Intramuscular Diclofenac for Analgesia after Cesarean Delivery: A Randomized Controlled Trial

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Objective: *To evaluate the effectiveness of intramuscular diclofenac in postoperative cesarean section pain control.*
Study design: *A randomized controlled trial.*
Setting: *Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital.*
Subjects: *Eighty patients scheduled for elective cesarean section between October 2007 and April 2008.*
Material and Method: *All patients had cesarean section performed under spinal anesthesia with spinal morphine and randomized into two groups by a table of randomization. They were to receive diclofenac 75 mg intramuscular every 12 hours for 2 doses or standard rescue drugs (Tramadol).*
Outcome measurements: *The number of patients who required rescue drugs, pain score (VAS), side effects of diclofenac, and satisfaction were evaluated for 48 hours postoperatively.*
Results: *In the diclofenac group, no patient required rescue drug compared to 20% of patients in the control group ($p < 0.05$). Median pain scores were less in the diclofenac group at 6 hours (1 (range 0-6) vs. 4 (range 0-6), $p = 0.002$), 12 hours (2 (range 0-5) vs. 3 (range 0-7), $p = 0.031$), and 24 hours (1.5 (range 0-4) vs. 3 (range 1-8), $p < 0.0001$), respectively. No side effects of diclofenac (e.g. gastrointestinal bleeding, bleeding tendency, uterine atony, or injection site irritation) were observed. Satisfaction was comparable in both groups.*
Conclusion: *Diclofenac can be used safely to reduce the requirement of rescue drugs for pain control in postoperative cesarean section.*

Keywords: *Cesarean section, Diclofenac, Injections, Intramuscular, Pain, Postoperative, Tramadol, Pain measurement*

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Cesarean section is the most common obstetrical surgery[1]. In the past, the major problems of cesarean section were hemorrhage and infection, but development of surgical techniques and antibiotics have reduced these problems. At present, postoperative cesarean section pain control is the major problem that confronts many physicians. In general, the most common anesthesia used in cesarean section is spinal block (hyperbaric bupivacaine 10-12 mg with morphine 0.2 mg)[1]. If patients develop pain after cesarean section, opioids derivatives are prescribed for control pain. Many alternative drugs are employed to control pain because many patients suffer from side effects of opioids and its derivatives such as respiratory depression (0.25%), itching (58%), and nausea and vomiting (39.9%)[2]. In King Chulalongkorn Memorial Hospital, 50 mg intramuscular tramadol (tramadol hydrochloride) is the rescue drug used for patients who have spinal anesthesia with morphine. The mode of action of tramadol has yet to be fully understood, but it is believed to work through modulation of the noradrenergic and serotonergic systems in addition to its mild agonism of the μ-opioid receptor. The contribution of non-opioid activity is demonstrated by the analgesic effects of tramadol not being fully antagonized by the μ-opioid receptor antagonist

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naloxone. The most commonly reported adverse drug reactions are nausea, vomiting, sweating and constipation. Drowsiness is also reported, although it is less than other opioids. Respiratory depression, a common side effect of most opioids, is not clinically demonstrated in normal doses. Tramadol is in the FDA pregnancy category C and its use by nursing mothers is not recommended by the manufacturer because the drug passes into breast milk[15]. However, the absolute dose excreted in milk is quite low, and tramadol is generally considered to be acceptable for use in breast-feeding mothers. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the analgesia that can be used for pain control and reduce requirement of opioids in 40-70%[3,4]. Diclofenac, one of the NSAIDs, is used with adequate pain control in many major surgeries. The exact mechanism of action is not entirely understood, but it is thought that the primary mechanism responsible for its anti-inflammatory/antipyretic/analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have therefore a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin. Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A_2 as part of its mechanism of action. These additional actions may explain the high potency of diclofenac-it is the most potent NSAID on a broad basis. Diclofenac inhibits the production of prostaglandins, so this effect can also reduce pain after cesarean sections[5-7]. Diclofenac is reported to be safely used in short-term (< 1week) without any complications (*e.g.* gastrointestinal bleeding, bleeding tendency, or injection site irritation)[8-10]. Diclofenac administration in post cesarean pain control may have an extended interval from 12 to 24 hours by intramuscular route or rectal suppository route[8,13]. In addition, in postpartum period, diclofenac is found to be used safely[15] without tocolysis effect[8] and diclofenac is not found in colostrum[11,12].

The objective of the present study was to evaluate the effectiveness of diclofenac intramuscular route to reduce the requirement of rescue drugs in postoperative cesarean section pain control.

Material and Method

Pregnant women who had elective cesarean section in King Chulalongkorn Memorial Hospital between October 2007 and April 2008 were enrolled in the present study. The patients who had single viable fetus in cephalic presentation and had no history of NSAIDs allergy or contraindication to NSAIDs administration were included into the present study. Low transverse cesarean sections were performed by the second or third year residents with low midline incision. The anesthetic and surgical techniques were standardized. Patients who had an operative time of more than 2 hours, intraopertive blood loss more than 1000 milliliters, or injury to bowel or bladder were excluded from the present study.

Sample size was calculated from the pilot study with type 1 (α) error of 0.05 and type 2 (β) error of 0.10 and 37 patients were required in each group. Therefore, the authors enrolled 80 patients in the present study, and randomized patients into two groups by table of randomization. All patients in each group had low transverse cesarean section performed (with or without tubal resection) under spinal anesthesia (hyperbaric bupivacaine 10-12 mg with morphine 0.2 mg)[1]. In the control group, if patients required rescue drugs postoperatively, tramadol 50 mg intramuscular was used for pain control. In the study group, patients received diclofenac sodium 75 mg intramuscular postoperatively (within 2 hours) and then at 12 hours, however, if patients developed intractable pain, tramadol 50 mg intramuscular was used for the rescue drug. All intramuscular drugs were injected at the gluteal area.

The researcher was blind from the present study to reduce the bias. The postoperative order protocols were inserted in the sealed envelope and opened by the surgeons when the patients met the inclusion criteria.

Visual analog score (VAS) was used to evaluate pain level (0 = no pain to 10 = worst pain) at 6, 12, 24, and 48 hours postoperatively by researcher and nurse. After 48 hours, the researcher collected the number of patients who required rescue drugs and defined patients in control group or study group from medical administration records. Satisfaction was evaluated at 24 and 48 hours postoperatively (1 = very unsatisfied to 5 = very satisfy). Side effects of diclofenac (*e.g.*, gastrointestinal bleeding, bleeding

tendency, uterine atony, injection site irritation, and anaphylaxis) were observed for 48 hours.

SPSS version 15 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Student t-test, Chi-square test, and Mann-Whitney U-Test were used where appropriate for statistical analysis. P-value of < 0.05 was considered statistically significant.

The present study was approved by the Institutional Ethical Committee and written informed consent was obtained from the patient.

Results

Eighty patients were enrolled and no one was excluded. After randomization, 40 patients were allocated in each group.

General data of the patients are shown in Table 1 and Table 2. No statistically significant difference was observed between groups in mean age, parity, number of repeat cesarean section, concurrent tubal resection, gestational age, no of ANC visits, anesthetic technique, and operative outcomes.

The number of patients who required rescue drugs and pain score (VAS) were compared between groups, the results are shown in Table 3 and Table 4. In the diclofenac group, no patient required a rescue drug while in the control group 20% ($p < 0.05$) required a rescue drug. Median pain scores were less in the diclofenac group compared to the control group at 6, 12, and 24 hours postoperatively (6 hours**:** 1 (range 0-6) vs. 4 (range 0-6), $p = 0.002$), 12 hours**:** 2 (range 0-5) vs. 3 (range 0-7), $p = 0.031$ and 24 hours**:** 1.5 (range 0-4) vs. 3 (range 1-8), $p < 0.0001$), respectively. In the diclofenac group, two patients were denied to receive a second dose of diclofenac in the next 12 hours because they had no pain and did not require any analgesia. All patients who required rescue drugs

Table 1. Patients characteristics and obstetric data

	Control group (n = 40)	Diclofenac group (n = 40)	p-value
Age (years) (mean ± SD)	30.80 ± 4.82	29.60 ± 5.19	0.297
Nulliparity (no) (%)	6/40 (15)	12/40 (30)	0.488
Multiparity (no) (%)	34/40 (85)	28/40 (70)	0.488
Repeat cesarean section (no) (%)	34/40 (85)	26/40 (65)	0.069
Cesarean section with tubal Resection (no) (%)	26/40 (65)	19/40 (47.5)	0.115
GA (days) (mean ± SD)	270.88 ± 5.90	270.95 ± 6.66	0.958
ANC (visits) (mean ± SD)	9.88 ± 2.65	9.18 ± 2.02	0.188

Table 2. Anesthetic and operative datas

	Control group (n = 40)	Diclofenac group (n = 40)	p-value
Bupivacaine (mg) (mean ± SD)	10.90 ± 0.30	10.98 ± 0.15	0.170
Morphine (mg) (mean ± SD)	0.20 ± 0.00	0.20 ± 0.00	1.000
Operative time (mins) (mean ± SD)	58.63 ± 18.08	59.00 ± 19.61	0.929
Blood loss (ml) (mean ± SD)	546.25 ± 183.76	550.00 ± 190.81	0.170

Table 3. Number of patients who required rescue drugs and pain score (VAS) evaluation after cesarean section

	Control group (n = 40)	Diclofenac group (n = 40)	p-value
Rescue drugs used (no) (%)	8/40 (20)	0/40 (0)	0.003
VAS at 6 hours (median) (range)	4 (0-6)	1 (0-6)	0.002
VAS at 12 hours (median) (range)	3 (0-7)	2 (0-5)	0.031
VAS at 24 hours (median) (range)	3 (1-8)	1.5 (0-4)	<0.001
VAS at 48 hours (median) (range)	3 (1-8)	3 (0-4)	0.136

Table 4. Pain score (VAS) evaluation after cesarean section (subgroup analysis)

Group	Control		p-value	Diclofenac		p-value
Parity	Nulliparity	Multiparity		Nulliparity	Multiparity	
VAS at 6 hours (median) (range)	5 (0-5)	3 (0-6)	NS	0.5 (0-5)	1.5 (0-6)	NS
VAS at 12 hours (median) (range)	4 (0-7)	3 (0-5)	NS	1 (0-3)	3 (0-5)	NS
VAS at 24 hours (median) (range)	4.5 (2-8)	3 (1-8)	NS	1.5 (0-3)	1.5 (0-4)	NS
VAS at 48 hours (median) (range)	3 (3-4)	3 (1-8)	NS	2 (0-3)	3 (0-4)	NS

Table 5. Mean satisfaction of the treatment after cesarean section

	Control group	Diclofenac group	p-value
Satisfaction at 24 hours (mean $\pm$ SD)	4.05 $\pm$ 0.59	4.33 $\pm$ 0.52	0.073
Satisfaction at 48 hours (mean $\pm$ SD)	4.00 $\pm$ 0.50	4.25 $\pm$ 0.54	0.120

requested the rescue drugs within the first 24 hours postopertively (2-20 hours) and four patients required multiple doses of rescue drug (2-4 doses).

Satisfaction evaluation at 24 and 48 hours postoperatively is shown in Table 5. In the diclofenac group, patients had more satisfaction at 24 hours with the treatment than in the control group without statistically significant difference. Diclofenac complication (*e.g.* gastrointestinal bleeding, bleeding tendency, uterine atony, injection site irritation, or anaphylaxis) was not observed in the present study.

Discussion

In previous studies for pain control after cesarean section[7,13,14], most opioids and its derivatives administered were used with patient controlled analgesia (PCA) or patient controlled epidural analgesia (PCEA) that required anesthesiologists, special instrumentations, and well trained nurses to take care of the patients. However, PCA or PCEA are not available in many general hospitals in Thailand. In addition, side effects of opioids and its derivatives must be observed until discontinuation of PCA or PCEA and thereafter 24 hours in PCEA. Diclofenac is available in all general hospitals and its administration requires no special close observation or instrumentation. Therefore, in general practice, diclofenac has more advantages and availability to be used in postoperative cesarean pain control.

From the present study, diclofenac has adequate pain control and can significantly reduce the requirement of rescue drugs in post cesarean section under spinal block with intrathecal morphine ($p = 0.003$). Tramadol may have less effectiveness than diclofenac to control pain in post cesarean section patients because in control group, patients who required rescue drug, four out of eight patients required multiple doses of tramadol to control pain. However, the present study cannot directly demonstrate the effectiveness of tramadol compared to diclofenac. Many patients in the diclofenac group described less periodic uterine cramping pain (after pain). Diclofenac may be used as only a single dose in the postoperative period. Two patients in the diclofenac group had adequate pain control and were denied second dose of diclofenac. From the authors' findings, further study is required to establish this result.

Median pain scores were statistically significantly different between diclofenac and the control group at 6, 12 and 24 hours postoperatively (6 hours: 1 (range 0-6) vs. 4 (range 0-6), $p = 0.002$); 12 hours: 2 (range 0-5) vs. 3 (range 0-7), $p = 0.031$ and 24 hours: 1.5 (range 0-4) vs. 3 (range 1-8), $p < 0.0001$), respectively. Previous studies have shown that diclofenac has effective pain control for 12 hours for intramuscular route and 24 hours for rectal suppository route[4-6]. In the present study, the first dose of diclofenac was injected at gluteal area within 2 hours postoperatively and at 12 hours later, therefore evaluated time of pain score at 6, 12, and 24 hours still have effect of diclofenac more than the evaluated time at 48 hours postoperatively. Difference in range of

pain score was observed in the present study. The maximal pain score in the control group was higher than diclofenac group (8 vs. 4). In the diclofenac group, the minimal pain score reached 0 at all periods of evaluation, but in the control group, at 24 hours and 48 hours, nopatients had a pain score of 0. From subgroup analysis of parity, no statistically significant difference of pain scores were observed between nulliparity and multiparity.

Because the present study had no placebo control due to ethical consideration, the placebo effect could not be excluded. In addition, recall bias and measurement bias might also be found in the present study.

In conclusion, diclofenac can be prescribed in postoperative cesarean pain control with effectiveness and safety when wishing to avoid opioids and its derivatives because of side effects.

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การศึกษาแบบสุ่มในการฉีดยาไดโคลฟีแนคเข้ากล้ามเพื่อลดความเจ็บปวดหลังการผ่าตัดคลอด

จักรกฤษณ์ สุรการ, เยื้อน ตันนิรันดร

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการฉีดไดโคลฟีแนคเข้ากล้ามเนื้อเพื่อลดความเจ็บปวดหลังการผ่าตัดคลอด*
รูปแบบการศึกษา: *การศึกษาเชิงทดลองแบบสุ่ม*
ผู้เข้าร่วมการศึกษา: *หญิงตั้งครรภ์ครบกำหนด 80 รายที่นัดผ่าตัดคลอดที่โรงพยาบาลจุฬาลงกรณ์ ในช่วงเดือนตุลาคม พ.ศ. 2550 ถึงเดือนเมษายน พ.ศ. 2551*
วัสดุและวิธีการ: *หญิงตั้งครรภ์ครบกำหนด 80 รายได้รับการผ่าตัดคลอดโดยวิธีมาตรฐานและได้รับการระงับความรู้สึกด้วยวิธีฉีดยาชาเข้าช่องไขสันหลัง (spinal block) และได้รับมอร์ฟีน 0.2 มิลลิกรัมเข้าช่องไขสันหลังร่วมด้วย และแบ่งกลุ่มการศึกษาโดยวิธีการสุ่มเป็น 2 กลุ่ม โดยกลุ่มทดลองได้รับการฉีดไดโคลฟีแนค 75 มิลลิกรัมเข้ากล้ามเนื้อทุก 12 ชั่วโมง 2 ครั้ง ถ้าทั้ง 2 กลุ่มมีอาการปวดจะได้รับยาแก้ปวดเพิ่มเติม (ทรามาดอล)ตามความต้องการของผู้ป่วย*
การวัดผล: *จำนวนของผู้ที่ร้องขอยาแก้ปวดเพิ่มเติมในแต่ละกลุ่ม, ระดับความเจ็บปวด, ผลข้างเคียงของไดโคลฟีแนค และความพึงพอใจของผู้ป่วยในระยะ 48 ชั่วโมงหลังการผ่าตัด*
ผลการศึกษา: *จำนวนของผู้ที่ต้องการยาแก้ปวดเพิ่มเติมในแต่ละกลุ่ม, ระดับความเจ็บปวดในกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติและไม่พบผลข้างเคียงของไดโคลฟีแนค แต่ความพึงพอใจไม่แตกต่างในทั้ง 2 กลุ่ม*
สรุป: *การใช้ยาฉีดไดโคลฟีแนคเข้ากล้ามเนื้อเพื่อลดความเจ็บปวดหลังการผ่าตัดคลอดสามารถลดการใช้ยาแก้ปวดเพิ่มเติมและระดับความเจ็บปวดหลังการผ่าตัดได้โดยไม่พบผลข้างเคียง*