Prosperity of celecoxib for pain relief after elective cesarean delivery, a double-blind randomized controlled trial

Thunwipa Tuscharoenporn MD.[1]
Pahsuvudn Kongsin MD.[1]
Busaba Supawatttanabodee PhD. (Statistics)[2*]
Piyasak Vitayaburananont MD.[3]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
[2] Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
[3] Department of Anesthesiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
* Corresponding author, e-mail address: busabasupa@yahoo.com
Vajira Med J. 2020; 64(3) : 165-72
http://dx.doi.org/10.14456/vmj.2020.xx

Abstract

Objective: To determine the effectiveness of 400-mg celecoxib after elective cesarean delivery.

Methods: In this randomized double blinded controlled trial, 110 full-term pregnant women aged between 20-40 years old who were scheduled for elective cesarean delivery between May 2018 and November 2018 were enrolled. A total of 110 participants were randomly assigned equally into 2 groups to receive celecoxib or placebo. All patients from both groups received meperidine under PCA after operation. Pain score was measured 3 times with 2 different states: 6, 12 and 24 hour at rest and upon movement.

Results: The overall pain score in each time point between PCA meperidine plus celecoxib and PCA meperidine plus placebo was significantly different (p-value = 0.004). The use of meperidine at 24 hours in the group of PCA meperidine plus celecoxib was not significantly different from the group of PCA meperidine plus placebo (p-value =0.058)

Conclusion: Celecoxib could relieve post-operative pain after cesarean delivery statistic significantly.

Keywords: elective cesarean delivery, post-operative pain, celecoxib, effectiveness

ประสิทธิศักดิ์ในการลดระดับความปวดของยาเซเลโคซิบหลังผ่าตัดคลอดบุตรการทดลองแบบสุ่มมีกลุ่มควบคุม

ธัญวิภา ทัศน์เจริญพร พ.บ.[1]
พสุวัฒน์ คงศีล พ.บ.[1]
บุษบา ศุภวัฒน์ธนบดี วท.ม.[2*]
ปิยศักดิ์ วิทยบูรณานนท์ พ.บ.[3]

[1] ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช กรุงเทพมหานคร ประเทศไทย
[2] ภาควิชาวิทยาศาสตร์การแพทย์พื้นฐาน คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช กรุงเทพมหานคร ประเทศไทย
[3] ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์วชิรพยาบาล มหาวิทยาลัยนวมินทราธิราช กรุงเทพมหานคร ประเทศไทย
* ผู้ติดต่อ, อีเมล: busabasupa@yahoo.com
Vajira Med J. 2020; 64(3) : 165-72
http://dx.doi.org/10.14456/vmj.2020.xx

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพในการลดระดับความปวดของยาเซเลโคซิบขนาด 400 มิลลิกรัมในผู้ป่วยหลังผ่าตัดคลอดที่มีการวางแผน โดยใช้วิธีการระงับความรู้สึกโดยการฉีดมอร์ฟีนเข้าทางช่องไขสันหลัง

วิธีดำเนินการวิจัย: การศึกษาแบบสุ่มปกปิดทั้งสองฝ่ายและมีการควบคุมในหญิงตั้งครรภ์ครบกำหนด 110 คน อายุระหว่าง 20-40 ปี ซึ่งถูกกำหนดให้ผ่าตัดคลอดในช่วงเดือนพฤษภาคม 2561 ถึงเดือนพฤศจิกายน 2561 แบ่งเป็น 2 กลุ่ม โดยใช้วิธีการสุ่ม คือ กลุ่มที่ได้รับยาเซเลโคซิบและกลุ่มที่ได้รับยาหลอก โดยหญิงตั้งครรภ์ทั้ง 110 คนได้รับการติดตั้งเครื่องให้ยาแก้ปวดเพทีดีนทางหลอดเลือดดำโดยผู้ป่วยเป็นผู้ควบคุมทันทีหลังผ่าตัด และวัดระดับความปวดขณะพักและขยับร่างกายของผู้ป่วยหลังผ่าตัดคลอดที่ 6, 12 และ 24 ชั่วโมงหลังผ่าตัด

ผลการวิจัย: ระดับความปวดโดยรวมในทุกช่วงเวลาระหว่างกลุ่มผู้ป่วยที่ได้รับยาเซเลโคซิบและกลุ่มที่ได้รับยาหลอกลดลงอย่างมีนัยสำคัญทางสถิติ (ค่า p-value = 0.004) การใช้ยาเพทิดีนภายใน 24 ชั่วโมงในกลุ่มที่ได้รับยาเซเลโคซิบและในกลุ่มที่ได้รับยาหลอกไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p-value = 0.058)

สรุป: ยาเซเลโคซิบสามารถลดระดับความปวดในผู้ป่วยหลังผ่าตัดคลอดอย่างมีนัยสำคัญทางสถิติ

คำสำคัญ: การผ่าตัดคลอดที่มีการวางแผน, ความเจ็บปวดหลังผ่าตัด, เซเลโคซิบ, ประสิทธิภาพ

Introduction

Patients who undergo cesarean delivery experience acute postoperative pain. In Vajira hospital, postoperative pain management of cesarean delivery in first 24 hours generally use only opioids such as morphine, meperidine and tramadol. We found that our patients still had moderate to severe pain in first 24 hour. And at 24 hour postoperative cesarean delivery was the time that patients experience the most severe pain which VAS score average 7. Adequate pain relief promotes patients early mobilization, effective breast feeding, reducing stress and length of hospital stay.

Non-steroidal anti-inflammatory drugs (NSAIDs) combined with opioids have been found to reduce postoperative pain, postoperative opioid requirements, and opioid-related adverse effects. Researchers have found that a type of NSAID known as COX-2 inhibitors are less likely to cause GI bleeding, but they can also cause serious cardiovascular events including myocardial infarction, thrombosis, edema and death. These adverse effects are dependent on dosage and duration of treatment[1-2]. Celecoxib capsule is a COX-2 inhibitor, available as capsules containing 50 mg, 100 mg, 200 mg and 400 mg for oral administration.

The pharmacokinetics of celecoxib are dose-proportional, increasing exposure after oral administration of up to 400 mg daily. Celecoxib is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours. Peak plasma levels of celecoxib occur approximately 2-4 hours after an oral dose[3].

According to TW Hale et al., 2004 "Transfer of celecoxib into human milk" the average clinical dose transferred to an infant daily would be approximately 0.3% of the weight-adjusted maternal dose. This means that celecoxib is very unlikely to affect breastfed infants[4]. In 2008, Fong WP designed a randomized study of the efficacy of oral 400 mg celecoxib for reducing postoperative pain and opioid used in 60 patients who had undergone, elective cesarean delivery in Kaohsiung Municipal Min-Sheng Hospital and E-DA Hospital/I-Shou University, Taiwan. Comparing 3 groups, group one was given oral celecoxib 400 mg 30 minutes before surgery and oral placebo capsules after surgeon sutured skin, group two was given oral placebo 30 minutes before surgery and oral celecoxib 400 mg capsules after surgeon sutured skin and group three was given oral placebo capsules before surgery and after surgeon sutured skin. They found that group one and two reported a significant reduction in VAS score ($P < 0.05$) at 6 and 12 hours post operation, and opioid use ($P < 0.05$) compare with group three. No adverse event was detected[5]. This mean that celecoxib could induce a statistically significant reduction in postoperative pain.

Therefore, we wanted to confirm in the effectiveness of oral 400 mg celecoxib for pain relief after elective cesarean delivery whether it can relieve postoperative pain in our patient or not.

Methods

We designed a double blind randomized control trial, comparing 2 groups with 55 patients in each group: PCA (Meperidine IV) plus celecoxib 400 mg (study group) versus PCA (Meperidine IV) plus placebo (control group). The primary outcome was postoperative pain at 24 hours at rest and upon movement. Secondary outcomes were postoperative pain at 6 and 12 hours at rest and upon movement and opioid requirement 24 hours after cesarean delivery.

A randomized double-blinded placebo-controlled trial was registered in the Thai Clinical Trial Register (No. TCTR20190109003) and was approved by Vajira Institutional Review Board (COA041/2561). According to a previous study the difference of mean score and standard deviations during rest between both groups was 0.8 and 2 (Matsota et al)[6], with statistical power = 0.8 and type I error = 0.05, using STATA (V14.0 StataCorp LLC College Station,USA)[7]:10% drop-out was added for calculation. The number of patients required was determined to be 55 in each group. A box of four randomization was done in the Microsoft Excel 2010 by research assistant.

Patients with term singleton pregnancy, aged 20-40 years old, elective cesarean delivery or cesarean delivery with tubal sterilization, Pfannenstiel incision, spinal anesthesia with intrathecal morphine, BMI <35 kg / mm^2, and no medical contraindications were included and randomly numbered as assigned to either of 2 groups. The study group received PCA plus celecoxib while the control group received PCA plus placebo. Only the research assistant knew the group of each patient. Informed consent was obtained from eligible participants when they were scheduled to attend the cesarean delivery: the reasons for doing this research, reasons for selection, and also side effects were explained at antenatal care clinic by the doctors who met the patients. Patients who declined to participate, had duration of surgery > 2 hours, and blood loss during surgery > 1,000 milliliters did not received the intervention.

All participants were routinely prepared for cesarean delivery on the scheduled day of elective surgery. During operation spinal anesthesia was performed by attending staff anesthesiologist. Quincke type spinal needle No.27 was used for spinal anesthesia, 0.5% hyperbaric bupivacaine (Marcaine) 10 mg with 0.2 mg of morphine was used as anesthetic agents. Both study and control groups were administered IV PCA, using pethidine 1mg/ml and infusion bolus 10 ml/time with interval lock 5 minutes, maximum dose setting was 100 mg per 4 hours and continued until 24 hours post operation. The study group additionally received celecoxib 400 mg 1 capsule orally at 2 hour post-operation, while the control group received 1 placebo capsule. Both capsules were prepared with the same color, weight and smell, and enclosed in an opaque envelope which was numbered randomly by a pharmacist in order to blind doctors and nurses who gave the capsule to the patients. Postoperative pain at 6,12, and 24 hours at rest and upon movement was measured using a visual analog scale ranging between 0.0-10.0 (no pain- worst possible pain), each patient marked a cross " X" on a 10 cm straight line that we prepared, which we then measured in millimeters. Total consumption of PCA Meperidine in 24 hours and side effects such as rash, dyspepsia, or hypotension were monitored. All records were done by nurses who were not involved with this study.

Data were analyzed using STATA (V14.0 StataCorp LLC College station, USA) Categorical and continuous data were presented as number with percentage, or mean with standard deviation or median with interquartile range. Comparison pain score and pethidine consumption were analyzed using generalize estimating equation (GEE). A p-value of less than 0.05 was considered statistically significant.

Result

One hundred and ten patients admitted for elective cesarean section were enrolled in this study. Ten patients did not received the intervention due to declining to participate, intra-operative blood loss more than 1,000 ml, operative time > 2 hours and emergency cesarean section. Finally, a total of 100 participants were received allocated intervention (Figure 1). Between 2 group no significant different in baseline characteristics. No cases had any side effects from celecoxib (Tables 1). Results between groups were comparable with no significant differences (p>0.05). Postoperative outcomes between the two groups are shown in Table 2. Compared with control, the study group was significantly less likely to experience postoperative pain at rest and upon movement 6, 12 and 24 hours (p<0.05). No patients reported adverse effects.

The overall pain score between PCA plus celecoxib and PCA plus placebo was significantly different in each time point(p-value = 0.004) (figure2.) The use of meperidine in 24 hours in the group of PCA plus celecoxib was not significantly different from the group of PCA plus placebo (p-value = 0.058) (Table 2).

Discussion

This study showed that the addition of oral 400 mg of celecoxib can improve postoperative pain after cesarean delivery provided via IV PCA technique. Patients who received celecoxib experienced significantly less pain at rest and movement. No patients had adverse effects.

We designed this study because previous studies showed conflicting results. Fong and colleagues showed that 400 mg celecoxib after cesarean section significantly reduced pain scores and required less morphine[5], but Lee and colleagues showed celecoxib 200 mg did not improve pain score after cesarean section after spinal anesthesia[7] and Matsota andcolleagues showed 200 mg celecoxib cannot significantly reduce pain score, especially during movement and opioid consumption via PCEA[6]. These previous studies maybe explained by differences in doses of celecoxib used, the time of administration, and the main analgesic technique performed.

As a result postoperative pain scores showed was reduced statistical significance at every time point during rest and upon movement in the study group which received PCA plus celecoxib, although the difference was < 1 point, which wasn't clinically significant. However, a significant limitation is that all patients recorded their pain scores themselves. Therefore, these were subjective and depended on individuals. Furthermore, we didn't know the patients would require pethidine via PCA; it might have been just before they had to record their pain score. So the pain was already reduced by pethidine. Intrathecal morphine in 0.2 mg doses may provide a prolonged analgesic effect that can obscure the benefits of celecoxib.

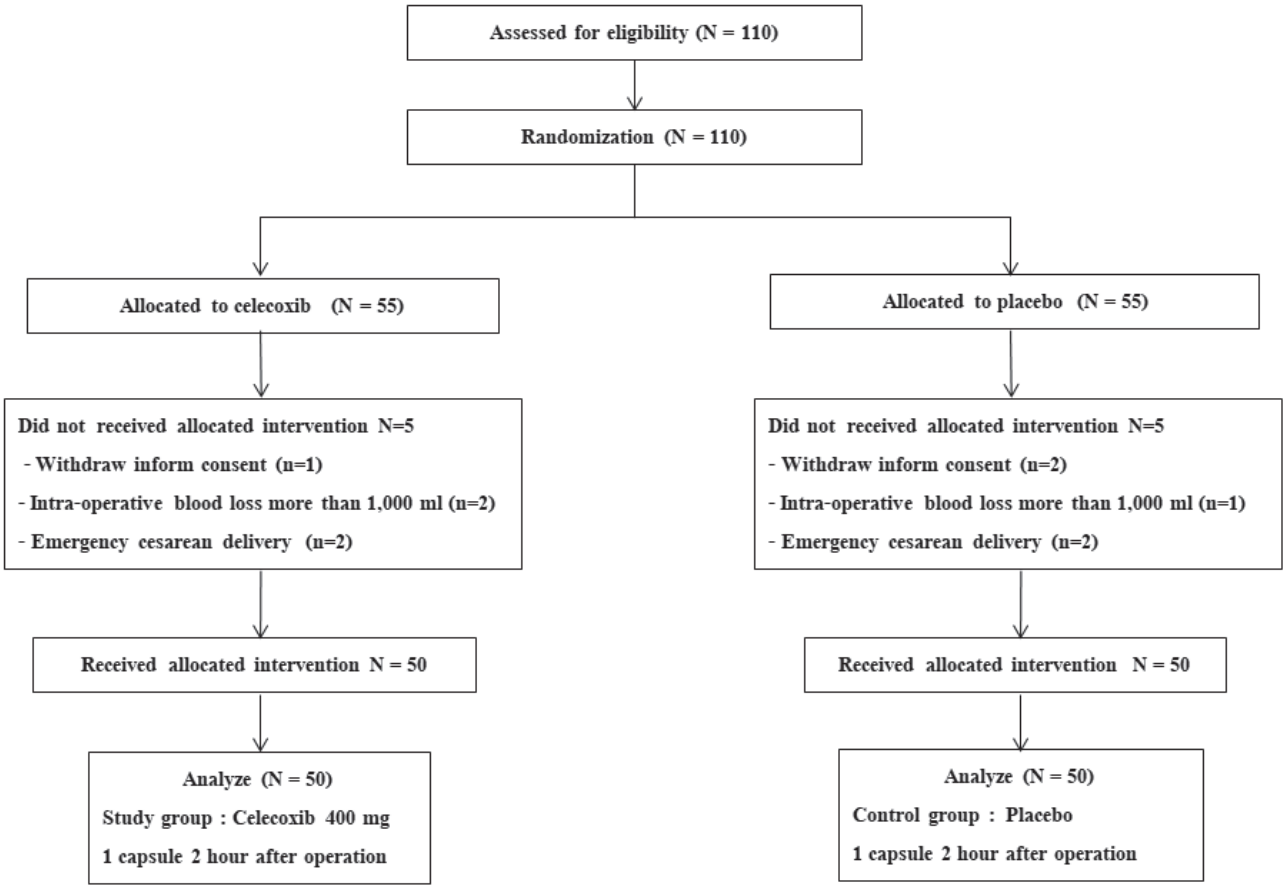

Figure 1: Consort diagram

Table 1:

Baseline characteristics

Characteristics	PCA plus Celecoxib (study group) (n=50)	PCA plus Placebo (control group) (n=50)
Part A. Demographic data	**Mean (SD)**	**Mean (SD)**
Age (year)	31.8 (5.8)	31.1 (5.8)
Body weight (Kg)	70.5 (13.3)	71.4 (10.5)
Height(m)	1.6 (0.1)	1.6 (0.1)
BMI(kg/m^2)	28.3 (4.2)	28.4 (3.9)
Part B. Obstetric history	**Mean (SD)**	**Mean (SD)**
Operative time (min)	75.8 (23.8)	74.3 (21.9)
Blood loss (ml)	507 (IQR = 200)	496 (IQR = 225)
Gestational age(wk)	38.6 (0.5)	38.5 (0.6)
Parity	**Number (%)**	**Number (%)**
Nulliparous	18 (36)	16(32)
Indication		
Previous C/S	25 (50)	29 (58)
Cephalopelvic disproportion	19 (38)	15 (30)
Breech presentation	5 (10)	3 (6)
HIV unknown viral load	0 (0)	2 (4)
Genital condyloma	0 (0)	1 (2)
Placenta previa	1 (2)	0 (0)
Underlying disease		
None	38 (76)	36 (72)
DM	10 (20)	12 (24)
HT	1 (2)	0 (0)
HIV	1 (2)	2 (4)
Operation		
Cesarean section	30 (60)	30 (60)
Cesarean section with tubal resection	20 (40)	20 (40)

Table 2:

Comparative pain score between study group and control group

Comparative meperidine used between study group and control group (n=50 per group)

	Study group (n = 50)	Control group (n = 50)	P-value
Pain at rest		**Mean (SD)**	
6 hr	0.8 (0.8)	1.8 (1.6)	0.004
12 hr	0.9 (1.0)	1.8 (1.6)	
24 hr	1.4 (1.6)	2.4 (1.7)	
Pain at movement			
6 hr	2.6 (1.7)	3.5 (2.2)	
12 hr	2.8 (1.8)	3.6 (1.9)	
24 hr	3.5 (2.0)	4.3 (2.2)	
Meperidine use in 24 hr		**Median (IQR)**	
	60 (80)	80 (143)	0.058

Study group : PCA plus Celecoxib, Control group : PCA plus placebo

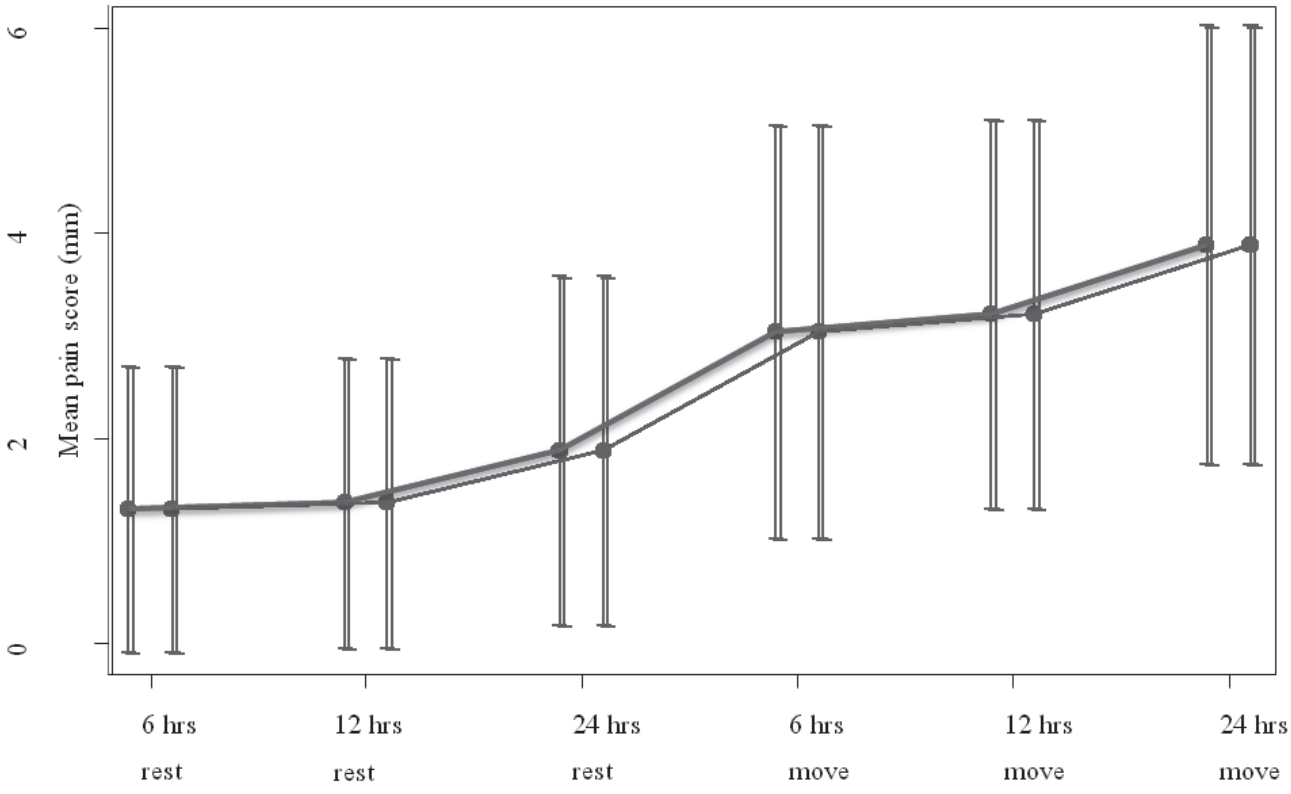

Figure 2: Comparative pain score between study group and control group (n=50 per group)

Strength in our study were randomized controlled trial and first time we assessed the efficacy of celecoxib in postoperative caesarean delivery.

There were no data regarding milk excretion of higher dose celecoxib (400mg). The only dose approved that was safe for breastfeeding was 200 mg of celecoxib. In our hospital 24 hours after operation, patients were not allowed to be with their baby because of the need for rest and routine postoperative monitoring. We assumed that celecoxib was almost all excreted from patients, as its half-life is 11 hours. Further investigation suggests exploring the effect of high-dose and long-term celecoxib on both mothers and breastfed newborns.

Conclusion

Celecoxib could relieve post-operative pain after cesarean delivery

Funding: The research was funded by Navamindradhiraj University Research Fund.

Conflicts of Interest: The authors declare no conflict of interest

References

1. Bujedo BM, Santos SG, Azpiazu AU, Noriega AR, Salaza DG, Andueza MA. Multimodal analgesia for the management of postoperative pain. Racz G. Pain and treatment.n.p.:Intechopen;2014. 134-40
2. Dajani EZ, Islam K. Cardiovascular and gastrointestinal toxicity of selective cyclo-oxygenase-2 inhibitors in man. J Physiol Pharmacol 2008; 59:117-33
3. Davies NM, Mclachlan AJ, Day RO, Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. Clin pharmacokinet 2000;38:225-42.
4. Hale TW, Mcdonald R, Boger J. Transfer of celecoxib into human milk. J Hum Lact 2004;20:397-403.
5. Fong WP, Yang LC, Wu JI, Chen HS, Tan PH. Does celecoxib have pre-emptive analgesic effect after Caesarean section surgery. Br J Anaesth 2008;100:861-2.
6. Matsota P, Nakou M, Kalimeris K, Batistaki C, Pandazi A, Kostopanagiotou G. A single dose of celecoxib 200 mg improves postoperative analgesia provided via patient controlled epidural technique after caesarean section. Arch Med Sci 2013;9:877-82
7. Lee L, Irwin M, Lim J, Wong C. The effect of celecoxib on intrathecal morphine-induced pruritus in patients undergoing Caesarean section. Anaesthesia 2004;59:876-80.