Effect of Intravenous Ketorolac on Postoperative Pain after Cesarean Section: A Randomized Double-Blinded Controlled Trial

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Objective: *Ketorolac is occasionally administrated for post cesarean delivery analgesia. The clinical efficacy of ketorolac for post cesarean analgesia had never been directly compared to meperidine. The purpose of the present study was to determine the efficacy of ketorolac for pain control in post cesarean delivery compare to meperidine.*
Material and Method: *This was a randomized double-blind controlled trial comparing the effectiveness of intravenous ketorolac compared to meperidine. The inclusion criteria were term pregnant women who were 18 to 40 years old and underwent cesarean delivery. The subjects were randomly divided into study and control groups. The study and control group received 30 mg of ketorolac and 50 mg of meperidine intravenously after surgery, respectively. Visual analog score (VAS) was used to assess the post operative pain ranged from 0 to 10. VAS was recorded at 3, 6, 12 and 24 hours postoperatively. Demographic data of parturient, newborn and side effects were also recorded.*
Results: *A total of 580 cases were recruited. There were 297 and 283 cases in study and control group. Both groups showed no statistical difference in mean age, gestational age, fetal weight, parity. Either ketorolac or meperidine group showed no significant post operative pain relief at 3, 6, 12 and 24 hours. After first initial post-operative pain assessment, 8% (24/297) and 7.4% (24/283) of participants needed and received rescue analgesia. Subjects in both groups who had VAS equal or more than six had equally post operative pain relief either by ketorolac or meperidine. There was no maternal, fetal complications and serious side effect in the present study.*
Conclusion: *Ketorolac had equal efficacy to meperidine. It could be an alternative medication for pain control in post cesarean delivery.*

Keywords: *Ketorolac, Cesarean delivery, Pain, Meperidine*

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Currently, the cesarean section (c/s) rate has risen dramatically worldwide[1]. The increasing c/s rate can be attributed to many factors, including more births among older women, the use of electronic fetal monitoring, the decreasing of operative vaginal deliveries, and as patient preference[1].

Neuraxial regional anesthesia for elective c/s is a preferable choice compared to general anesthesia[2]. Regional anesthesia is also preferable because it avoids the need for laryngoscopy intubation and is associated with fewer maternal complications compared to general anesthesia[2]. Patients who had c/s under regional anesthesia c/s reported less postoperative pain than those received general anesthesia[2].

Opioids drugs, such as morphine or meperidine, have been drugs of choice for post cesarean delivery. Opioid usage was reported to show side effects such as decreased lactation, sedation, respiratory depression, pruritus, nausea and vomiting as well as constipation and urinary retention[3]. Non-selective non steroidal anti-inflammatory drug (NSAID), for example, diclofenac and ketorolac, were later introduced for postoperative analgesia. They were proven to have high efficacy in the reduction of

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postoperative pain[4]. Most NSAIDs are not generally prescribed in the postoperative period until patients can tolerate liquid diet which often falls between 12 to 48 hours after surgery.

Ketorolac is a cyclooxygenase enzyme inhibitor. It is a member of NSAIDs group. It can be given in intravenous, intramuscular or oral forms. The use of ketorolac showed no respiratory depression or dependency and reported only a few side effects[5,6]. The use of ketorolac in opened or laparoscopic gynecologic surgery had been shown to be beneficial[7]. There are many studies involving the use of NSAIDs and delivery[8,9]. However, no study to date compared efficacy of ketorolac to meperidine in c/s pain control. This study aimed to determine the effectiveness of intravenous ketorolac post-operatively in patients who underwent cesarean delivery with spinal anesthesia compared to the use of opioid gold standard.

Material and Method

This prospective double-blind randomized controlled trial was approved by the Ethic Committee, Faculty of Medicine, Thammasat University. The present study was conducted in Thammasat University Hospital. Patients aged between 18 to 40 years old who underwent elective cesarean delivery between March and August 2016 were included in this study. Written inform consent was signed after each patient's counseling. Exclusion criteria were patients with cardiovascular or renal disease, on anticoagulants, BMI (body mass index) >30 kg/m^2, hypersensitivity to NSAID, had underwent repeated explored laparotomy within 24 hours postoperatively or refused to participate in the study. Patient's demographics data including age, BMI, occupation, education, underlying diseases, parity, gestational age and history of cesarean delivery were all collected. Participants were randomly assigned using a computer generated table of random number to one of two groups. Group's allocation was concealed in sealed opaque envelopes that were opened in the operating room.

Neuraxial regional block (spinal anesthesia) was the standard method of anesthesia in this study. A total of 11 mg of bupivacaine in a hyperbaric solution with the addition of 0.2 mg of morphine were used as standard anesthetic agents in the present study. This procedure was performed or under supervised by the anesthesiologist staff. The hospital standard of post operative care was applied for all participants.

Subjects were randomly assigned to two groups. The study group received 30 mg intravenous ketorolac (Ketolac® ATB, Thailand) after three hours postoperative assessment. Those who had severe pain (VAS $\geq$6) at 3 hours postoperatively will be prescribed analgesic agent per protocol. The whole 30 mg was administered within 5 minutes. The control group received 50 mg intravenous meperidine in the same manner.

The sample size in this study was calculated from the standard deviation between study and control group (SD = 0.9) from Cohen's literature[10]. The alpha and beta errors were set at 0.05 and 0.2 that needed the sample size at 50 cases per arm.

The degree of postoperative pain was assessed at 3, 6, 12 and 24 hours after surgery by asking question using visual analog scale (VAS) (0 = no pain, 10 = worst possible pain). Intravenous analgesia was given when the reported pain score was equal or greater than 6. After 24 hours, the amount of analgesia given was recorded for each patient. Possible side effects, i.e., nausea, vomiting, itching, respiratory depression and allergic reactions, were also recorded.

Five hundred milligrams acetaminophen was orally administered every 6 hours if patients reported pain after 24 hours onward.

Data were analyzed by using statistical package for the social science (SPSS Inc, Chicago, IL USA) for Windows version 17. Continuous data was analyzed by using mean and unpaired t-tests. Chi-square tests were used for categorical data. Level of statistical significance was set at *p*-value less than 0.05.

Results

Six hundred patients were recruited in the present study. They were randomly assigned as study and control group. Seventeen and three cases in control and study group were excluded from study due to lacking of completed data and refuse to participate study after enrollment, respectively. The study and control group consisted of 297 and 283 cases, respectively. Treatment flow diagram was represented in Fig. 1. Ketorolac and meperidine were administered to the study and control group for pain control. Both groups showed no statistical significant among age, weight, height, underlying diseases and other demographic data (Table 1). Nearly half of cases worked as daily hire. Eighty percent of subjects were bachelor degree graduates or with higher education.

After three hour post operative period, 24 and 21 subjects in study and control group with VAS equal or more than six requested additional analgesia. They received post-operative analgesic medication per

protocol. Pain assessment after intravenous medication were recorded and represented in Fig. 2. Both groups showed no significant difference in their pain relief after intravenous medication (Fig. 2). All participants received 500 mg acetaminophen per oral at 24 hours after surgery.

VAS of subject who had pain score equal or less than 5 (low pain) was represented in Fig. 3. Both study and control groups in low pain category had no significant difference in their post operative pain. Pain assessment was continuously collected until 24 hour after surgery.

There was no side effect, i.e., nausea, vomiting, itching, respiratory depression and allergic reactions, in the present study.

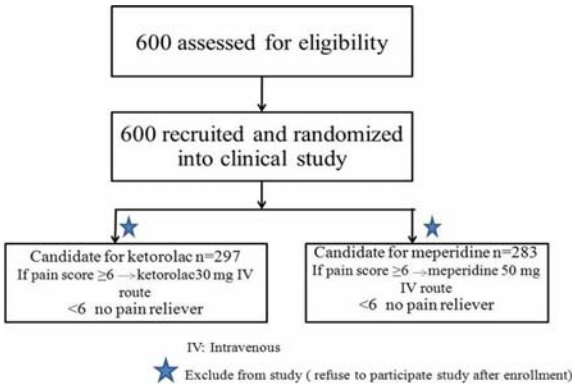
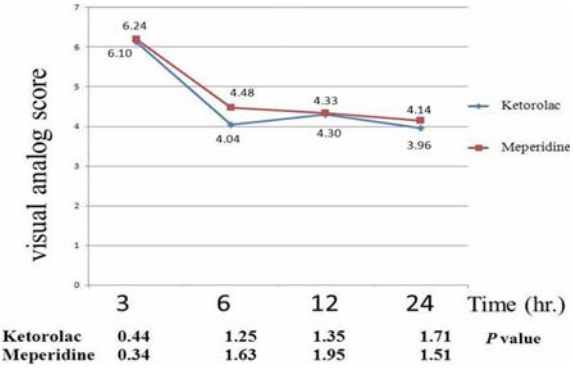


Fig. 1 Participant flow diagram.

Discussion

The present study of ketorolac and meperidine



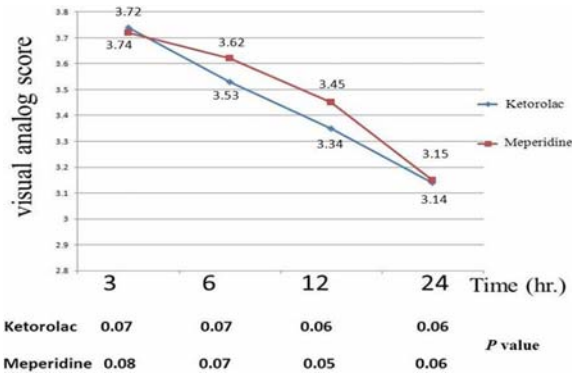
VAS = visual analog score

Fig. 2 Average post operative pain score in participant who had severe pain (VAS ≥6).

Table 1. Demographic character of participants

	Ketorolac (n = 297)	Meperidine (n = 283)	*p*-value
Weight (kg)	65.80±6.20	65.80±6.80	0.99
Height (cm)	159.10±5.60	158.40±6.04	0.57
BMI (kg/m^2)	26.30±20	26.20±2.40	0.60
Age (year)	32.20±4.80	31.80±5.37	0.31
Occupation (%)			
Government officer	24	29.5	
Daily employer	48.2	45.6	
Own business	23.5	19.2	
Other	4.3	5.7	
Education			0.08
High school or less	39	53	
Under graduated	144	115	
Bachelor	112	115	
Underlying diseases (%)*	4.70	7.70	0.12
History of C/S (%)	39.70	41.30	0.54
Parity			0.87
Nulliparous	105	91	
Multiparous	192	192	
Gestational age (weeks)	37.88±0.54	37.87±0.52	0.82
Blood loss (ml)	390.07±133.70	448.06±149.07	<0.001
Fetal weight (g)	3,186.66±248.62	3,200.17±255.42	0.52

* Diabetes mellitus, hypertension, anemia, heart disease
BMI = body mass index; C/S = cesarean delivery



VAS = visual analog score

Fig. 3 Average post operative pain score in participant who had severe pain (VAS ≤5).

in parturient that underwent c/s with regional anesthesia in Thailand may be one of the large number of study recruitment. Around ten percent of both groups had high post operative pain level at three hour assessment (VAS ≥6). All of them received post operative analgesia per protocol. There was no statistical significant of pain relief at 6, 12 and 24 hours. Standard dose of bupivacaine and morphine were used for anesthetic agent in this study. It gave duration of analgesia for surgery between 90 to 150 minutes[2]. At 3 hour of post operation was the estimate time of analgesia effects. The additional analgesia either ketorolac or meperidine gave the equal pain relief effect.

Around 90 percent of both groups had low level post operative pain (VAS ≤5). Patients needed only 500 mg of acetaminophen per oral for pain control after 3 hours post operatively. Both groups had equal pain relief with no statistical significant.

Ketorolac had equal effective control pain and not less than meperidine during the first 24 hours. The result of this study was similar to the work of El-Tahan et al from Egypt. El-Tahan's work reported the same efficacy of ketorolac and meperidine in subjects who underwent cesarean delivery with general anesthesia[11].

Overall analgesic requirement of ketorolac and meperidine group were 8 and 7.4 percent, respectively without statistical difference. It showed that the participants who received ketorolac had equal pain relief to those of meperidine group. Meperidine had more sedative effect than ketorolac. The alteration of participant consciousness may effect the drug requirement. However, the pain relief of both groups had similar result.

Ketorolac, an injectable COX-1 inhibitor, is widely used in postoperative pain control. It had excellent pain relief and opioid consumption reduction. Brocks et al reported in year 1992 that the ketorolac concentration in the breast milk was only a small fraction of the maternal exposure[12]. The safety dose of ketorolac in breast milk should not exceed than 3.16 to 7.9 mg/day based on 400 ml of breast milk consumption per day[13].

Kulo et al reported the half life of ketorolac in pregnant and non-pregnant women were similar. Ketorolac was rapidly clear from maternal circulation after cesarean delivery[14]. Potential effect of NSAID to neonate was premature closure of the patent ductus arteriosus[15]. In the present study, initial dose of ketorolac was administered after c/s to avoid intrauterine fetal exposure[16].

Literature in year 2010 from Taiwan reported[17] the efficacy of ketorolac was the same efficacy as parecoxib with morphine administer with patient controlled anesthesia (PCA). Fetal exposure effect of parecoxib was reported in Paech's literature[18]. It can be used for post cesarean delivery analgesia with an opioid sparing effect[17]. Ketorolac efficiency was reported to be less than of parecoxib.

The study of Pavy et al from Australia reported the same efficacy of ketorolac and meperidine[19]. The side effects such as pruritus, nausea and sedation in ketorolac group were less than the meperidine group. These resulted from reduction of opioid consumption in ketorolac group. There was no pruritus, nausea and sedation in the present study. Ketorolac had a minimal side effect from opioid consumption reduction. The subject in Pavy's study who received ketorolac had better pain control than control group at 24 hours. This present study had the same effect of pain control result to Pavy's literature.

In the present study the characteristic data of participant were equally homogenous in term of weight, height and BMI. Average age in this study was 30 years old that higher than general population. The present study conducted in university hospital based population. One-third of participant had bachelor education level. It should not influence to the study result. The communication between the patient and health care providers were excellent. The estimate blood loss in meperidine group was higher than ketorolac group (448 and 390). This character can not explain the result.

Ketorolac can be used in women who have no contraindication. It has the same efficacy in

decreasing pain when compared to meperidine. Meperidine is legally restricted by the Thai government while ketorolac is not.

The limitation of this study was the number of participant who received either ketorolac or meperidine (24 and 21 cases). Postoperative analgesic need was lower than expectation. Around 10% of cases had severe pain score that met criteria for analgesic drug. It may be the excellent expertise of anesthesiologist in conducting regional analgesia. We recruited the more subject in this study for compensation of the excellent effect of regional analgesia. More than five hundred of cases were enrolled till the end of study period that received the permission from the ethical committee. This may decrease the study strength that need the further study in the near future.

Sedation is the major opioid side effect that interferes with breast feeding activity. Ketorolac had no sedation effect. It can promote breast feeding in mothers more quickly by decreasing the patient recovery time. Ketorolac is easily eliminated from the body and is not toxic to the newborn. In the present study, ketorolac had equal pain control efficacy to meperidine. In the situation were the opioid usage was considerably tightly restricted, a narcotic alternative is highly recommended.

Conclusion

Neuraxial regional block is still the method of choice for obstetric anesthesia in cesarean delivery. Most of them needed only oral acetaminophen for post operative pain relief. Both ketorolac and meperidine had equal addition pain relief in parturient who had high level of post operative pain. Ketorolac can be used for pain control in post cesarean delivery. It had equal efficacy and fewer side effects than meperidine.

What already know on this topic?

Neuraxial regional anesthesia for elective cesarean delivery is a preferable choice compared to general anesthesia. Regional anesthesia is also preferable because it avoids the need for laryngoscopy intubation and is associated with fewer maternal complications compared to general anesthesia. Opioids drugs, such as morphine or meperidine, are drugs of choice for post operative pain control. Opioid usage was reported to show side effects such as decreased lactation, sedation, respiratory depression, pruritus, nausea and vomiting as well as constipation and urinary retention. NSAIDs were proven to have high efficacy in the reduction of postoperative pain.

What this study adds?

Both ketorolac and meperidine had equal addition pain relief in parturient that had high level of post operative pain. Ketorolac can be used for pain control in post cesarean delivery. It had equal efficacy and fewer side effects than meperidine.

Acknowledgements

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Ethical approval

The study was approved by Ethics Committee, Faculty of Medicine, Thammasat University, and study protocol numbers MTU-EC-OB-6-209/58

Potential conflicts of interest

None.

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การศึกษาผลของยาคีโตโลแลคโดยการบริหารยาด้วยการฉีดเข้าหลอดเลือดดำเพื่อลดอาการปวดหลังการผ่าตัดคลอดบุตร: โดยวิธีการแบบสุ่ม มีการควบคุมและอำพรางสองฝ่าย

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วัตถุประสงค์: เพื่อศึกษาประสิทธิผลของยาคีโตโลแลคโดยการบริหารยาด้วยการฉีดเข้าหลอดเลือดดำเทียบกับยาเมเพอริดีน

วัสดุและวิธีการ: เป็นการศึกษาโดยการสุ่มเพื่อเปรียบเทียบผลของคีโตโลแลคและเมเพอริดีน เกณฑ์คัดเลือกผู้เข้าร่วมวิจัยประกอบด้วย ผู้ป่วยตั้งครรภ์ครบกำหนดอายุระหว่าง 18 ถึง 40 ปีที่เข้ารับการผ่าตัดคลอดบุตร โดยผู้เข้าร่วมวิจัยได้รับการแบ่งออกเป็น 2 กลุ่ม คือกลุ่มศึกษาและกลุ่มควบคุม โดยกลุ่มศึกษาจะได้รับยาคีโตโลแลค 30 มิลลิกรัม และกลุ่มควบคุมจะได้รับยาเมเพอริดีน 50 มิลลิกรัม โดยการฉีดเข้าหลอดเลือดดำเพื่อลดอาการปวดภายหลังการผ่าตัดคลอดบุตรโดยการนัด ผู้เข้าร่วมวิจัยจะได้รับการประเมินระดับความเจ็บปวด visual analog scale (VAS) ที่ระดับศูนย์ถึงสิบโดยประเมินที่ 3, 6, 12 และ 24 ชั่วโมงหลังเข้ารับการผ่าตัดคลอด โดยมีการบันทึกผลข้างเคียง ภาวะแทรกซ้อนและผลต่อทารก

ผลการศึกษา: มีผู้เข้าร่วมวิจัยทั้งหมด 580 คน แบ่งเป็น 297 และ 283 ในกลุ่มที่ศึกษาและกลุ่มควบคุมตามลำดับ จากการศึกษาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติทั้งในกลุ่มอายุเฉลี่ยของคนไข้ อายุครรภ์เฉลี่ย น้ำหนักทารกแรกเกิดและจำนวนบุตรร้อยละ 8 (24/297) และ 7.4 (24/283) ของกลุ่มศึกษาและกลุ่มควบคุมที่มีความเจ็บปวดระดับมากกว่าหรือเท่ากับ 6 และได้รับยาระงับปวดโดยทั้งสองกลุ่มที่ได้รับยาระงับปวดทั้งคีโตโลแลคและเมเพอริดีน มีฤทธิ์ลดอาการปวดหลังผ่าตัดไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ โดยไม่พบผลข้างเคียงในมารดาและทารกในการศึกษานี้

สรุป: ยาคีโตโลแลคและเมเพอริดีนมีผลในการลดอาการปวดหลังผ่าตัดได้ไม่แตกต่างกัน โดยสามารถใช้เป็นทางเลือกเพื่อลดอาการปวดหลังจากการผ่าตัดคลอดได้