Effect of Intramuscular Diclofenac after Explore Laparotomy for Gynecologic Surgery: A Randomized Double-Blinded Placebo Controlled Trial

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Background: *Several adjuvant analgesic agents proposed to treat the postoperative pain while reducing the doses of opioid and its derivatives. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in several operative procedures. The present study aimed to demonstrate the morphine-sparing effects of single-dose intramuscular diclofenac sodium in explore laparotomy gynecologic surgery.*

Material and Method: *Forty-six patients were randomly assigned to receive 75-mg of diclofenac sodium or normal saline with intramuscular morphine during immediate postoperative period. Additional morphine for pain control was given by patient-controlled analgesia. 24-hour morphine consumption, pain score, adverse effects and satisfaction of the patients were recorded.*

Results: *Median morphine consumption among groups was significant difference between placebo and diclofenac group (32 and 19 mg) (p = 0.041). Greater difference was shown in patients who underwent total abdominal hysterectomy (p = 0.009). Catagorical pain score at 6-hour postoperatively was significant lower in diclofenac group (p = 0.006). No significant difference was found between groups in visual analogue pain score, patients' satisfaction, presence of bleeding or nausea and vomiting.*

Conclusion: *The present study demonstrated that single dose of diclofenac sodium has morphine-sparing effects and can be safely used in explore laparotomy gynecologic surgery without significant adverse effects.*

Keywords: *Intramuscular diclofenac, Randomized controlled trial, Gynecologic surgery*

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Management of postoperative pain is one of the most challenging issues in surgery, including gynecological practice. Uncontrolled pain may contribute to cause several postoperative complications. Lack of early mobilization due to surgical wound pain may lead to atelectasis, respiratory infection and bowel dysmotility. Pulmonary function could be decreased due to shallow breathing and ineffective cough[1]. Mostly, analgesic drugs used in controlling postoperative pain in gynecologic surgery are morphine and its derivatives. They are excellent analgesic agents, acting on opioid receptors in both brain stem and spinal cord[2]. Increasing dosage of morphine to provide effective pain control is associated with several adverse effects such as nausea, vomiting, bowel dysmotility, constipation and respiratory depression[3]. Thus, several adjuvant analgesic agents proposed to improve the surgical pain control while reducing the doses of opioid analgesics.

Traditional non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, ibuprofen and naproxen are widely used in postoperative pain control. The major mechanism of action is decreasing prostaglandin E_2 production by inhibiting both cyclooxygenase-1 (COX-1) and cyclohoxygenase-2 (COX-2) enzymes. Inhibition of COX-2 promotes anti-inflammatory effect, reduction of fever, pain and also promote gastrointestinal adverse effect and bleeding by inhibiting COX-1 pathway[4]. However, short-term uses of NSAIDs in post-operative period demonstrate

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low prevalence of such gastrointestinal side effects[5]. COX-2 selective inhibitors are currently prescribed in acute pain control, postoperative pain management in many dental and orthopedic procedures[6-8]. They are also well-established treatment of endometriosis in gynecological practice[9,10]. However, there are some concerns in patients at risk of thromboembolic event and expensiveness of the parenteral form.

Diclofenac sodium is a widely used, traditional NSAIDs with non-selective inhibiting action of both COX-1 and COX-2 enzymes[11]. Continuous wound infiltration and intramuscular use of diclofenac has been reported to decrease the dose of morphine used in postoperative period of cesarean section[12,13]. Rectal diclofenac has been shown to reduce morphine consumption following total abdominal hysterectomy[14]. The primary aim of the present study is to demonstrate the morphine-sparing effects of intramuscular diclofenac in the short-term use after explore laparotomy gynecologic surgery. The secondary objectives are to demonstrate its role in postoperative pain reduction, adverse effects and satisfaction of the patients.

Material and Method

Patients who scheduled for explore laparotomy gynecologic surgery were enrolled in the present study. After obtaining the approval by institutional ethical committee of Thammasat University, written inform consents were done. Exclusion criteria are presence of cardiovascular, renal or hepatic disease, bleeding disorders; patients with previous history of GI bleeding or peptic ulcers; known asthma or allergy to acetylacetic acid; recieving ACE inhibitors, aspirin, methotrexate, rifampicin, warfarin, lithium or cimetidine.

46 patients were randomly assigned to receive 75-mg of diclofenac sodium or normal saline according to block of four randomization. The patients received single dose of each medication with morphine intramuscularly at 1-hour postoperative period in recovery room. The patients and investigator were blinded. Additional morphine for pain control was administered by patient-controlled analgesia (PCA), delivering morphine 1 mg with a lockout time of 5 minute. The medication codes were declared when the patients discharged.

Pain assessment after operation were measured using visual analog scale (VAS) and category pain score (CPS) at 1, 2, 6 and 24 hours after receiving medication. VAS recorded pain as a 10-cm running scale of 0 to 10 (0 = no pain and 10 = worst pain). CPS defined pain by each patient as no pain = 1, mild = 2, moderate = 3 and severe pain = 4. Pain scores were assessed at rest and during having daily activity by a nurse blinded to the treatment. Presence and severity of adverse side effects of both morphine and diclofenac such as nausea, vomiting, bleeding and allergic symptoms were evaluated. Satisfaction of the patients to the study medications was also evaluated at 48 hours after the operation.

Data were presented as mean $\pm$ SD. Binomial variables were analyzed using Chi-square test. Others were analyzed using student t-test, Mann-Whitney test and analysis of variance as appropriate. P-value < 0.05 was considered statistically significant.

Results

Of 46 patients enrolled in the present study, 23 patients received placebo and 23 received diclofenac as well as intramuscular morphine at 1-hour postoperatively. None dropped out from the present study. Thirty-nine patients underwent total abdominal hysterectomy (TAH) with or without salpingo-oophorectomy (19 in placebo and 20 in treatment group). Seven patients underwent salpingo-oophorectomy or other surgical procedures other than TAH (4 in placebo and 3 in treatment group). There was no significant difference in age, body mass index, incision type, operative time and intra-operative blood loss between the two groups (Table 1). Median morphine consumption in placebo group was significantly higher than diclofenac group (32 and 19 mg respectively; $p = 0.041$). Greater difference in morphine dosage was demonstrated when analyzed only in patients who underwent TAH (Table 2). CPS at 6-hour postoperatively was significantly lower in diclofenac groups as compared to control. However, no significant difference was found between groups in VAS or CPS at other interval and patients' satisfaction at the end of the study (Table 3). Presence of possible adverse side effects of diclofenac such as dyspepsia and headache were not significantly different between groups. No patients had diarrhea or gastrointestinal bleeding. The presence of fever as well as nausea and vomiting between the two groups were not significantly different (Table 4). No patient was unsatisfied or dropped out from the present study.

Discussion

The present study demonstrated that single dose of intramuscular diclofenac sodium added to morphine administration was associated with

Table 1. Baseline characteristics of the patients

	Placebo (n = 23)	Diclofenac (n = 23)	p-values
Age (years)	45.1 ± 6.9	43.5 ± 7.6	0.47
Body mass index (kg/m^2)	26.29 ± 5.15	24.10 ± 4.58	0.14
Incision (No. of patients (%)*			
Vertical	4 (17.4%)	8 (34.8%)	
Pfannensteil	16 (69.6%)	11 (47.8%)	
Maylard	3 (13.0%)	4 (17.4%)	0.30
Operative time (minutes)	101.7 ± 38.3	102.2 ± 25.4	0.96
EBL (mL)#	200 (100-300)	200 (100-500)	0.38

Data were expressed as mean ± SD and analyzed using student t-test
*Data was analyzed using Chi-square test
Data was expressed as median (interquartile range) and analyzed using Mann-Whitney test

Table 2. Morphine consumptions according to operative procedures in study groups

	Placebo (n = 23)	Diclofenac (n = 23)	p-values
All patients	32 mg (19-45)	19 mg (15-31)	0.041
Hysterectomy (n = 39)	33 mg (28-45)	19 mg (14-28)	0.009
Adnexal surgery (n = 7)	22 mg (12-30)	31 mg (23-39)	0.154

Data were expressed as median (interquartile range) and analyzed using Mann-Whitney test

Table 3. VAS, CPS and satisfaction of the patients

	Placebo (n = 23)	Diclofenac (n = 23)	p-values
VAS at 1 hr	7.3 ± 1.9	7.5 ± 2.4	0.74
VAS at 2 hr	6.1 ± 1.8	5.7 ± 2.5	0.52
VAS at 6 hr	5.3 ± 1.7	4.6 ± 2.4	0.23
VAS at 24 hr (rest)	3.2 ± 1.7	2.8 ± 1.9	0.41
VAS at 24 hr (activity)	4.9 ± 1.9	4.5 ± 1.9	0.50
CPS at 1 hr	3.5 ± 0.6	3.4 ± 0.7	0.66
CPS at 2 hr	3.2 ± 0.5	2.9 ± 0.8	0.13
CPS at 6 hr	3.0 ± 0.5	2.5 ± 0.6	0.006
CPS at 24 hr (rest)	2.3 ± 0.6	2.1 ± 0.7	0.26
CPS at 24 hr (activity)	2.7 ± 0.6	2.7 ± 0.6	0.82
Satisfaction score	2.7 ± 0.5	3.1 ± 0.8	0.09

Data were expressed as mean ± SD and analyzed using student t-test

Table 4. Presence of other symptoms

	Placebo (n = 23)	Diclofenac (n = 23)	p-values
Dyspepsia	4 (17.4%)	1 (4.3%)	0.16
Headache	6 (26.1%)	3 (13.0%)	0.27
Nausea/vomiting	12 (52.2%)	11 (47.8%)	0.74
Diarrhea	0	0	
Bleeding	0	0	
Fever	12 (52.2%)	7 (30.4%)	0.134

significant reduction of 24-hour morphine consumption in post-operative gynecologic patients compared to placebo. A large reduction of morphine consumption as 59 percents was demonstrated. Subgroup analysis in patients underwent TAH demonstrated greater reduction in morphine dosage (Table 2). Adnexal surgery is easier, consumes less operative time than TAH and may produce less postoperative pain that could not demonstrate the significant difference among placebo and morphine group.

Diclofenac sodium, a traditional and inexpensive medication, has morphine sparing effect without increment of adverse effect in patients underwent gynecologic surgery. This finding concurs with other studies in several surgical procedures, such as cesarean section, orthopedic operations and TAH[14-17]. Pain score, in term of VAS and CPS tend to be lower in diclofenac group as compared to placebo, but significant difference could be demonstrated only in CPS at 6-hour interval. Several studies of post-cesarean section pain were also unable to demonstrate difference in VAS pain score. Although one study of repeated doses of intramuscular diclofenac sodium showed higher number of pain-relieved patients and significant difference in pain score. Another study of repeated rectal diclofenac administration in TAH patients demonstrated 52 percent reduction in 24-hour morphine consumption[14]. They also found significant difference in pain score among diclofenac and placebo group. As compared to the present study, the non-significant difference in VAS pain score among groups may be attributable to the single use of diclofenac compared with repeated doses in previous report. In addition, sample size of the present study may be not enough to demonstrate the difference of VAS and CPS at other intervals.

There were several routes of NSAIDs' administration, *i.e.* intramuscular, rectal or local wound infiltration. The best route of administration is not known. Intramuscular use may be more accustomed, comfortable and convenient in immediate post-operative nursing care. Moreover, from a study of post-cesarean analgesia, single use of intramuscular diclofenac offers better postoperative analgesia than the rectal route, in addition to meperidine consumption in postoperative period[18]. Thus, intramuscular use of diclofenac sodium in the present study would be considered appropriate route for demonstrating its efficacy.

Despite large reduction of morphine consumption was measured, no significant reduction in opioid side effect, such as nausea and vomiting, demonstrated from this trial. Study population may be not enough to empower this secondary outcome.

Conclusion

The present study demonstrated that intramuscular diclofenac sodium given with morphine at postoperative period produced a large reduction of 24-hr morphine consumption. Single-dose administration of diclofenac sodium could be safely used in major gynecologic surgery without significant adverse effects.

Potential conflict of interest

None.

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ผลของการฉีดยาไดโคลฟีแนคเข้ากล้ามเนื้อภายหลังการผ่าตัดเปิดหน้าท้องทางนรีเวช: การทดลองที่มีการสุ่มและมีกลุ่มควบคุม

ยุทธเดช ทวีกุล, คมสันติ์ สุวรรณฤกษ์, กริชา ไม้เรียง, เย็นฤดี ภูมิถาวร

***วัตถุประสงค์**: เพื่อศึกษาการลดปริมาณการใช้ยามอร์ฟีนในผู้ป่วยที่ได้รับการผ่าตัดเปิดหน้าท้องทางนรีเวชเมื่อได้รับยาไดโคลฟีแนคเข้ากล้ามเนื้อภายหลังการผ่าตัดโดยเปรียบเทียบกับยาหลอก*

***วัสดุและวิธีการ**: ผู้ป่วยที่เข้าร่วมการศึกษาทั้งหมด 46 คน ถูกสุ่มเลือกเป็นสองกลุ่มคือ กลุ่มที่ได้รับยาไดโคลฟีแนคผสมยามอร์ฟีนและกลุ่มที่ได้รับยาหลอกผสมมอร์ฟีนโดยการฉีดเข้ากล้ามระหว่างนอนพักฟื้นในห้องสังเกตอาการหลังผ่าตัด ภายหลังจากนั้นหากมีอาการปวดผู้ป่วยทั้งสองกลุ่มจะได้รับยามอร์ฟีนผ่านเครื่องให้ยาโดยผู้ป่วยเป็นคนควบคุมเอง (patient-controlled analgesia: PCA) เป็นเวลา 24 ชั่วโมง ข้อมูลที่นำมาวิเคราะห์ ได้แก่ ปริมาณยามอร์ฟีนที่ใช้ ระดับความรุนแรงของอาการปวด ผลข้างเคียงของยา และ ความพึงพอใจของผู้ป่วย*

***ผลการศึกษา**: ปริมาณยามอร์ฟีนที่ใช้ภายในระยะเวลาหลังผ่าตัด 24 ชั่วโมง ในกลุ่มที่ได้รับยาไดโคลฟีแนคฉีดเข้ากล้ามน้อยกว่ากลุ่มที่ได้รับยาหลอกอย่างมีนัยสำคัญทางสถิติ คือ มีค่ากลางเท่ากับ 19 และ 32 มิลลิกรัมตามลำดับ (p = 0.041) ความแตกต่างดังกล่าวเด่นชัดมากขึ้นในกลุ่มที่ผ่าตัดมดลูกออกทางหน้าท้อง (p = 0.009) พบว่าอาการปวด โดยการประเมินระดับความรุนแรงเป็นลำดับขั้น (catagorical pain score) ที่ 6 ชั่วโมง ในกลุ่มที่ได้รับยาไดโคลฟีแนค ฉีดเข้ากล้ามน้อยกว่าในกลุ่มที่ได้รับยาหลอกอย่างมีนัยสำคัญทางสถิติ (p = 0.006) อย่างไรก็ตาม ไม่พบความแตกต่าง ของระดับความรุนแรงของอาการปวดโดยการประเมินจาก visual analogue pain score ความพึงพอใจของผู้ป่วย และอาการข้างเคียงจากยาระหว่างผู้ป่วยทั้งสองกลุ่ม*

***สรุป**: การให้ยาไดโคลฟีแนคชนิดฉีดเข้ากล้ามครั้งเดียวหลังการผ่าตัดเปิดหน้าท้องทางนรีเวชสามารถลดปริมาณการใช้ยามอร์ฟีนในช่วงระยะเวลา 24 ชั่วโมง หลังการผ่าตัดได้อย่างมีนัยสำคัญทางสถิติ โดยไม่พบผลข้างเคียง*