Original article

Combination of gabapentin and celecoxib for analgesia after major orthopedic surgery: a randomized, controlled trial

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Background: The use of analgesics with different mechanism of action enhances post-operative pain relief by opioids. Both celecoxib and gabapentin have opioid-sparing effect, but it is unclear whether combination of the two drugs accentuates postoperative analgesia and further reduced opioid requirement.

Objective: Determine whether the perioperative use of celecoxib in combination with gabapentin reduces the amount of post-operative opioid consumption in comparison to celecoxib alone or gabapentin alone in patients that have major orthopedic surgery.

Materials and methods: Randomized double-blinded placebo controlled trial was done in 99 patients underwent major orthopedic surgery. They were randomly allocated into four groups. One to two hours before anesthesia, they received midazolam 7.5 mg plus study drugs. Group P received placebo plus placebo at 12 and 24 hours later. Group C received celecoxib 400 mg plus celecoxib 200 mg at 12 and 24 hour later. Group G received gabapentin 400 mg plus gabapentin 300 mg at 12 and 24 hour later. Finally, group CG received celecoxib 400 mg + gabapentin 400 mg plus celecoxib 200 mg + gabapentin 300 mg at 12 and 24 hour later. The patients underwent surgery under general anesthesia. Post-operative pain was treated by intravenous morphine patient-controlled analgesia.

Results: Median morphine consumption (minimum-maximum) in twenty-four hours was 18.0, 15.0, 15.5, and 8.0 mg, in group P, C, G, and CG, respectively. The group CG significantly consumed less morphine (41%) in 24 hour than group G, but not significantly less (38%) than group C. Pain score, sedation score, and nausea/vomiting at post-operative hour 1, 4, 8, 12, 16, 20, and 24 was not significantly different.

Conclusion: Combination of celecoxib and gabapentin further accentuated post-operative analgesia by morphine comparing to celecoxib or gabapentin alone without change in pain score and other side effects of the medications.

Keywords: Analgesia, celecoxib, gabapentin, multimodal analgesia, opioid-sparing, orthopedic surgery, postoperative, pain

Major orthopedic surgery, such as spine, major limb, and joint, usually causes moderate-to-severe postoperative pain that requires strong opioids to relief. The merit of strong opioids in severe pain reduction is obscured by its dose-related unwanted side effects. The concurrent use of more than one analgesic agent provided effective analgesia with smaller doses of each component, thereby minimizing adverse effects.

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Multimodality approaches for the treatment of postoperative pain have been widely practiced. Recently, several types of drug have been reported in many clinical trials, especially non-steroidal anti-inflammatory drugs (NSAIDs) and coxibs. These drugs provide analgesic effect by inhibition of prostaglandins synthesis at the site of tissue injury and in the central nervous system. When given in perioperative period, they have shown significant opioid-sparing effect, reduction in opioid analgesic consumption, postoperative pain reduction, and patient satisfaction compared with placebo [1].

Gabapentin is an anti-epileptic drug that has demonstrated analgesic effect in neuropathic pain. Recently, it has been effectively used to reduce pain and opioid requirement during postoperative period of various kinds of surgery [2-4]. Some trials showed that the side effects of opioids such as vomiting and pruritus were reduced and the sedation increased [2, 5-7]. Gabapentin provides analgesia by binding to the α_2 -d subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P from presynaptic afferent neurons [8]. It is generally safe and has no clinically important drug interactions. The main dose-limiting side effects are somnolence and dizziness [9].

While celecoxib and gabapentin produce analgesia by different mechanisms, a question was raised if the combinations of opioid-sparing drugs in major surgery would provide additive or synergistic effect in postoperative pain relief. Few trials were done to directly evaluate the combination. In addition, two of them were the studies of gabapentin plus rofecoxib, an obsolete coxib [5, 10]. One trial reported the use of meloxicam and gabapentin [11]. There is no study comparing combination of gabapentin plus celecoxib with either drug alone in the treatment of pain after major orthopedic surgery. In this study, we evaluated the efficacy and side effects of combination of celecoxib and gabapentin comparing to celecoxib alone or gabapentin alone in alleviation of pain after major orthopedic surgery. Primary outcome measurement was 24-hour postoperative morphine consumption and the secondary outcomes were pain score, opioid-related adverse effects, and patient satisfaction.

Materials and methods

The study was designed as a randomized, placebo controlled, double-blind trial. It was approved by the Ethics Committee of the Faculty of Medicine Ramathibodi Hospital.

The patients who underwent major orthopedic surgery at Ramathibodi Hospital and had all of the inclusion criteria and none of the exclusion criteria were included. The major orthopedic surgery was defined as major spinal surgery (decompression or fixation or reconstruction, not include minor surgery such as microdiscectomy and vertebroplasty), reconstructive surgery of the shoulder, elbow, hip and knee, major tumor resection and amputation of the extremities and sacrum, and major limb surgery.

The inclusion criteria were the age 18-80 years

old, American Society of Anesthesiology (ASA) physical status I, II, or III, and personally signed and dated informed consent document.

The exclusion criteria were patient allergic to the trial drugs and sulfonamides, patient with a history of coagulopathy, thromboembolic event, unstable angina, myocardial, or cerebral infarction within one year prior to operation, and woman with plasma creatinine >100 $\mu\text{mol/L}$ and >115 $\mu\text{mol/L}$ in men. Exclusion included pregnant woman or in lactation period, participation in any other studies, and history of significant alcohol, analgesic, or narcotic substance abuse within six months prior to screening.

The participants were randomly allocated into four treatment groups with a 1:1 ratio to either group. The randomization allocation was done by a statistician. The code was concealed in a sealed opaque envelop. Patients, doctors, and nurses were blinded to the treatment. The placebo drugs were produced in the forms identical to the active counterparts to conceal allocation group from both patients and evaluators.

Intervention

The patient was visited the day before surgery to enroll the study. An investigator taught the patient how to use the pain assessment tool and PCA device. One to two hours before anesthesia, the patient took midazolam 7.5 mg orally as premedication together with the drug according to his/her group allocation. The patients were allocated into four groups. The first group was placebo group (Group **P**). They received placebo celecoxib + placebo gabapentin followed by placebo celecoxib + placebo gabapentin 12 and 24 hours later. The second group was the Celecoxib only group (Group **C**). They received celecoxib 400 mg + placebo gabapentin followed by celecoxib 200 mg + placebo gabapentin 12 and 24 hours later. The third group was the Gabapentin only group (Group **G**). They received placebo celecoxib + gabapentin 400 mg followed by placebo celecoxib + gabapentin 300 mg 12 and 24 hours later. The last group was the combination group (Group **CG**). They received celecoxib 400 mg + gabapentin 400 mg followed by celecoxib 200 mg + gabapentin 300 mg 12 and 24 hours later. The drugs used were celecoxib (Celebrex[®], Pfizer, Illertissen, Germany) and gabapentin (Neurontin[®], Pfizer, Freiburg, Germany).

All the patients underwent surgery under general anesthesia. Anesthesia was induced with propofol (2 mg/kg) or pentothal (4mg/kg), and maintained with

morphine 0.1 mg/kg and either Isoflurane, Sevoflurane, or Desflurane in 50% N₂O and O₂. Neuromuscular blocking agent was used as required. Intra-operative morphine used was recorded.

In the operating theatre, the data recorded were patient's baseline data (age, sex, body weight, type of surgery, surgical time, and intra-operative blood loss), vital signs and O₂ saturation. In the post-anesthesia care unit (PACU), patient was asked to rate his/her pain every 15 minutes using a numerical rating scale (NRS) ranging from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain. Analgesia, if required, was initially managed with intravenous morphine 1-2 mg every 15 minute until the pain was relieved. The loading dose of morphine was recorded. The patient was connected to a PCA pump (IVAC®) on arrival to the wards. Initial setting was patient-controlled dose 1-2 mg, lockout interval eight minutes, and four-hour limit 40 mg. The incremental dose was increased to 2-2.5 mg, and the four-hour limit was increased to 50 mg if analgesia was inadequate after one hour. If analgesia remained inadequate after an additional hour, the incremental dose was further increased to 3.0 mg, and the four-hour limit was increased to 60 mg.

Outcome measurement and data collection

The outcome assessors were the principal investigator and well-trained orthopedic ward nurses and evaluated the patients the day before surgery and postoperatively. The primary outcome was total morphine requirement in 24 hours. The cumulative morphine consumption at hour 1, 4, 8, 12, 16, 20 and 24 hour were also recorded. Time zero was the time the patient arrived in PACU. The secondary outcomes were pain score at 1, 4, 8, 12, 16, 20, and 24 hours postoperatively using NRS, sedation score, nausea, vomiting, dizziness, other side effects, and patient satisfaction.

Sedation score was graded into five categories as the following: 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus and 5 = asleep and not responsive to any stimulus. Nausea/vomiting classified as follow: 0 = not present, 1 = nausea, 2 = vomit and 3 = repeated vomit or need treatment. Other side effects were recorded as dichotomous data, yes or no.

Major surgical error such as malpositioning of the prosthesis, incorrect osteotomy, and direct major nerve

injury were considered 'drop out' because this situation might alter postoperative pain and patient's psychological condition and satisfaction. In addition, patients who could not take the studied drugs by mouth postoperatively were also considered 'drop out'. The data was treated as 'per protocol'.

Statistical analysis

Sample size was calculated from mean morphine consumption in 24 hours of previous study using nQuery advisor 6.01 program to calculate as factorial design, two-way ANOVA, type I error = 0.05, type II error = 0.2. The calculated sample size was 24 subjects per group. When calculated 20% of subjects added to compensate drop out, the sample size was 28 subjects per group, overall of 112 subjects. The data was analyzed by SPSS version 15 program to demonstrate the outcomes.

The baseline demographic characteristics; age, body mass index (BMI), and anesthetic time were presented as mean $\pm$ SD. Intra-operative blood loss and intra-operative morphine used were presented as median, minimum, and maximum. The test used to compare intra-operative blood loss, intra-operative morphine used and blood pressure between groups was Kruskal-Wallis test. Gender, physical status, and operative types were categorical data and were presented as numbers and percents. Chi square's test was done to compare among those groups.

Post-operative morphine consumption included morphine used in PACU plus at the wards. Analysis of cumulative dose of morphine consumption in 24-hour and pain score at time interval: hour 1, 4, 8, 12, 16, 20, and 24 was done by Kruskal-Wallis. When there was significant difference at any time, three pair-wise comparisons by Mann-Whitney U tests were done to demonstrate difference in morphine consumption or pain score between groups at each hour. To maintain the overall significance level at 0.05, p-value for each of three pair-wise comparisons was compared with a new significance level of 0.0167 according to the Bonferroni adjustment.

Sedation score, nausea and vomiting, other complications was analyzed by Chi square's or Fisher's exact test. Satisfaction score was presented as the percentage of patients who had score >8 and was analyzed by Chi square's test.

Results

Ninety-nine patients completed the trial. Thirteen

participants dropped out. The reasons for the drop outs were inadvertent intra-operative ondansetron to prevent nausea/vomiting in three cases, the operations were cancelled three cases, regional anesthesia instead of general anesthesia in two cases, fentanyl used instead of morphine in two cases, local anesthesia infiltration at the surgical sites by surgeons in two cases, and the used of intra-operative valdecoxib in one case. Out of 99 participants, 24, 23, 26, and 26 were in Placebo (P), Celecoxib only (C), Gabapentin only (G), and Celecoxib+Gabapentin (CG) group, respectively.

Demographic characteristics

The demographic characteristics of participants are shown in **Table 1**. There was no statistical significant difference in age, gender, ASA physical status, and body mass index (BMI) between the four study groups. Anesthetic time, intra-operative blood loss, intra-operative morphine doses, and distribution of type of operation were also comparable. There was no inadvertent event during the anesthesia and surgery.

Table 1. Demographic data of the participants and clinical characteristics.

	Treatment group				P-value
	Placebo (n = 24)	Celecoxib (n = 23)	Gabapentin (n = 26)	Celecoxib + Gabapentin (n = 26)	
Age	50.4 ± 13.6	53.6 ± 15.9	44.7 ± 19.4	50.4 ± 17.0	0.415
Gender					
Male	14 (58.3%)	10 (43.5%)	17 (65.4%)	12 (46.2%)	0.378
Female	10 (41.7%)	13 (56.5%)	9 (34.6%)	14 (53.8%)	
ASA physical status					
I	6 (25.0%)	9 (39.1%)	10 (38.5%)	6 (23.1%)	0.258
II	11 (45.8%)	13 (56.5%)	14 (53.8%)	16 (61.5%)	
III	7 (29.2%)	1 (4.3%)	2 (7.7%)	4 (15.4%)	
Body mass index	24.2 ± 3.1	24.4 ± 3.5	24.3 ± 3.7	24.1 ± 3.3	0.988
Anesthetic time (minute)	200.2 ± 96.4	191.5 ± 68.3	191.9 ± 93.2	195.5 ± 97.2	0.973
Intra-operative blood loss (mL)					
Median	140	150	100	50	0.329
Range	0 - 3000	0 - 1600	0 - 2000	0 - 1800	
Intra-operative morphine (mg)					
Median	8.0	9.0	8.0	7.0	0.329
Range	5 - 16	3 - 13	5 - 14	2 - 10	
Operation					
Spine	6 (25.0%)	6 (26.1%)	6 (23.1%)	6 (23.1%)	0.464
Major joint	14 (58.3%)	10 (43.5%)	12 (46.2%)	13 (50.0%)	
Tumor	2 (8.3%)	0 (0%)	0 (0%)	0 (0%)	
Major limb	2 (8.3%)	7 (30.4%)	8 (30.8%)	7 (26.9%)	

Morphine consumption

Figure 1 demonstrates comparison of cumulative morphine consumption between treatment groups at

each hour interval. Descriptive statistics of morphine consumption in 24 hours postoperatively is shown in **Table 2**.

Fig. 1 Comparison of morphine consumption between groups in time from 1 to 24 hours. The combination group had less morphine consumption than both C and G group at every time interval.

Table 2. Cumulative morphine consumption (mg) at different times in 24 hours post-operatively. The difference in morphine consumption was significant only at hour 24 and 20.

Cumulative morphine consumption at hour	Group (median, minimum-maximum)				P-value
	Group P	Group C	Group G	Group CG	
1	2.5 (0-9)	4.0 (0-8)	2.5 (0-10)	2.0 (0-7)	0.482
4	5.0 (0-14)	5.0 (0-18)	4.5 (0-11)	4.0 (0-18)	0.417
8	8.0 (0-19)	7.0 (1-18)	6.0 (0-15)	4.0 (0-24)	0.088
12	9.0 (0-37)	8.0 (2-18)	8.5 (0-17)	5.5 (0-24)	0.095
16	11.0 (1-50)	10.0 (2-24)	10.5 (0-24)	6.0 (0-26)	0.068
20	14.0 (1-63)	12.0 (2-24)	13.5 (0-33)	7.0 (0-36)	0.017*
24	18.0 (1-63)	15.0 (2-30)	15.5 (0-37)	8.0 (0-38)	0.007*

* Statistical significant ($p \leq 0.05$).

Three pairwise comparisons by Mann-Whitney U tests were done to demonstrate difference in morphine consumption between groups at hour 20 and 24 ($p=0.0167$) shows significant difference. The group G significantly consumed more morphine in 20 and 24 hours than the group CG ($p=0.011$ and 0.006) but the group C did not ($p=0.048$ and 0.049). In addition, group C was not significantly different from group G ($p=0.703$ and 0.528).

Pain score

Pain score from NRS showed no significant difference between the four groups at all time interval except hour 24 (p -value 0.014) as shown in **Table 3**. Comparing group by group at hour 24, no significant difference was found.

Sedation score

Sedation scores were significantly different at hour 4 and 8 (Fisher's exact test, $p=0.0174$ and 0.045 , respectively). However, when compared group by

group at hour 4 and 8, no difference was found ($p=0.881$ and 0.170 for hour 4 and 8 in **C** vs. **G**, 0.31 and 0.083 for hour 4 and 8 in **C** vs. **CG**, and 0.117 and 0.667 for hour 4 and 8 in **G** vs. **CG**, respectively).

Nausea and vomiting, other complications and patient satisfaction

There was no difference regarding nausea/vomiting between the four groups at any time point. Moreover, other complications such as: itching, urinary retention, dizziness, somnolence, and ileus were not significantly different as shown in **Table 4**. Patients who had satisfaction score $>8/10$ were not different between the four groups.

Blood pressure and respiratory rate

There was no difference regarding systolic and diastolic blood pressure together with respiratory rate between the four groups at any time point as shown in **Table 5**.

Table 3. Pain score (NRS) in time from 1 to 24 hours.

Pain score at hour	Group: Median (minimum-maximum)				P-value
	Group P (n = 24)	Group C (n = 23)	Group G (n = 26)	Group CG (n = 26)	
1	6.0 (0-10)	6.0 (0-10)	6.5 (0-10)	5.0 (0-10)	0.681
4	6.0 (0-10)	5.0 (0-10)	5.0 (0-10)	3.0 (0-10)	0.223
8	4.5 (0-10)	3.0 (0-9)	5.0 (0-10)	3.0 (0-6)	0.049
12	3.5 (0-10)	4.0 (0-7)	3.0 (0-9)	2.0 (0-9)	0.558
16	4.0 (0-10)	3.0 (0-6)	4.0 (0-8)	4.0 (0-8)	0.690
20	4.5 (0-9)	3.0 (0-8)	4.0 (0-10)	3.0 (0-5)	0.149
24	3.5 (0-7)	3.0 (0-8)	3.0 (0-8)	1.0 (0-6)	0.014*

*Statistical significant ($p < 0.05$).

Table 4. Other postoperative complications in 24 hours.

Complications	Treatment group (number, %)				P-value
	Group P (n=24)	Group C (n=23)	Group G (n=26)	Group CG (n=26)	
Itching	2 (8.3)	0 (0)	0 (0)	0 (0)	.109
Urinary retention	0 (0)	0 (0)	1 (3.8)	1 (3.8)	1.00
Dizziness	1 (4.2)	0 (0)	0 (0)	1 (3.8)	.861
Somnolence	0 (0)	0 (0)	1 (3.8)	1 (3.8)	1.00
Ileus	0 (0)	0 (0)	0 (0)	1 (3.8)	1.00

Table 5. Blood pressure respiratory rate.

BP		Treatment group (mean $\pm$ SD)				P-value
		Group P (n=24)	Group C (n=23)	Group G (n=26)	Group CG (n=26)	
Hour 1	SBP	133.7 $\pm$ 17.4	124.3 $\pm$ 18.2	132.0 $\pm$ 19.3	125.0 $\pm$ 20.6	0.219
	DBP	75.5 $\pm$ 9.5	69.7 $\pm$ 10.4	76.3 $\pm$ 11.0	72.5 $\pm$ 9.8	0.141
	RR	19.7 $\pm$ 2.0	19.1 $\pm$ 1.9	18.7 $\pm$ 2.1	19.6 $\pm$ 2.4	0.223
Hour 4	SBP	125.0 $\pm$ 15.3	115.7 $\pm$ 12.0	125.4 $\pm$ 16.8	118.5 $\pm$ 14.1	0.048
	DBP	73.8 $\pm$ 9.7	69.1 $\pm$ 10.8	71.1 $\pm$ 10.5	68.5 $\pm$ 9.8	0.201
	RR	18.8 $\pm$ 1.5	18.7 $\pm$ 1.4	19.1 $\pm$ 1.4	18.8 $\pm$ 2.0	0.767
Hour 8	SBP	121.8 $\pm$ 19.2	115.7 $\pm$ 14.1	120.0 $\pm$ 15.3	117.7 $\pm$ 16.8	0.738
	DBP	71.8 $\pm$ 10.1	66.5 $\pm$ 9.3	73.2 $\pm$ 8.5	68.5 $\pm$ 7.8	0.089
	RR	19.4 $\pm$ 1.5	18.8 $\pm$ 1.3	19.1 $\pm$ 1.3	18.4 $\pm$ 1.9	0.137
Hour 12	SBP	121.8 $\pm$ 20.6	116.4 $\pm$ 14.3	117.7 $\pm$ 14.8	114.2 $\pm$ 12.8	0.762
	DBP	73.6 $\pm$ 10.5	67.3 $\pm$ 12.0	68.2 $\pm$ 11.0	68.5 $\pm$ 9.2	0.106
	RR	19.5 $\pm$ 1.4	19.3 $\pm$ 1.2	19.4 $\pm$ 1.4	19.5 $\pm$ 1.0	0.724
Hour 16	SBP	127.0 $\pm$ 20.3	117.6 $\pm$ 14.1	118.1 $\pm$ 13.6	113.5 $\pm$ 13.4	0.100
	DBP	73.0 $\pm$ 11.5	71.0 $\pm$ 10.0	70.0 $\pm$ 8.9	66.3 $\pm$ 8.8	0.430
	RR	19.6 $\pm$ 0.8	19.3 $\pm$ 1.5	19.8 $\pm$ 1.2	19.8 $\pm$ 0.8	0.367
Hour 20	SBP	122.1 $\pm$ 13.2	117.4 $\pm$ 13.2	118.8 $\pm$ 13.1	111.6 $\pm$ 14.1	0.056
	DBP	72.9 $\pm$ 9.1	70.0 $\pm$ 9.5	71.2 $\pm$ 7.1	67.0 $\pm$ 10.6	0.192
	RR	19.7 $\pm$ 1.1	19.5 $\pm$ 1.2	19.8 $\pm$ 1.5	19.8 $\pm$ 0.9	0.606
Hour 24	SBP	123.8 $\pm$ 13.5	117.0 $\pm$ 12.2	120.0 $\pm$ 19.6	115.4 $\pm$ 13.9	0.249
	DBP	72.1 $\pm$ 8.8	70.4 $\pm$ 9.3	73.5 $\pm$ 10.2	67.1 $\pm$ 12.0	0.545
	RR	19.8 $\pm$ 1.2	19.7 $\pm$ 0.9	19.8 $\pm$ 1.6	19.8 $\pm$ 0.9	0.606

SBP = systolic blood pressure, DBP = diastolic blood pressure, RR = respiratory rate.

Discussion

The study showed that morphine consumption in the combined celecoxib and gabapentin was reduced by 55% compared to placebo group, 8.0 (0-38) *vs.* 18.0 (1-63) mg. The combination was yet not as strong as morphine and could not replace it in relieving postoperative pain. Even though the morphine consumptions in this study were not big doses compared to previous studies [12-14], the difference in morphine used was shown. Celecoxib alone reduced mean morphine requirement about 30% compared to placebo (14.7 $\pm$ 8.3 *vs.* 20.8 $\pm$ 15.1 mg), and 17% by median 15.0 (2-30) *vs.* 18.0 (1-63). But gabapentin did only 21% (16.4 $\pm$ 8.7 *vs.* 20.8 $\pm$ 15.1 mg) by considering mean and about 14% ;15.5 (0-37) *vs.* 18.0 (1-63); by median. There were few trials directly compared the combination drugs [5, 10] but using rofecoxib, a potent COX2 inhibitor. Turan, et al, in order to test the same hypothesis as in our study, found that total morphine requirement was decreased by 43%, 24%, and 50% in patients receiving rofecoxib 50 mg/day, gabapentin 1200 mg/day, and combination

respectively, compared with placebo in patients that underwent abdominal hysterectomy [10]. Our findings have consistent results.

It has been clear that celecoxib were beneficial in reducing postoperative pain, analgesic consumption, and patient satisfaction compared with placebo. In addition, the recommended dose of celecoxib has been well-established [15-17]. On the other hand, gabapentin doses used in postoperative multimodal analgesia varied widely. The commonly used doses were about 300 – 1200 mg, 1-2 hour before surgery [18,19]. One of the prominent side effect of gabapentin is sedation and it has been reported that gabapentin for postoperative use increased dizziness and sedation compared to placebo [3, 18, 20, 21]. In our study, we used the dose 400 mg preoperatively and 300 mg 12 and 24 hours later, 700 and 600mg/day. We found that sedation score was not significantly different even though the gabapentin group had more drowsy patients at hour 4 (20.8%, 34.8%, 42.3%, and 69.2% in P, C, G, and CG group, respectively) and hour 8 (13.6%, 22.7%, 44.0%, and 50.0%). As a result, we suggest that the

dose is acceptable for procedures in general but further study should be done to find the optimal dose. Van Elstraete, et al, in their study of pain after posterior lumbar spinal fusion, found that median effective analgesic dose (median value and 95% confidence interval) of gabapentin was 21.7 mg/kg (19.9-23.5 mg/kg) [22]. They also suggested that further powered studies should be done to assess side effects when using such high doses.

Post-operative morphine consumption in the CG was significantly less than G group only at hour 20 and 24, but not earlier. This may be due to overall pain and morphine requirement in our patients were small compared to other studies. Argument may arise if basic pain in our patient groups was not consistently strong. However, we included four types of operation instead of confining in only one, such as spine surgery. There were three main reasons. First, post-operative pain intensity does not exclusively depend on type of surgery that reflects the degree of tissue injury, but several factors are involved. Accordingly, big operation does not always result in severe pain. On the contrary, small-to-medium operation such as appendectomy may produce excruciating pain. Secondly, there are wide intra- and inter- individual variation in pain perception. Pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood, and ability to cope. Therefore, we are not convinced that confining to the same type of operation can control the homogenous pain intensity in the study samples. Finally, this study was conducted in normal situations of which we hope to generalize to populations of orthopedic patients.

It is understandable why major orthopedic surgery usually produces moderate to severe pain. It has more liability to produce nerve injury thus, to turn to chronic pain. Gabapentin is a first line drug in the treatment of neuropathic pain [23] and may have a role in perioperative pain according to this point of view. There was also evidence that peri-operative use of gabapentin had long-term benefit in postoperative period [14], but more study is needed.

Primary outcome of this study was morphine consumption in 24 hours. This was just only one parameter to measure effectiveness of analgesic effect and was not the answer to the struggle for overall patient comfort in the postoperative period. McQuay, et al. [24] demonstrated in their meta-analysis that the analgesic consumption outcome measure is valid only when treatment groups achieve

similar pain scores, which is a difficult-to-control parameter. While the use of either celecoxib alone or gabapentin alone was still questionable in the reduction of side effects such as nausea/vomiting, dizziness, and sedation, our study of combination drugs did not have the power to answer either. Pain score was perhaps a mislead outcome to be compared because the final goal of pain relief in any surgical situation should be "no pain". Pain score is inherently a monitoring sense more than in a treatment. Consequently, an ideal pain score outcome in the study should be zero while rescue analgesic consumption varies. However, morphine consumption and pain score were the best direct way that we have to assess pain and its treatment. More parameters should be included such as quality of life issues. This would need a much bigger sample size to gain enough power.

Our study showed that morphine consumption in C and G group was more than CG group, but significantly different only between G and CG group. Did it mean that celecoxib was more potent than gabapentin in the dose used? When comparing C and G group, we did not find significant difference. This might be because we had too small sample size to demonstrate the difference. However, when considering the morphine consumption, we can conclude that the combination of celecoxib and gabapentin further increase analgesia compared to either drug.

The study showed that the combination of celecoxib and gabapentin had additive effect compared to either of the drug alone. Because of the evidence that various NSAIDs and coxibs gave comparable analgesic effect, the drug in this group may have additive analgesic efficacy when combined to gabapentin. Further study is encouraged in this regard. The combination will benefit major operation that produce severe pain and use large amount of post-operative opioid. It should also reduce opioid side effects such as nausea/vomiting and ileus. The patients with hypotension and/or hypovolemia will have benefits because opioids have dose-related side effects in cardiovascular function as morphine reduces blood pressure and fentanyl reduces heart rate, but celecoxib and gabapentin do not. Moreover, pregabalin, a new generation of gabapentinoid that has analgesic property by the same mechanism of gabapentin, may be another interesting drug to study. However, cost-effectiveness study of the combination is still needed before it is generalized into routine use.

In conclusion, celecoxib or gabapentin or the combination was of benefit in the relief of pain after major orthopedic surgery. Celecoxib 400 mg preoperatively and 300 mg every 12 hours reduced 24 hour postoperative morphine consumption by approximately 17%. Gabapentin in the dose 400 mg preoperatively and 300 mg in the same interval reduced morphine consumption by approximately 14%. The combination of both drugs further reduced morphine consumption to 55% but did not reduce the pain score.

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