

# A single dose of celecoxib 200 mg improves postoperative analgesia provided via patient-controlled epidural technique after caesarean section

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## Abstract

**Introduction:** Celecoxib in a dose of 200 mg is safe for the breast feeding mother, as its milk levels are extremely low. We investigated the efficacy of celecoxib in improving postoperative pain management in parturients under patient-controlled epidural analgesia (PCEA).

**Material and methods:** We studied 64 healthy parturients undergoing elective caesarean section under combined spinal-epidural anesthesia. Postoperative analgesia was performed via PCEA with ropivacaine 0.15% and fentanyl 2 µg/ml (4 ml bolus administration, lock-out 15 min). Patients were randomly allocated to receive either only PCEA ( $n = 32$ ) or PCEA plus celecoxib 200 mg orally ( $n = 32$ ). Paracetamol 500 mg was given orally as rescue analgesia. We recorded visual analogue scale (VAS) scores for pain at rest and movement, attempted and given PCEA doses, Bromage scores, level of sensory blockade, rescue doses of paracetamol, maternal side effects during the first 24 h after the PCEA instrumentation, and the overall patient satisfaction.

**Results:** Fifty-six patients completed the entire protocol. Patient demographics, duration of surgery, side effects, attempted and given PCEA doses, and motor and sensory blockade did not differ between the groups. Significantly lower VAS scores at rest and movement, fewer paracetamol doses ( $p = 0.039$ ) and increased patient satisfaction ( $p = 0.001$ ) were found in the celecoxib group compared to controls.

**Conclusions:** A single dose of 200 mg of celecoxib effectively improved pain management in parturients with PCEA, limited the need for supplemental analgesics and improved efficacy of analgesia, increasing patient satisfaction.

**Key words:** caesarean section, celecoxib, patient-controlled epidural analgesia, postoperative analgesia.

## Introduction

Adequate control management of postoperative pain following caesarean section is of great importance in obstetrics because it reduces the neurohormonal response to stress, contributes to rapid mobilization of parturients and facilitates the initiation of breast-feeding [1]. Nowadays, patient-controlled epidural analgesia (PCEA) is common practice for pain relief in the obstetric setting [2, 3].

The addition of non-steroidal anti-inflammatory drugs (NSAIDs) has been found to improve postoperative analgesia in the general surgical

population, although controversies exist regarding their side effects [4]. Studies performed in obstetric patients have shown increased perioperative bleeding and gastrointestinal or renal dysfunction after administration of both ketorolac and ibuprofen [5, 6]. Moreover, NSAIDs' excretion in breast milk and their effect on newborns is an additional risk and a major concern in the obstetric population. Naproxen administration has been reported to increase neonatal haemorrhagic diathesis and incidence of acute anaemia, while indomethacin has been related to neonatal seizures and nephrotoxicity [7, 8]. Celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, possesses a safer profile, depending on the dose, for both surgical patients [9] and breast feeding mothers [10, 11].

The primary aim of the study was to investigate the effect of a single postoperative oral dose of celecoxib 200 mg on the efficacy of postoperative analgesia performed with PCEA in parturients undergoing caesarean section. Secondary outcomes were its safety in parturients and maternal overall satisfaction regarding analgesia.

## Material and methods

The present prospective randomized clinical trial took place at the "ATTIKON" University Hospital (Athens, Greece). The study protocol was approved by the hospital ethics and research committee (Ref: 5/18-06-08). Written informed consent was obtained from all parturients.

### Parturients

Pregnant women aged 22 to 41 years, American Society of Anesthesiologists (ASA) physical status I and II, scheduled for elective caesarean delivery, were invited to participate in the study. The night before surgery, all parturients were informed about the protocol, which included caesarean delivery under combined spinal-epidural regional anaesthesia followed by PCEA. Patients who were willing to participate were trained in the use of PCEA.

### Exclusion criteria

Exclusion criteria included patient refusal to participate in the study or inability to understand the concept of PCEA; a history of severe cardiovascular, respiratory, hepatic, renal, neurological, psychiatric, or metabolic disease, morbid obesity and peptic ulcer disease; a known history of allergy to local anaesthetics and/or to non-steroidal anti-inflammatory agents; use of NSAIDs during the last preoperative days; gestation less than 37 weeks; women with preeclampsia, diabetes mellitus or multiple pregnancy; significant peripartum haemorrhage; and the existence of an absolute or relative contraindication for the application of the epidural technique

such as neuromuscular disease, bleeding tendency, and local skin infections in the lumbar region.

## Study design

Before surgery, in the preparation room two venous catheters (18 G) were inserted in each parturient. Thereafter, each parturient was pre-hydrated with 500 ml crystalloid solution (Ringer's Lactated) and 200 ml of 6% hydroxyethyl starch 130/0.4 (Voluven, Fresenius Kabi France, F-27406 Louviers) administered over 30 min and was premedicated with intravenous ranitidine 50 mg and metoclopramide 10 mg. A combined spinal-epidural technique was performed at the L3-L4 lumbar vertebral interspace with 10-15 mg 0.75% ropivacaine and fentanyl 20 µg by a needle-through-needle technique (Portex Spinal/Epidural Minipack with Lock Pencil Point Spinal Needle 27G/18G; Smiths Medical International Ltd, Hythe, Kent, UK), with the parturient in the sitting position. Then, the spinal needle was removed and the epidural catheter was inserted 4 cm further from the end of the Tuohy needle into the epidural space and secured aseptically. Afterwards, each parturient was positioned supine with left lateral tilt. Sensory and motor assessments were performed at 1 min intervals using pinprick and the modified Bromage score, respectively. Surgery was allowed to begin when adequate anaesthesia to T4 dermatome was achieved. The time of ropivacaine and fentanyl spinal administration, skin incision, delivery, the period from skin incision until delivery, and the duration of the surgery (skin incision until last stitch) were recorded.

Intraoperative monitoring included non-invasive arterial pressure measurement (NIBP – non-invasive blood pressure), electrocardiogram, oxygen saturation (SpO<sub>2</sub>) measurement (Datex-Ohmeda, 5250 RGM, Louisville, USA), and urine output. Hypotension was defined as a decrease in systolic blood pressure by more than 15% of the pre-anaesthetic value or less than 100 mm Hg, and was treated with intravenously administered boluses of ephedrine 5 mg, as required. The time of newborn delivery and the Apgar scores at the first and fifth minute were recorded.

Postoperative analgesia was provided with PCEA ropivacaine 0.15% and fentanyl 2 µg/ml. When the motor blockade of both limbs had elapsed, the PCEA device (Rythmic™ Plus, micrel Medical Devices, Pallini 15344, Greece) was connected to all patients. The PCEA device was programmed to allow a bolus dose of 4 ml with a lockout period of 15 min, without background infusion. Upon instrumentation of the PCEA device, the patients were randomly divided by the method of closed envelope to have either only PCEA (control group, *n* = 32) or PCEA plus celecoxib 200 mg given orally (celecoxib group, *n* = 32). The time of PCEA initiation was recorded. The patients were evaluated by an independent blinded observ-

er at 1 h, 2 h, 4 h, 6 h, 12 h, 18 h and 24 h after the PCEA device was started. The attempted and given PCEA doses, and PCEA volume received at 1 h, 2 h, 4 h, 6 h, 12 h, 18 h and 24 h after the PCEA device initiation were recorded. Motor blockade was assessed using the Bromage scale with values of 0-3 (0 = free movement of legs and feet, 1 = just able to flex knees with free movement of feet, 2 = unable to flex knees, but with free movement of feet, and 3 = unable to move legs or feet), while sympathetic and sensory level of analgesia was estimated by response to cold and to pinprick, respectively. Postoperative analgesia was assessed using a visual analogue scale (VAS 0-10). Paracetamol 500 mg orally was allowed as rescue analgesia, when the VAS score was  $\geq 4$ .

The primary end-point of our study was the administered doses through the PCEA device. Secondary end-points were postoperative pain intensity measured with the visual analogue pain scale at rest and movement and the administration of rescue doses of paracetamol. The level of sympathetic and sensory blockade, and the Bromage scores were also noted. In addition, at the same time intervals parturients' systolic and diastolic blood pressure, heart rate, breath rate, SpO<sub>2</sub>, as well as reports of maternal adverse events, such as paraesthesia, hypaesthesia, headache, fever, chills, dizziness, urinary retention, respiratory depression, fatigue, peripheral oedema, rash, itching, sleeplessness, abdominal pain, nausea and vomiting, diarrhoea or postpartum haemorrhage were also documented. The study was terminated 24 h after the initiation of the PCEA device, and at this time point the overall patient satisfaction regarding postoperative analgesia management was assessed using the following labels of the categorical scale for patient satisfaction: 0 = unsatisfied, 1 = little satisfied, 2 = mildly satisfied, 3 = very satisfied.

### Statistical analysis

To calculate the number of participants needed to ensure a power of 0.80, data from 10 pilot patients were used with the endpoint being the administered PCEA dosages at 24 h. Cohen's coefficient was found to be 0.40 and the total number of patients needed was calculated as  $n = 52$ . The 10 pilot patients were included in the final analysis, since no change in the sampling frame or methodology was made. In order to compensate for possible dropouts, 64 patients were enrolled in the study and the missing data were handled with complete case analysis. Normal distribution of variables was tested with the Kolmogorov-Smirnov test of normality. Variables not normally distributed were analysed with the Kruskal-Wallis test or the Mann-Whitney *U* test. Normally distributed data were analysed with one-way analysis of variance.

Qualitative variables were compared with contingency tables. The analysis was performed with the Statistical Package for Social Sciences v.15. Level of statistical significance was set at  $p < 0.05$ .

### Results

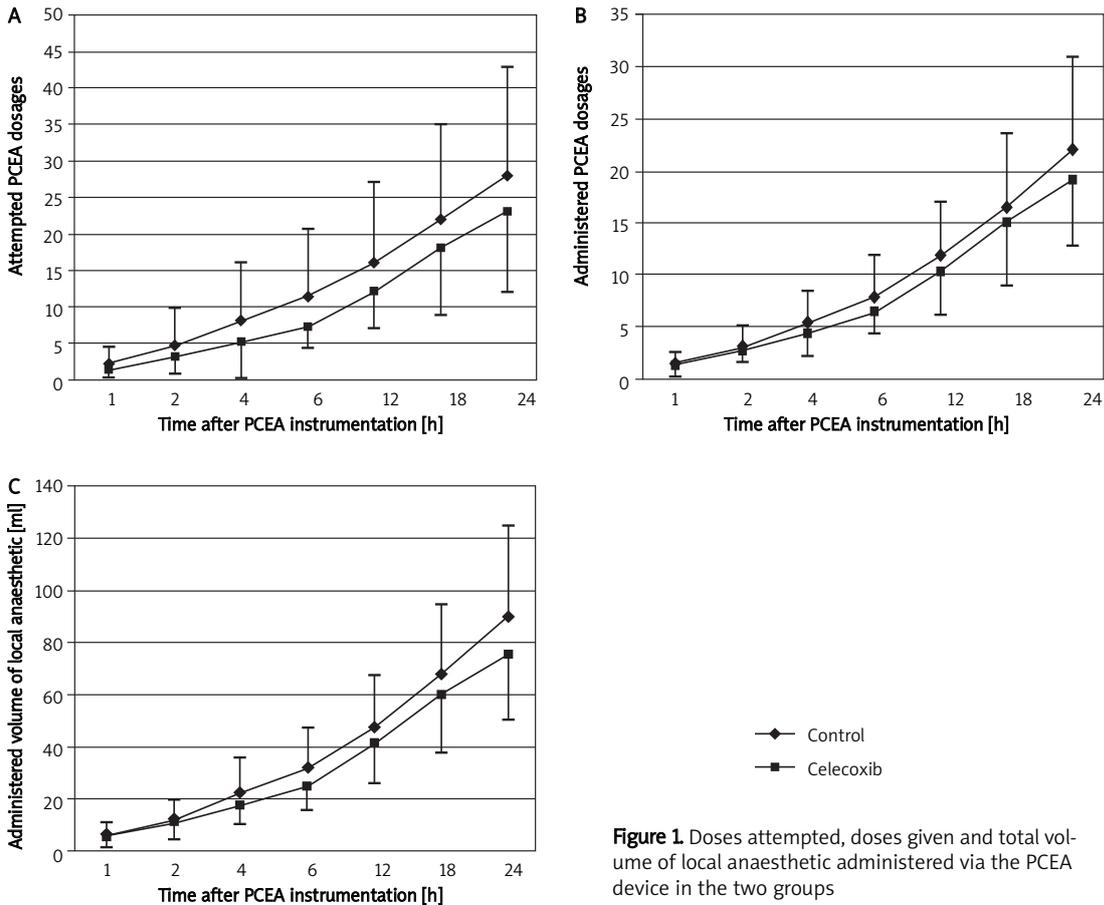
Seventy-seven patients were screened for inclusion in the protocol, of whom 13 were excluded (4 refused regional anaesthesia and 9 did not meet inclusion criteria, of whom 5 had diabetes mellitus, 1 had asthma and 3 had a history of severe cardiovascular disease). The study enrolled 64 patients (32 patients in each group), but 8 patients did not complete the entire protocol (2 due to inadvertent administration of other NSAIDs, and 6 due to dislodgement of the epidural catheter). Thus, only 56 parturients were included in the final analysis. Demographic characteristics, duration of surgery and Apgar scores of the neonates were similar between the groups (Table 1).

Regarding the primary end-point of our study, no statistical differences were found in the given doses, nor in the attempted doses or the total volume of the local anaesthetic administered between the two groups (Figure 1), although the use of the PCEA device was constantly less in the celecoxib group. Also, no significant difference was noted with respect to the time of PCEA initiation ( $p = 0.429$ ), which was  $80.3 \pm 50.8$  min (median = 80, interquartile range = 70) in the control group ( $n = 27$ ), and  $71.0 \pm 36.1$  min (median = 75, interquartile range = 45) in the celecoxib group ( $n = 29$ ).

Significant differences were observed in our secondary outcomes between the groups. The VAS scores at rest and at movement were constantly lower in the celecoxib group compared to the control group (Figure 2). Statistically significant differences

**Table 1.** Demographic and intraoperative characteristics

Parameter	Group	Value
Age [years]	Control	31 $\pm$ 5
	Celecoxib	32 $\pm$ 5
Weight [kg]	Control	78 $\pm$ 11
	Celecoxib	77 $\pm$ 9
Height [cm]	Control	165 $\pm$ 6
	Celecoxib	165 $\pm$ 5
ASA I [%]	Control	40.7
	Celecoxib	27.6
Duration of surgery [min]	Control	55 $\pm$ 13
	Celecoxib	56 $\pm$ 13
Apgar score of neonate at 1 <sup>st</sup> min	Control	9 $\pm$ 2
	Celecoxib	9 $\pm$ 1
Apgar score of neonate at 5 <sup>th</sup> min	Control	10 $\pm$ 0
	Celecoxib	10 $\pm$ 0



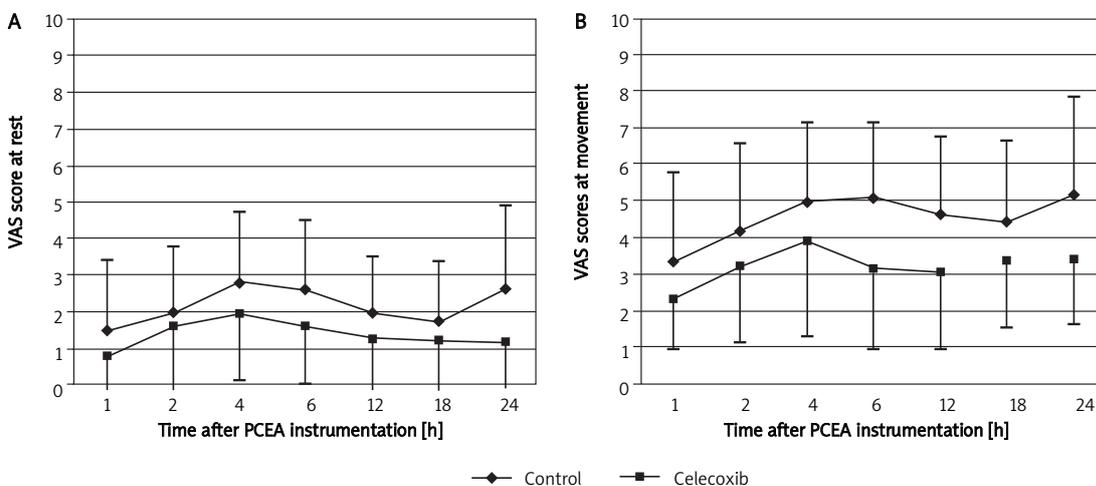
**Figure 1.** Doses attempted, doses given and total volume of local anaesthetic administered via the PCEA device in the two groups

between the two groups were noted for VAS scores at rest at 6 h ( $p = 0.040$ ) and 24 h ( $p = 0.009$ ) and for VAS scores at movement at 4 h ( $p = 0.021$ ), 6 h ( $p = 0.001$ ), 12 h ( $p = 0.007$ ) and 24 h ( $p = 0.008$ ) after the instrumentation of the PCEA device.

The doses of paracetamol administered as rescue analgesia during the first 24 h postoperatively were significantly less in the celecoxib group ( $0.6 \pm 0.7$ )

compared to the control group ( $1.2 \pm 1.1$ ) ( $p = 0.039$ ). The percentage of patients requiring rescue analgesia was lower in the celecoxib group at all 6-hour intervals and for the entire 24-hour interval, being statistically significant for the time interval of 12-18 h after PCEA instrumentation (Table II).

In addition, patient satisfaction was significantly better in the celecoxib group ( $2.9 \pm 0.3$ ) (most patients



**Figure 2.** VAS scores at rest and movement in the two groups

were very satisfied) compared to the control group (2.5 ±0.5) ( $p = 0.001$ ). However, the remaining secondary outcome measures did not reveal any significant difference.

Bromage scores for motor blockade did not differ between the 2 groups. In addition, the maximal level of sensory and the maximal level of sympathetic blockade also did not differ between groups at any time point (data not shown).

Mean arterial pressure and heart rate were within normal ranges. Mean arterial pressure was lower at 6 h and heart rate lower at 24 h in the celecoxib group compared to the control group (Table III). Pulse oximetry values were normal in all patients (> 95%) and did not differ between the 2 groups (data not shown).

No patient presented paraesthesias, headache, dizziness, sleeplessness, fever, chills, bladder dysfunction, respiratory depression, fatigue, peripheral oedema, rash, itching, vomiting, diarrhoea or postpartum haemorrhage. Two patients from the control group presented nausea which was self-limited.

### Discussion

The present study investigated the hypothesis that the addition of an oral postoperative single dose of 200 mg celecoxib could improve postoperative analgesia after caesarean section provided via PCEA technique, and revealed the superiority of this combination regarding the adequacy and quality of postoperative pain control. The majority of parturients who received celecoxib achieved better postoperative analgesia and expressed improved satisfaction compared to those who received only epidural analgesia via PCEA technique. Although no differences were found with respect to the primary endpoint of the study (doses administered through the PCEA device), parturients who additionally received celecoxib experienced significantly less pain at rest and during movement and demanded fewer rescue paracetamol doses compared to those who received PCEA only. It is noteworthy that no parturient presented postoperative haemorrhage or any other maternal adverse effect during the observational period of the present study.

The safety of celecoxib at the dose of 200 mg, unlike most COX-2 inhibitors, has been proven for both breastfeeding mothers and breastfed infants

**Table II.** Percentage of patients who required rescue analgesia at 6-hour intervals and for the entire 24 h (% of patients)

Time frame [h]	Control group	Celecoxib group	Value of $p$
1-6	29.6	13.8	0.149
6-12	44.4	31.0	0.300
12-18	22.2	3.4	0.034
18-24	18.5	6.9	0.189
0-24	59.3	41.4	0.181

[10, 11]. The estimated absolute dose of celecoxib transferred via milk to the infant is about 9.8 µg/kg/day, and the relative infant dose is 0.34% of the maternal dose, an amount which is considered very low and unlikely to pose harm [10, 11]. Noticeably, levels of celecoxib in milk samples at 12 and 24 h were too low to be detected (< 10 ng/ml) [10].

The analgesic efficacy of a single dose of celecoxib 200 mg has also been demonstrated after spinal fusion surgery, tonsillectomy, laparoscopic surgery and orthopaedic surgery [12-15]. However, there are limited studies regarding the use of celecoxib in the obstetric population, with conflicting results. Lee *et al.* showed that celecoxib 200 mg did not improve pain scores after caesarean section under spinal anaesthesia [16]. Similar results were obtained for valdecoxib after caesarean section under spinal anaesthesia [17]. In contrast, in our study there was a clear benefit from the administration of celecoxib, which yielded clinically significant reductions in pain scores, especially during movement. In accordance with our results, Fong *et al.* showed that 400 mg celecoxib after caesarean section significantly reduced pain scores and improved quality of analgesia [18]. However, the concern regarding their study is that there are no data regarding milk excretion of celecoxib at the higher dose (400 mg). The differences between the above studies may be explained by differences in the doses of celecoxib used, the time of administration, as well as the main analgesic technique performed. For instance, intrathecal morphine in the doses used (100-300 µg) [16, 17] may provide such a prolonged analgesic effect that any potential benefit from addition of celecoxib is obscured, as is shown by the low pain scores obtained in the aforementioned studies.

**Table III.** Mean arterial pressure and heart rate in the two groups

Parameter	Group	1 h	2 h	4 h	6 h	12 h	18 h	24 h
MAP [mm Hg]	Control	84 ±6	84 ±7	84 ±8	87 ±7	86 ±5	84 ±7	85 ±6
	Celecoxib	84 ±5	85 ±6	85 ±7	84 ±5*	84 ±7	85 ±6	84 ±7
Heart rate [bpm]	Control	74 ±7	74 ±6	73 ±5	75 ±6	75 ±7	76 ±9	77 ±5
	Celecoxib	75 ±8	75 ±6	74 ±8	74 ±7	74 ±8	75 ±6	73 ±7*

MAP – mean arterial pressure. \* $p < 0.05$  between the two groups at the corresponding time point

In contrast, celecoxib seems to be a useful adjuvant to PCEA or patient-controlled intravenous analgesia with morphine after caesarean section [18]. Particularly, in our study the benefit from celecoxib was clinically relevant throughout the observational period, but it became notably obvious after the first 4 h of administration. This could be because analgesia from intrathecal fentanyl subsided early, as opposed to intrathecal morphine, but also due to delayed gastric emptying and drug absorption of the parturients [19], making analgesic efficacy of celecoxib more obvious at later time points.

The amount of local anaesthetic and opioid administered epidurally is of certain clinical importance, since it affects patient discomfort, paraesthesias, respiratory depression, motor blockade and mobilization [20, 21]. Although the addition of celecoxib did not reduce epidural drug requirements, which was the primary end-point of our study, it did reduce pain and improved satisfaction of the patients, a fact of obvious clinical importance, especially considering the lack of studies regarding patient satisfaction with PCEA after caesarean section. Therefore, based on the present findings, celecoxib seems to be a useful component of a multimodal analgesic regimen after caesarean section. Considering the limited number of drugs that can be safely used in the breastfeeding mother and the concerns over adverse outcomes of NSAIDs in parturients [5, 8], celecoxib should be considered as a safe and useful adjuvant in parturients under PCEA.

In conclusion, under the conditions of this study, celecoxib seems a useful adjunct to PCEA analgesia after elective caesarean section. In view of the undesirable effects of NSAIDs and the limitations encountered in the use of many other analgesics in the breastfeeding mother, we conclude that celecoxib is beneficial as part of a multimodal analgesic technique in the obstetric setting. Further investigation is warranted to explore the effect of long-term administration of celecoxib on both mother and breastfed newborn.

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