperative Celecoxib should be administered to provide the better pain control and reduce the expense of post-thyroidectomy pain treatment.

We conclude that Rofecoxib and Celecoxib provide better pain relief than traditional pethidine in thyroid surgery. Preoperative rofecoxib administration had the most cost-saving, and Celecoxib had more cost-saving than only traditional postoperative pethidine administration regarding to the same effectiveness of pain relief.

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