

Original Article

Comparison the Efficacy of Pre-Emptive Oral Celecoxib with Acetaminophen in Controlling Post-Operative Pain and Nausea after Lower Limb Surgery under General Anesthesia

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Abstract

Background: Up to now, there is no single opinion on how to control pain after surgery and molecular and clinical research in this area has been continuing. This study aimed to compare the effect of premedication with oral administration of celecoxib and acetaminophen on postoperative pain relief in the lower extremity surgery under general anesthesia.

Materials and Methods: In a prospective, randomized, double-blinded, clinical trial study, 70 patients undergoing lower limb surgery under general anesthesia were distributed into two equal groups. In the first and second group, oral acetaminophen 1000 mg or celecoxib 400 mg capsules were prescribed one hour before the operation, respectively. Postoperative pain and nausea severity in both groups were evaluated by visual analog scale (VAS) score and compared with each other.

Results: Assessment of pain intensity at 1, 2, 6, 12 and 24 hours after surgery revealed that acetaminophen group at the first hour had more intensity of postoperative pain (5.46 ± 1.17) compared with celecoxib group (4.31 ± 1.32) ($p < 0.001$). In rest of the time, there was no significant difference between the two groups. Analysis of variance with repeated observations showed the trend of postoperative pain intensity during the study in both groups had a significant difference ($p = 0.013$). The intensity of nausea in the first hour after surgery was significantly more in acetaminophen group compared with celecoxib group (2.8 ± 1.1 vs. 2.2 ± 1.3 , $p < 0.034$).

Conclusion: Celecoxib may be a better choice in reducing pain and nausea after surgery compared with acetaminophen. Considering no significant adverse effects in many studies, celecoxib may be used as a pre-emptive medication to reduce pain after lower extremity surgery.

Keywords: Premedication, Post-operative, PONV, pain, Celecoxib, Acetaminophen

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Introduction

Pain is one of the common unpleasant postoperative side effects which is intensified by tissue damage and release of histamine and inflammatory mediators during surgery (1). The pain causes increase in sympathetic tone, the production of catabolic hormones like cortisol and catecholamines, anti-diuretic hormone, ACTH, glucagon, renin, angiotensin II and decrease the production of anabolic hormones. The stress response can also create a hypercoagulable state and inhibition of fibrinolysis, increase of plasma viscosity and platelet reactivity. These factors increase the risk of deep-vein thrombosis, vascular graft failure and myocardial infarction (2). Even suppression of inflammatory mediators during surgery could result in lower postoperative pain and morphine requirements (3).

Pre-emptive analgesia reduces pain receptor sensitivity, especially reduces central sensitization to pain (4-6). Opioids for postoperative pain control have side effects such as unbearable itching, nausea and ventilatory suppression. Prostaglandins as a production of tissue damage during surgery are synthesized and cause the sensitivity of the receptors to pain and inflammation (7). Common non-steroidal anti-inflammatory drugs (NSAIDs) as inhibitors of the enzyme cyclooxygenase 1 (COX 1) would prevent the synthesis of these prostaglandins (8). However, a major drawback of these drugs which have restricted their use is inhibition of platelet function and increased risk of postoperative bleeding and gastrointestinal side effects. Enzyme inhibitor cyclooxygenase 2 (COX 2) with fewer side effects may reduce postoperative pain (7). Celecoxib is one of these drugs that its analgesic effects have been proven to produce morphine sparing effect without inducing opioid complications such as respiratory suppression (7, 8). Acetaminophen is an analgesic medication that does not have the side effects of NSAIDs and has been widely used for postoperative pain control (4). According to our literature review, there were few previous studies comparing the preemptive analgesic effect of celecoxib with acetaminophen. Therefore, this study was designed in the patients undergoing lower limb surgery under general anesthesia.

Methods

After approval of Anesthesiology and Critical Care Research Center and obtaining informed consent from patients, this randomized double-blind clinical trial study was performed in 2014. Our study population consisted patients undergoing elective surgery of the lower limbs, aged 18-65 years with American society of anesthesiologists (ASA) physical status I or II. Inclusion criteria included lack of psychiatric problems, coagulopathies, gastrointestinal bleeding, peptic ulcer, chronic pain syndrome, history of seizure, and drug addiction. In any event outside the study protocol resulted in exclusion of the patients.

Based on the formula to estimate sample size to compare averages and by taking 95% confidence level, the power of test as 80%, the standard deviation of postoperative pain score equal to 0.7, the sample size was calculated as 32 patients, but 35 cases were studied in each groups.

Randomization was done by random allocation software and simple random allocation method. The study was designed as blinded in a way that the physician who evaluated the pain and nausea was different from the one who prescribed the premedication.

Oral premedication, included acetaminophen 1000mg or celecoxib 400 mg in capsules of similar color and shape was done. The drugs were given one hour before surgery with about 100 mL of water. After pre-oxygenation, induction of anesthesia in both groups was performed with the same dose of thiopental sodium (6mg/kg) and atracurium (0.6mg / kg /) and fentanyl (100µgr). Then 1.2% isoflurane + %50 oxygen + %50 N₂O was used for maintenance of anesthesia. For analgesia 0.15mg/kg of morphine after induction of anesthesia was used. During anesthesia, pulse oximetry, ECG, blood pressure monitoring, and body temperature monitoring were used and data recorded.

After the operation, in accordance with existing standards, extubation was performed. Extubation time was considered as the duration between the ends of surgery until the time of tracheal extubation. The patients were discharged from recovery room based on modified Aldrete score. The level of consciousness

of the patients at 1, 2, 6, 12 and 24 hours after surgery, according to Ramsay sedation scale (score from 1 to 6), was determined. The intensity of pain was recorded according to visual analog scale (VAS) score at admission to recovery and then 1, 2, 6, 12 and 24 hours after surgery. If the VAS score was 4 or more, intravenous pethidine 0.5mg/kg was administered. Also nausea with a VAS score of more than 4 or any episodes of vomiting was treated with intravenous metoclopramide 0.15 mg/kg. All medications and their possible side effects, accompanying with the time of receiving the first analgesic dose were recorded.

Data were analyzed by SPSS software (Version 22.0. Armonk, NY: IBM Corp.). T-test for intergroup comparison of quantitative variables, Chi square test to compare nominal data, and the analysis of variance with repeated observations for trend changes in variables during study was used.

Results

In this study, 70 patients were studied in the two groups of 35 recipients of the acetaminophen and celecoxib during the intervening period. No patient was excluded from the study because of adverse events (Figure 1). In Table 1, the distribution of general demographic characteristics of both groups is

shown. The average age, weight, gender, ASA status, duration of surgery, anesthesia and extubation time and recovery duration were not significantly different between the two groups. Hemodynamic parameters in patients during the study period showed no statistically significant difference between the two groups in regard to mean changes in heart rate and blood pressure. In Table 2, severity of pain and nausea according to VAS score is shown. Acetaminophen group had more pain in the first hour after surgery, but in other times, there was no significant difference between the two groups in this regard. Analysis of variance with repeated observations during the study showed that the two groups had significant difference in mean pain intensity trend ($p = 0.013$). The intensity of nausea in the first hour after surgery was significantly more in acetaminophen group compared with celecoxib group. Vomiting episodes during the postoperative period are shown in Figure 2 and according to Fisher's exact test; the difference between the two groups was not significant ($p > 0.05$).

Average time to initial analgesic requirement in the postoperative period was 1.74 ± 1.4 and 2.49 ± 2.7 hours in acetaminophen and celecoxib groups, respectively ($p = 0.16$). The mean total analgesic drug prescribed during the postoperative period in acetaminophen and celecoxib groups was

Table 1: Distribution of demographic characteristics in the two groups.

Group	Acetaminophen	Celecoxib	P value
Variable			
Age (year)	28.6 ± 5.2	29.7 ± 5.5	0.4
Weight (kg)	68.4 ± 9.7	69.9 ± 8	0.47
Sex	Male 28 (80)	32 (91.4)	0.17
Number (%)	Female 7 (20)	3 (8.6)	
ASA	I 32 (91.4)	29 (82.9)	0.28
	II 3 (8.6)	6 (17.1)	
Operation time (min)	107 ± 28.4	115.4 ± 27	0.21
Anesthesia time (min)	122.9 ± 27.4	128.6 ± 25.9	0.21
Recovery time (min)	94.86 ± 15.2	91.42 ± 14.4	0.34
Extubation time (min)	6.09 ± 1.04	6.37 ± 1.08	0.27

Table 2: Mean±SD of postoperative pain and nausea intensity in both groups.

Group Time	Postoperative pain intensity			Postoperative nausea intensity		
	Acetaminophen	Celecoxib	P value*	Acetaminophen	Celecoxib	P value*
1 st hour	5.5 ± 1.2	4.3 ± 1.3	0.001	2.8 ± 1.1	2.2 ± 1.3	0.034
2 nd hour	5.9 ± 1.3	5.4 ± 1.4	0.1	2.5 ± 1.1	2.2 ± 1.7	0.4
6 th hour	4.6 ± 1.2	4.2 ± 1.3	0.14	1.5 ± 0.9	1.5 ± 1.5	0.92
12 th hour	4 ± 1.2	3.5 ± 1.6	0.12	1 ± 0.9	1.1 ± 1.2	0.74
24 th hour	2.6 ± 1.2	2.7 ± 1.3	0.85	0.2 ± 0.4	0.8 ± 0.9	0.002
P value**	0.013			0.81		

* The difference between the two groups at any time by t-test analysis

** The difference between the two groups change according to analysis of variance with repeated views

Table 3: Dosage (mean±SD) of rescue drug administration (mg) for control of postoperative pain (acetaminophen) and nausea (metoclopramide) in the two groups.

Group Time	Analgesic			Metoclopramide		
	Acetaminophen	Celecoxib	P value*	Acetaminophen	Celecoxib	P value*
1 st hour	28.7 ± 9.2	26.7 ± 6.5	0.46	10 ± 0	10 ± 0	1
2 nd hour	32 ± 16.8	30 ± 10.2	0.62	10 ± 0	10 ± 0	1
6 th hour	25 ± 0	26.6 ± 6.2	0.4	0	10 ± 0	1
12 th hour	25 ± 0	25 ± 0	1	0	0	1
24 th hour	25 ± 0	25 ± 0	1	0	0	1
P value**	0.51			0.99		

*the difference between the two groups at any time by t-test analysis

**the difference between the two groups changes according to analysis of variance with repeated views

58.57±27.1 mg and 54.29±23.9 mg, respectively (p=0.49) (Table 3).

Discussion

The primary objective of this study was to compare the effect of pre-emptive oral administration

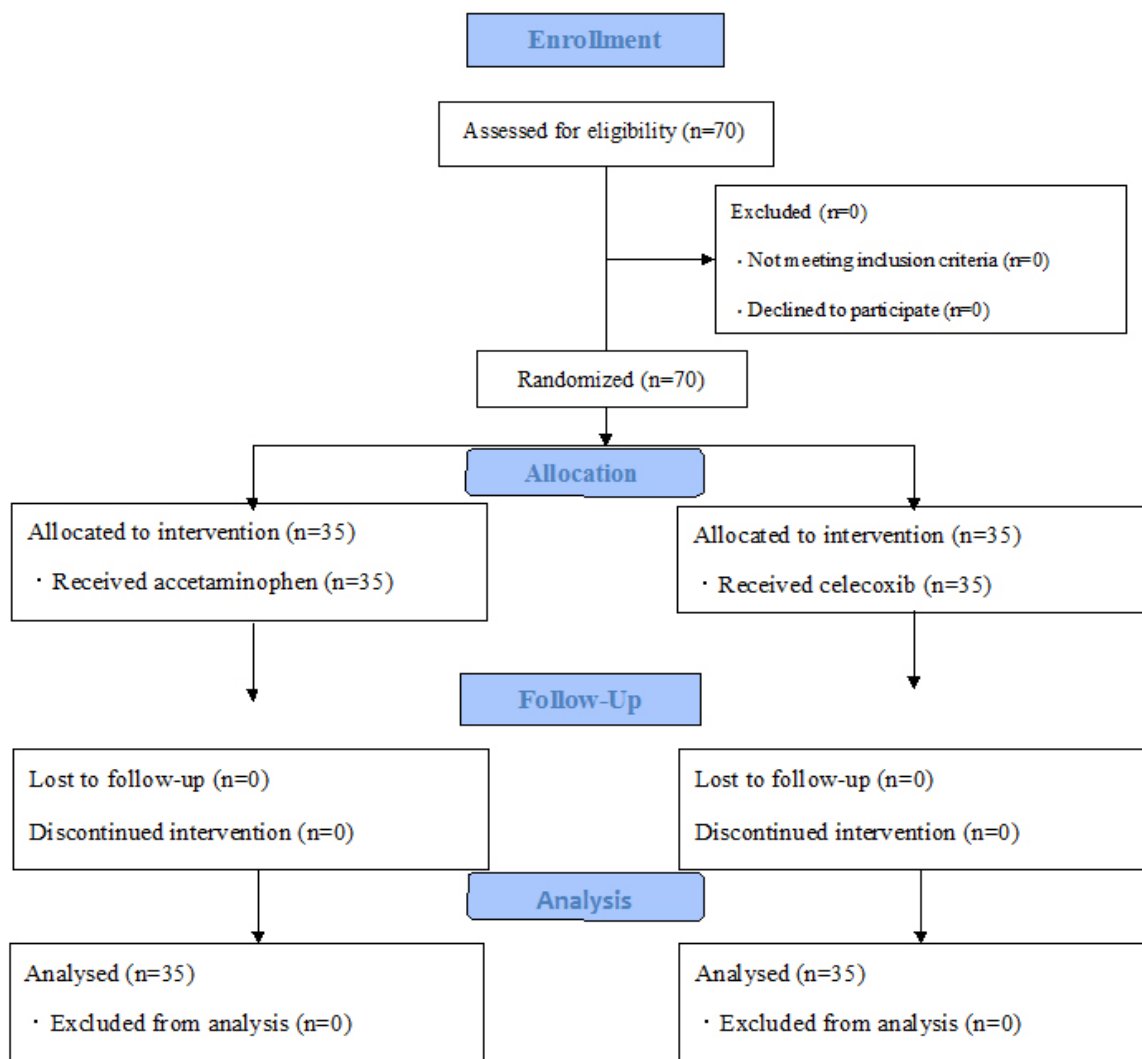


Fig. 1. CONSORT Flow Diagram.

of celecoxib and acetaminophen for pain relief after lower limb surgery under general anesthesia. The secondary outcome of the study was to measure rescue analgesic consumption and duration of recovery stay, and occurrence of PONV. In this study celecoxib and acetaminophen did not have any adverse effects on patient’s hemodynamic parameters, and in this sense, the use of both drugs is safe. Celecoxib compared to acetaminophen, particularly at one hour after surgery, was associated with a further reduction in patients' pain and nausea and less rescue analgesic drug requirements. However, considering other times of measurement and the total dose of rescue analgesic and average time to initial analgesic requirement, it could be concluded that both drugs

can be administered in preoperative period. In this study placebo group was not considered because previous studies had shown that acetaminophen or celecoxib has more efficiency than placebo in controlling perioperative pain.

Mardani-Kivi et al., showed that pre-emptive administration of celecoxib, 2 hours before knee arthroscopic surgery, resulted in significant reduction in pain intensity and opioid consumption at 6 and 24h post operation, but side effects of analgesics such as nausea and vomiting, sedation, and dizziness were not significantly different from the placebo group (9). In our study acetaminophen was used instead of placebo one hour before surgery. In another study conducted by Zhang et al., pre-emptive administration of 200 mg

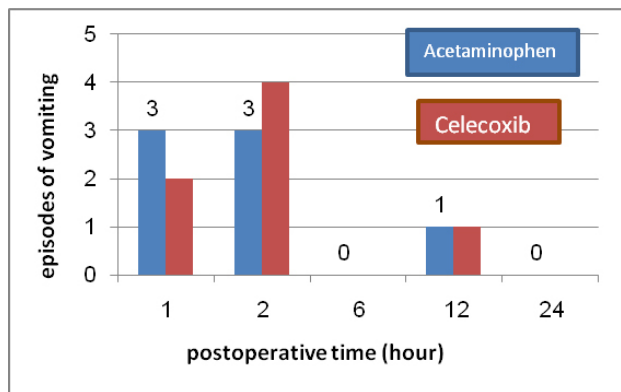


Fig. 2. The frequency of vomiting episodes after surgery in both groups ($p > 0.05$, according to Fisher's exact test).

celecoxib, one hour before arthroscopic hip surgery under spinal anesthesia, resulted in less pain and narcotic consumption at 12 and 24 h postoperatively, but the VAS score of pain was not different from the placebo group in the recovery room (10).

In one study by Fenlon et al., oral vs. intravenous paracetamol for lower third molar extractions under general anesthesia was compared. They concluded that single dose oral paracetamol given 45 min before surgery was not inferior to intravenous preparations given after induction of anesthesia in controlling post-operative pain (11). Therefore, oral premedication can be administered for post-operative pain control as in our study. In one study by Alimian *et al*, patients scheduled for elective laparotomy, intravenous paracetamol or morphine was administered by infusion pump after surgery. They concluded that paracetamol is insufficient for postoperative pain control in the first eight hour postoperatively (12). This is in accordance with our study. However, the effect of central pain pathways involved in abdominal surgeries and the efficacy of oral medications such as paracetamol or celecoxib may be assessed in future studies. In two other independent studies, the effect of celecoxib and acetaminophen for pain relief after surgery has been investigated separately.

Lin et al., in a systematic review showed that perioperative administration of COX-2 selective inhibitors resulted in less pain scores, opioid consumption, itching and PONV and better active range of motion in patients undergoing total knee arthroplasty. Meanwhile, the volume of blood loss

was not significantly increased post-operatively (13). Also in our study the patients who received celecoxib, suffered less from PONV and this is another benefit of using COX-2 selective inhibitors in preoperative period. Khalili and colleagues have shown that prescription of preemptive and preventive intravenous acetaminophen, in patients under spinal anesthesia, reduces pain intensity and additional analgesic consumption in the first 24 hours after lower limb surgery (14). In their study acetaminophen was compared to placebo, but in our study acetaminophen compared to celecoxib was less efficient. Kashefi and colleagues showed that oral administration of celecoxib 200mg compared to 320mg of acetaminophen, administered 2 hours before surgery significantly reduced pain in the first 4 hours after surgery (15). They used lower doses of celecoxib and more vomiting episodes may be related to this lower dose comparison with our study.

Some limitations of our study were: Postoperative pain severity after the first hour and total rescue analgesic requirements did not differ in both groups. It may be related to low sample size or time of premedication. Therefore, performing studies with larger sample sizes are recommended. In our study we did not measure the real need for intraoperative analgesic requirement and all patients received a fixed dose of intraoperative morphine. It is recommended that in future studies, this point will be considered. Also comparing biomarkers of pain may be considered, as pain diagnosis and management need more objective markers than VAS score or monitoring changes in the autonomic nervous system.

Conclusion

Considering the results of the present study and comparison with other studies, it seems that celecoxib has better efficacy in reducing post-operative pain and nausea than acetaminophen. Given the indications of drug and the medical advice, celecoxib can be used as a drug for pain and nausea relief after surgery.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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