Diclofenac Intramuscular Single Dose to Decrease Pain in Post Operative Caesarean Section: A Double Blind Randomized Controlled Trial

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Objective: *To compare the use of diclofenac intramuscular single dose to decrease pain in post operative Caesarean section with none used.*
Study design: *A double blind randomized controlled trial.*
Setting: *Department of Obstetrics and Gynecology, Ranong Hospital.*
Subjects: *Sixty-four patients who underwent post operative Caesarean section in Ranong Hospital from October 2003 to March 2004.*
Intervention: *The subjects were randomized by allocation to receive diclofenac intramuscular or placebo, both groups received morphine by Patient Controlled Analgesia (PCA).*
Main outcome measures: *Amount of morphine sulfate used, in both groups by Patient Controlled Analgesia (PCA) and level of pain using Visual Analog Score (VAscore).*
Results: *Morphine was used significantly less in the group of patients who had diclofenac intramuscular single dose in post operative Caesarean section but the level of pain was not significantly different.*
Conclusion: *A single dose of diclofenac intramuscularly decreases the use of morphine during the in post operative period of Caesarean section.*

Keywords: *Diclofenac, Morphine, Patient Controlled Analgesia, Caesarean section, Visual Analog Score*

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Pain is a major problem in surgery, including Caesarean section. The patients require medications for analgesia, most commonly used are the opioids and derivative group such as morphine sulfate and pethidine hydrochloride. They act by inhibiting opioids receptors both in the brain stem and the spinal cord. At the spinal cord level opioids inhibit signal of pain at the dorsal horn. At the level of brain stem, they decrease the sensation of pain and decrease the response of pain at the limbic cortex[1,2].

Non-steroid anti-inflammation drugs are substances used for relief of pain mostly in minor surgery and have been used for many years. Non-steroid anti-inflammation drugs act by anti-inflammation. They inhibit the production of prostaglandins. Another, non-steroid anti-inflammation drugs decrease pain by inhibiting phosphodiesterase enzyme which increase cyclicAMP in the white blood cells, so white blood cell decreases the release of prostaglandins, lekotrienes, bradykinin, serotonin and histamine which will decrease pain at the periphery[3-5].

Because non-steroid anti-inflammation drugs have less potency than the opioids or derivative group, they can not be use alone in major surgery such as Caesarean section. However, non-steroid anti-inflammation drugs have been use with the opioids or the derivative group for relief of pain. The dose of non-steroid anti-inflammation drugs is not related to the reduction of pain[6,7].

The most common complication associate with non-steroid anti-inflammation drugs is gastro-intestinal irritation. Patients who used non-steroid anti-inflammation drugs for long term have an increased risk of peptic ulcer. However non-steroid anti-inflammation drugs used post operatively for a short period of time therefore this side effect is low. Kehlet and

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Dahl reported cases using non-steroid anti-inflammation drugs post operatively in a short course of, for not more than 1 week, 927 cases had only one case of hemorrhagic vomiting occurred[8].

Diclofenac is a benzene acetic acid derivative that acts, like other non-steroid anti-inflammation drugs, by inhibit cyclo-oxygenase enzyme that mediate the body's production of the prostaglandins implicated in pain and inflammation[9].

Patient Controlled Analgesia or PCA, developed by Sechzer in 1968, is a machine for patient self administration of medication when he feels pain. This reduced the need for excessive medication[10]. Laitinen J, Nuutinen L reported in 1992, intravenous diclofenac with PCA fentanyl for pain relief after total hip replacement. They concluded that the addition of diclofenac led to reduction in fentanyl requirement but did not have any other significant advantages in the treatment of pain following major orthopedic surgery[11].

The objective of this paper is to report the result of a double blind randomized study of a single muscular dose of diclofenac.

Material and Method

Patients who had Caesarean section with Pfannenstiel incision at Ranong Hospital from October 2003 to March 2004 were enrolled in the present study, informed consent was obtained. Exclusion for participation included patients who had obstetrics complications such as pregnancy induced hypertension, placenta previa, twin pregnancy, abruptio placentae, patients who had a previous Caesarean section with a midline incision and patients who had intra-operative complication.

The sample size was calculated in statistically at type I error = 0.05 and typeII error = 0.20 were 41 cases per group controlled or 82 cases in totally. The sample size of Laitinen J, Nuutinen L reported in Anesthesiology 1992, intravenous diclofenac with PCA fentanyl for pain relief after total hip replacement, were 20 cases per group controlled or 40 cases in totally[11]. So this trial sample size was designed 35 cases per group controlled or 70 cases in totally which were less than calculated size about 14.6% because there were limited in the time, cases participated in the study and budgets. Thirty-five patients were injected with diclofenac sodium 75 mg intramuscularly (diclofenac group) and thirty-five patients were injected with sterile water intramuscularly (placebo group) post operative Caesarean section.

The evaluator and the patients were blinded. All ampoules were numbered. A computer was used to randomize selection the drug and placebo. At the same time morphine sulfate 10 milligrams was injected intramuscularly.

PCA was applied by using morphine sulfate in concentration 1 mg/ml, bolus dose 1.5 mg/time, continuous dose 0.5 mg/hr, drug interval 8 minute.

Patients recorded pain by using Visual Analog Score (VAscore) with running scale of 0 to 10. Scale 0 referred to no pain and scale 10 referred to severe pain. Pain was recorded 4 times, after the start of PCA 1 hour, 2 hours, 6 hours, and 20 hours.

The statistical methods for analysis of data generated during this clinical trial include student t-test and chi-square test. A p-values less than 0.05 were considered significant.

Results

The final study group included 64 patients, after 6 were more excluded because they did not receive medication according to protocol or had drug hypersensitivity after the starting medication such as severe vertigo, or severe vomiting. Thirty-four cases were randomly received diclofenac, morphine intramuscular and morphine in Patient Controlled Analgesia (PCA) (diclofenac group), and thirty cases received sterile water, morphine intramuscular and morphine in Patient Controlled Analgesia (PCA) (placebo group).

The mean age of the diclofenac group was 29.29 ± 5.02 years and 27.40 ± 5.96 years in the placebo group. The mean operative time in the diclofenac group was 33.16 ± 8.11 years and 31.33 ± 6.96 years in the placebo group. The mean maternal body weight in diclofenac group was 69.59 ± 13.60 kilograms and 69.70 ± 12.00 kilograms in placebo group. All mean age, operative time and maternal body weight (see in Table 1), were not significantly different between the two groups.

Because the pain between repeat Caesarean section may be more than primary Caesarean section, therefore test the proportion of repeat Caesarean section to primary Caesarean section between diclofenac group and placebo group. The Overall test was not significantly different (see in Table1).

Because the pain between Caesarean section with tubal ligation may be more than without tubal ligation, so we test the proportion of those who had concomitant tubal ligation with those who did not between diclofenac group and placebo group. The Overall test was not significantly different (see in Table1).

The mean amount of morphine used in the diclofenac group (21.688 ± 9.78) was significantly less

Table 1. Characteristics of patients, risk factors and amount of morphine used for post operative Caesarean section pain

Characteristics	diclofenac group (n = 34)	placebo group (n = 30)	p-value
Ages (years ± SD)	29.29±5.02	27.40±5.96	0.173
Operative-time (mins ± SD)	33.16±8.11	31.33±6.96	0.340
Maternal body weight (kgs ± SD)	69.59±13.60	69.70±12.00	0.973
Number of repeat Caesarean section	8/34	7/30	1.000
Number of primary Caesarean section	26/34	23/30	1.000
Number of Caesarean section with tubal ligation	17/34	13/30	0.625
Number of Caesarean section without tubal ligation	17/34	17/30	0.625
Mean used of morphine (in mg) by PCA	21.69±9.78	27.41±11.09	0.016

This trial, the maternal body weight used pre operative Caesarean section body weight because their difficulties to measured the post operative Caesarean section maternal body weight. The trial assumed the lost of maternal body weight post operative Caesarean section were the same proportion in both group.

than the placebo group (27.410 ± 11.09) (see in Table 1). Diclofenac intramuscularly can decrease the amount of morphine used in post operative Caesarean section. This intern reduces the risk of complications from morphine such as, respiratory depression, nausea, vomiting and vertigo.

Mean of VAscore post operative Caesarean section at 1 hour in the diclofenac group was 4.71 ± 1.98 and 4.70 ± 1.64 in the placebo group (see in Table 2). This was no difference statistically (p = 0.99). The same as, at 2 hours, 6 hours and 20 hours (at 2 hours p = 0.535, at 6 hours p = 0.307 and at 20 hours p = 0.50, see in Table 2). By observation, in both groups from 1 hour to 20 hours, the VAscore decreased serially.

During the present clinical trial, one patient had a dyspnea, one had a severe nausea and vomiting and one had a severe vertigo. They were excluded from the trial because they could not take the medication. There were also other three cases excluded, because of incomplete data collection. Another, in the diclofenac group had dyspepsia, in the placebo group there were two cases develops mild nausea and vomiting but all were included in the present trial after symptomatic treatment.

Table 2. Mean of VAscore at post operative Caesarean section

Vas at post-op	diclofenac group n = 34	placebo group n = 30	p-value
VAscore at 1 hr (mean ± SD)	4.71±1.98	4.70±1.64	0.990
VAscore at 2 hr (mean ± SD)	3.65±1.76	3.93±1.91	0.535
VAscore at 6 hr (mean ± SD)	3.32±1.32	3.70±1.60	0.307
VAscore at 20 hr (mean ± SD)	3.41±2.02	3.10±1.60	0.500

Discussion

The result of this prospective clinical trial has shown the effectiveness of diclofenac intramuscular. The drug can decrease the amount of morphine used in post operative Caesarean section. This is the same as orthopedic operation, hip replacement, which used diclofenac intravenous coupled with fentanyl by PCA[11]. The pain in the diclofenac group were less than the placebo group. In the present trial, the post operatives assessed by pain VAscore in both groups was significantly different. This is similar to orthopedic operation, hip replacement, which had more pain than Caesarean section. In some studies, diclofenac intravenously can reduce pain better than intramuscular route[12]. Reduction in amount of morphine use reduce the risk of morphine side effect such as respiratory depression, nausea vomiting[13].

Diclofenac, which was used in the present trial, like other non-steroid anti-inflammation drugs such as ibuprofen, piroxicam and naproxen, have been used for many years because of its low price and its popularity in Thailand, its low risk of severe drug hypersensitivity, though sometimes its produce gastrointestinal complications[14-16]. Specific COX-2 inhibitors may help the gastrointestinal complication but they are more expensive[17,18]. Another potential disadvantage of non-steroid anti-inflammation drugs is its effect on platelet function, though this was not detected in the present trial. The incidence of post partum hemorrhage, in both groups, was small but we could not be concluded about this risk due to the sample size in the present trial was too small.

In conclusion, the present trial indicated that there were decreases in morphine used by the diclofenac group. But pain in both groups using VAscore was not significantly different. The limitation of the present trial was due to sample size which was

not large enough to study the side effects of diclofenac and morphine. Further study needs to be done with larger sample size. The future study should include new non-steroid anti-inflammation drugs, specific COX-2 inhibitor, which is said to have fewer side effects than diclofenac.

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การให้ยาไดโคลฟีเนคเข้ากล้ามเนื้อในผู้ตั้งครรภ์หลังผ่าตัดคลอดเพื่อลดความเจ็บปวด

อธิคม บัวเลิศ

วัตถุประสงค์*: เพื่อศึกษาเปรียบเทียบการฉีดไดโคลฟีเนคเข้ากล้ามเนื้อหลังผ่าตัดคลอดจะมีผลลดความเจ็บปวดและลดปริมาณความต้องการยาแก้ปวดมอร์ฟีน*

รูปแบบการวิจัย*: การวิจัยเชิงทดลอง*

ผู้เข้าร่วมการวิจัย*: ผู้ตั้งครรภ์ครบกำหนด จำนวน 64 ราย ซึ่งได้รับการผ่าตัดคลอดที่โรงพยาบาลระนอง ในช่วงเดือนสิงหาคม 2003 ถึง เดือนกุมภาพันธ์ 2004*

วิธีการศึกษา*: กลุ่มที่เข้าศึกษาแบ่งเป็น 2 กลุ่ม โดยกลุ่มแรก ได้รับยาไดโคลฟีเนคฉีดเข้ากล้ามเนื้อ กลุ่มที่ 2 ได้รับน้ำบริสุทธิ์ฉีดเข้ากล้ามเนื้อ ทั้งสองกลุ่มจะได้รับยามอร์ฟีน ขนาด 10 มก.ฉีดเข้ากล้ามเนื้อ และมอร์ฟีนความเข้มข้น 1 มก./มล. โดยทางเครื่องให้ยาระงับความเจ็บปวดด้วยตนเองเข้าทางหลอดเลือดดำ*

การวัดผล*: วัดจากความรู้สึกเจ็บปวดของผู้ตั้งครรภ์ ในชั่วโมงที่ 1,2,6,20 หลังจากเริ่มให้ยาแก้ปวด และวัดจากปริมาณการใช้ยามอร์ฟีนทางเครื่องให้ยาระงับความเจ็บปวดด้วยตนเอง*

ผลการศึกษา*: มีระดับการใช้ยามอร์ฟีนทางเครื่องให้ยาระงับความเจ็บปวดด้วยตนเองในกลุ่มที่ได้รับยาไดโคลฟีเนคน้อยกว่ากลุ่มที่ไม่ได้รับอย่างมีนัยสำคัญทางสถิติ แต่ระดับความเจ็บปวดของทั้งสองกลุ่มไม่มีความแตกต่างอย่างมีนัยสำคัญ*

สรุป*: การให้ยาไดโคลฟีเนคเข้ากล้ามเนื้อหลังผ่าตัดคลอดช่วยลดปริมาณความต้องการมอร์ฟีนของผู้ตั้งครรภ์ในขณะที่มีระดับความเจ็บปวดที่เท่ากัน*