PREOPERATIVE ORAL ADMINISTRATION OF DEXTROMETHORPHAN AND/OR ETORICOXIB FOR PAIN MANAGEMENT AFTER LAPAROSCOPIC SURGERY.

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นายปิ่น ศรีประจิตติชัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ปิ่น ศรีประจิตติชัย: การรับประทานเด็กซ์โตรเมทรอแฟนและ/หรืออีโทริค็อกสิบก่อนผ่าตัดเพื่อระงับปวดหลังการผ่าตัดผ่านกล้อง. (PREOPERATIVE ORAL ADMINISTRATION OF DEXTROMETHORPHAN AND/OR ETORICOXIB FOR PAIN MANAGEMENT AFTER LAPAROSCOPIC SURGERY.) อ.ที่ปรึกษา : รศ.พญ.อรนุช เกี่ยวข้อง, อ.ที่ปรึกษาร่วม : รศ.นพ.สมรัตน์ จารุลักษณานันท์, 58 หน้า.

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลของการระงับปวดหลังการผ่าตัดผ่านกล้องในผู้ป่วยที่รับประทานเด็กซ์โตรเมทรอแฟน, อีโทริค็อกสิบและรับประทานยาทั้งสองชนิดก่อนผ่าตัด

รูปแบบการศึกษา: การศึกษาเชิงทดลองทางคลินิกแบบปกปิดสองฝ่ายโดยการสุ่ม

สถานที่ทำวิจัย: โรงพยาบาลจุฬาลงกรณ์ ซึ่งเป็นโรงพยาบาลระดับตติยภูมิ

วิธีการศึกษา: ผู้ป่วย 66 ราย อายุระหว่าง 18-65 ปี มีสุขภาพก่อนผ่าตัดตามเกณฑ์ของ The American Society of Anesthesiologists (ASA) ระดับ I-II ที่มารับการผ่าตัดผ่านกล้องแบบไม่ฉุกเฉิน ให้รับประทานยาเด็กซ์โตรเมทรอแฟน 60 มก. หรืออีโทริค็อกสิบ 120 มก. หรือทั้งสองชนิดก่อนผ่าตัดโดยการสุ่ม ผู้ป่วยทุกรายได้รับการระงับความรู้สึกแบบทั่วไปด้วยวิธีการที่เหมือนกัน หลังการผ่าตัดได้รับมอร์ฟีนแก้ปวดผ่านเครื่องระงับปวดด้วยตนเองที่ตั้งค่าต่างๆเหมือนกันหมด บันทึกปริมาณมอร์ฟีนที่ใช้เมื่อเวลา 2, 6, 12, และ 24 ชั่วโมงหลังผ่าตัด และบันทึกความรุนแรงของความปวดขณะพักและขณะไอที่เวลา 0, 2, 6, และ 24 ชั่วโมงหลังผ่าตัด ตลอดจนอาการไม่พึงประสงค์ต่างๆ

ผลการศึกษา: ผู้ป่วย กลุ่มเด็กซ์โตรเมทรอแฟน, กลุ่มอีโทริค็อกสิบ, และกลุ่มที่รับประทานยาทั้งสองใช้มอร์ฟีน 24 ชั่วโมงหลังผ่าตัดโดยเฉลี่ย 14.6, 13.3, และ 10.9 มก. ตามลำดับ ซึ่งไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ จำนวนมอร์ฟีนต่อน้ำหนักตัว 24 ชั่วโมงหลังผ่าตัดโดยเฉลี่ยไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ (0.26, 0.21, และ 0.18 มก./กก. ในกลุ่มเด็กซ์โตรเมทรอแฟน, กลุ่มอีโทริค็อกสิบ, และกลุ่มที่ได้รับยาทั้งสองตามลำดับ) ความรุนแรงของความปวดขณะพักและขณะไอของผู้ป่วยทุกกลุ่มไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ อุบัติการณ์ของการปวดไหล่ของผู้ป่วยทั้งหมดคิดเป็นร้อยละ 40.9 อาการข้างเคียงที่เกิดขึ้นในผู้ป่วยทุกกลุ่มไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ ยกเว้นอาการเวียนศีรษะเกิดน้อยกว่าอย่างมีนัยสำคัญทางสถิติ (p=0.032) ในกลุ่มที่รับประทานอีโทริค็อกสิบคิดเป็นร้อยละ 9.1 ในขณะที่กลุ่มเด็กซ์โตรเมทรอแฟนและกลุ่มที่รับประทานยาทั้งสองคิดเป็นร้อยละ 40.9 และ 27.3 ตามลำดับ

สรุป: ผู้ป่วยที่รับประทานยาเด็กซ์โตรเมทรอแฟน 60 มก., อีโทริค็อกสิบ 120 มก. หรือรับประทานยาทั้งสองชนิดก่อนผ่าตัดผ่านกล้องใช้มอร์ฟีน 24 ชั่วโมงหลังผ่าตัดโดยเฉลี่ยไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ ความรุนแรงของความปวดหลังผ่าตัดไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ อาการข้างเคียงที่เกิดขึ้นไม่ต่างกันอย่างมีนัยสำคัญทางสถิติ ยกเว้นอาการเวียนศีรษะซึ่งเกิดน้อยกว่าอย่างมีนัยสำคัญทางสถิติในกลุ่มที่รับประทานอีโทริค็อกสิบ

สาขาวิชาการพัฒนาสุขภาพ..... ลายมือชื่อนิสิต.....ปิ่น ศรีประจิตติชัย.....

ปีการศึกษา 2549.....ลายมือชื่ออาจารย์ที่ปรึกษา.....อรนุช เกี่ยวข้อง.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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KEY WORDS: DEXTROMETHORPHAN/ ETORICOXIB/ PAIN MANAGEMENT/ LAPAROSCOPIC SURGERY

PIN SRIPRAJITTICHAI: PREOPERATIVE ORAL ADMINISTRATION OF DEXTROMETHORPHAN AND/OR ETORICOXIB FOR PAIN MANAGEMENT AFTER LAPAROSCOPIC SURGERY. THESIS ADVISOR: ASSOC.PROF. ORANUCH KYOKONG. THESIS COADVISOR: ASSOC.PROF. SOMRAT CHARULUXANANAN. 58 pages.

Objectives: To compare the efficacy of pain relief after laparoscopic surgery between the patients taking preoperative oral dextromethorphan (DM), etoricoxib, and their combination.

Design: Randomized double-blind controlled trial.

Setting: King Chulalongkorn Memorial Hospital which is a 1500-bed tertiary care center.

Research Methodology: Sixty six patients, aged between 18-65 years with ASA physical status I-II undergoing elective laparoscopic surgery under general anesthesia (GA), were randomly allocated into three groups. Group D received DM 60 mg orally, group E received etoricoxib 120 mg and group DE received the combination of DM 60 mg and etoricoxib 120 mg orally. All patients were given the same GA protocol and received IV morphine patient-controlled analgesia (PCA) with identical setting for 24 hours. Efficacy outcomes including the amount of morphine used during 2, 6, 12, and 24 hours and numerical pain rating scale (NRS) at rest and on coughing at 0, 2, 6, and 24 hours after surgery were recorded and analyzed. In addition, adverse events were also measured and analyzed.

Results: Mean total morphine used during 24 hours after surgery (14.6, 13.3, and 10.9 mg in D, E, and DE group respectively), mean total morphine used per body weight during 24 hours (0.26, 0.21, and 0.18 mg/kg in D, E, and DE group respectively), NRS at rest and on coughing in three groups were not statistically different. The overall incidence of shoulder pain was 40.9%. There was no statistically significant difference in side effects among the groups except dizziness (40.9%, 9.1% and 27.3% in D, E, and DE group respectively) (p=0.032).

Conclusion: DM 60 mg, etoricoxib 120 mg, and their combination as an oral medication before laparoscopic surgery did not alter the 24-hour postoperative morphine consumption significantly. NRS at rest, NRS on coughing and other adverse events were not statistically different except dizziness which was less in etoricoxib group.

Field of Study Health Development.....Student's signature.....Pin Sriprajittichai.....

Academic Year 2006.....Advisor's signature.....Kyokong.....

Co-advisor's signature.....

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CONTENTS

CONTENTS

TABLE OF TABLES

TABLE OF FUGURES

CHAPTER I
INTRODUCTION

1.1 Rationale and background

Dextromethorphan (DM) has been widely used for more than 40 years [1, 2]. It is available for oral administration as an over-the-counter cough depressant with a long safety record. Adverse effects are mild and uncommon, and may include dizziness and gastrointestinal disturbances such as nausea and vomiting. Recently there has been interest in its role as a moderate to low affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist [3, 4]. The antitussive effect of a single dose of DM 30 mg lasts 4-6 hours, and 60 mg 6-8 hours [5]. DM undergoes extensive first-pass metabolism in the liver. After a single oral dose of 60 mg in volunteers, the peak concentrations of DM in plasma are achieved at 2-3 hours. The elimination half-life of DM is approximately 3.5 hours [6].

Intraoperative and postoperative noxious inputs may cause central sensitization which includes an altered processing of innocuous, tactile impulses from myelinated afferents so that activation of these fibers produces painful sensation [7]. The neurophysiological and biochemical mechanisms of these alterations include a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability, mediated by wind-up, neurokinin and NMDA receptor mechanism [7].

According to a quantitative and qualitative systematic review [8], it concluded that in the first 24 hours after surgery, ketamine, another non-competitive NMDA antagonist, reduced morphine requirement. It also reduced postoperative nausea and vomiting. Its adverse effects were mild or absent. Regarding DM, its perioperative analgesic effect is controversial. Several clinical trials demonstrated DM could provide analgesic benefit perioperatively [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. Some studies, however, did not show any analgesic effect of DM [28, 29, 30, 31].

Etoricoxib is a 2nd generation of cyclooxygenase (COX-2) -specific inhibitor with 106-fold selectivity for COX-2 over COX-1 [32]. Its rapid onset time (20 minutes) and long duration of action (half-life of approximately 25 hours) allows convenient once-daily dosing [33]. Its analgesic efficacy is comparable to traditional non-steroidal anti-inflammatory drugs (NSAIDs), and this has been demonstrated in the management of acute postoperative pain [34, 35, 36]

It is now well recognized that pain is a complex and multifactorial phenomenon and therefore requires a multimodal therapy. The concept of "multimodal" or "balanced" analgesia suggests that combinations of several analgesics of different classes and different sites of analgesic administration rather than single analgesic or single technique provide superior pain relief with reduced analgesic-related side effects [37, 38]. The use of multimodal analgesia decreases pain scores and/or the requirement for postoperative analgesics in different surgical procedures [39, 40, 41].

Pain after laparoscopy is significantly less and shorter than that caused by the same surgical procedure made by laparotomy [42, 43, 44, 45]. Pain after laparoscopy involves three different components which are incisional pain (parietal pain component), deep intra-abdominal pain (visceral pain component), and shoulder pain (presumably referred visceral pain) [46]. The sites of pain may occur in the upper abdomen, lower abdomen, back, and/or shoulders. It may be transient or persist for at least 3 days [47]. Report of pain (at any site) is greatest after operation, decreases to a low level within 24 hours [47, 48].

After laparoscopic cholecystectomy (LC), visceral pain predominates in the first 24 hours but subsides from a peak soon after operation, whereas shoulder pain, minor on the first day, increases and becomes significant on the following day [49]. Pain at rest and on coughing after gynecological laparoscopic surgery (GLS) is moderate to severe for the first hour and 12 hours after the procedure respectively [50, 51, 52]. Similar to LC, patients undergoing GLS have shorter hospital stay, less IV pain medication, and faster return to full activity compared to gynecological laparotomy [53].

Pain following GLS and LC is similar in pathogenesis and is moderate in severity. Without pain, patients can early ambulate and return to normal daily activities on day 1 after the procedure. Opioids can provide postoperative analgesia but occasionally patients cannot tolerate side effects and impede early ambulation which is one of the most important advantages of laparoscopy. Single analgesic, DM or etoricoxib, or multimodal analgesia, DM and etoricoxib, may overcome moderate pain following these laparoscopic surgeries with fewer side effects. If DM and/or etoricoxib can replace opioid, it will be of good opportunity in postoperative pain management. Furthermore, the cost of DM is very low. It is very useful and interesting in term of economic consideration.

Nowadays laparoscopy with surgical procedures is being performed more and more. To date, many clinical trials demonstrate postoperative analgesic benefit of DM and etoricoxib but no demonstration of this advantage in laparoscopy with surgical procedures yet. So I introduce the study of DM and/or etoricoxib for their efficacy in reduction of postoperative pain in case of laparoscopic surgery.

1.2 Literature review

Literature search strategy

The literature search strategy used to locate the information in this review was in the MEDLINE, an electronic journal database provided by National Library of Medicine, reference database and additionally by going through the reference lists of other articles. The portal website for free access is http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed or known as "PubMed". The key words used were dextromethorphan, etoricoxib, cyclooxygenase 2 inhibitor, perioperative, postoperative pain, postoperative analgesia, laparoscopic cholecystectomy, gynaecological laparoscopy, and gynecological laparoscopy.

Clinical studies of DM and postoperative pain

Nineteen clinical trials demonstrated that DM could provide analgesic benefit perioperatively [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. DM was administered preoperatively in all of the trials. For the studies comparing time administered of DM [9, 10, 11], preincisional administration provided postoperative analgesic effect. The analgesic effect was demonstrated by decreased opioid requirement and visual analog pain score. Wu *et al* [9] showed that preincisional 40 mg of DM intramuscularly (IM) offered preemptive analgesic effect. Similarly Chia *et al* [10] compared DM 5 mg/kg intravenously (IV) before and after incision in major abdominal surgery under randomized, double-blind design. They found that preoperative administration reduced postoperative morphine requirement. A study of Helmy SAK and Bali A [11] demonstrated that 120 mg of DM IM 30 minutes before skin incision of upper abdominal surgery compared with the same postincisional dose significantly reduced postoperative pethidine consumption (mean[SD]: 140[60] and 390[80] mg respectively).

Clinical studies of DM were conducted in a variety of operations i.e., LC [9, 12, 13, 14], lower abdominal surgeries [10], upper abdominal surgeries [11, 15], lower body surgeries [16, 17, 18,], total abdominal hysterectomy (TAH) [19, 20], orthopedic oncology [21, 22, 23] colonic surgery [24], tonsillectomy [25], hemorrhoidectomy [26], and modified radical mastectomy [27]. Table 1 summarized the clinical trials of DM.

For studying in LC, Wu *et al* [9] demonstrated preemptive analgesic effect of preincisional 40 mg DM IM. Weinbroum *et al* [12] in LC and hernioplasty revealed that oral 90 mg DM enabled reduction of postoperative analgesics consumption, improved well-being, and reduced sedation, pain intensity, and primary and secondary thermal hyperalgesia. While Wu *et al* [13] and Yeh CC [14] studied DM 40 mg IM combined with IV lidocaine 3 mg/kg and DM 40 mg IM combined with tenoxicam respectively. Their researches revealed that combined medications provided significantly better pain relief than the control group.

For upper abdominal and lower body surgeries, Wu and colleagues [15] demonstrated dose-dependent pain relief after upper abdominal surgery. Wadhwa *et al* [16] conducted a randomized double-blind control trial between a large dose of oral DM 200 mg 8 hourly and a placebo for postoperative pain relief in knee surgery. They found that 24-hour morphine consumption after surgery in DM group was 29% statistically significant less than the placebo group. Weinbroum and colleagues [17] found that 90 mg of oral DM reduced postoperative analgesics in patients undergoing hernia repair and surgical knee arthroscopy. Another study of Weinbroum *et al* [18] studied analgesic effect of combined preincisional oral 60 or 90 mg of DM and epidural lidocaine in patients undergoing hernia repair and arthroscopy. The study revealed both DM groups required less pain medications both immediately (first 6 hours) and for 3 days afterwards. Henderson *et al* [19] prescribed preoperative 40 mg of oral DM and three times a day for next two postoperative days. Their study revealed reduced postoperative analgesics in the first 24 hours and over the next 48 hours. In TAH setting like Henderson and friends, Ilkaer *et al* [20] ordered 150 mg of preoperative oral DM. They found analgesic effect of DM only 4 hours after TAH. The authors suggested that continued administration of DM into the postoperative period should have been considered.

Regarding more extensive and tissue injury operations, Weinbroum and colleagues [21] showed that 60 mg of oral DM provided similar analgesic effect to the dose of 90 mg did in bone and soft tissue malignancy operation. Another two studies of Weinbroum *et al* [22, 23] combined oral DM with epidural analgesia. The results also supported analgesic effect of DM.

DM was administered in different routes which were by mouth, intravenous injection and intramuscular injection (table 1). Several doses of DM were explored: 5mg/kg, 10, 20, 30, 40, 60, 90, 120, 150, and 200 mg (table 1). Ten milligrams of IM DM was not superior to placebo and 40 mg was more efficacy than 20 mg [15]. The oral dose between 60-200 mg of DM showed postoperative analgesic effect [16, 17, 18, 19, 20, 21, 22, 23]. Although high dose of DM provided analgesic effect, but it also caused high incidence and severity of side effects. Wadhwa *et al* [16] conducted a randomized double-blind control trial between

a large dose of oral DM 200 mg 8 hourly and a placebo for postoperative pain in knee surgery. They found that the opioid-sparing analgesic effect occurred but incidence of nausea was also high. The authors concluded that high dose DM was not clinically useful in the treatment of postoperative pain at a cost of increased nausea. A study of Helmy SAK and Bali A [17] using 120 mg of DM IM reported nausea and vomiting were the most frequent side effect but they were of mild severity.

Oral dosage of DM less than 90 mg offered both postoperative pain relief and mild side effects. Sixty and 90 mg of DM revealed no difference in postoperative pain intensity and morphine requirement [18, 21]. Weinbroum *et al* [18] studied analgesic effect of preincisional oral 60, 90 mg of DM and placebo combined with epidural lidocaine in patients undergoing hernia repair and arthroscopy. The study revealed both DM groups required similar amount postoperative morphine PCA. Side effects, however, were dose-related. Weinbroum *et al* [21] demonstrated that patients taking preincisional oral 60 and 90 mg of DM similarly experienced less morphine consumption compared with those in placebo group.

Four studies, however, did not show any analgesic effect of DM [28, 29, 30, 31]. Time given of DM was preoperative period in all of the trials. The clinical studies were performed in TAH [28], adenotonsillectomy [29], laparotomy [30], and cesarean section [31]. Several doses of DM were explored: 0.5mg/kg [29], 1.0mg/kg [29], 27 mg [28], and 60 mg [30, 31].

McConaghy *et al* [28] found no obvious benefit in perioperative administration of oral 27 mg of DM. The authors believed that studied doses were probably too small. Rose and colleagues [29] studied 0.5 and 1.0 mg/kg of oral DM compared with placebo in children undergoing adenotonsillectomy. The three groups were similar with respect to the number of patients who required morphine and the mean dose of morphine administered. The authors' explanation was similar to that of Rose's work. Grace *et al* [30] studied patients taking DM 60 mg or placebo before laparotomy. The DM group required less morphine intraoperatively but similar consumption after surgery for 24 hours compared with the placebo group. A possible explanation was that DM might need to be continued

postoperatively. Addition of oral DM 60 mg an hour before surgery and 6 and 12 hours after operation to intrathecal morphine for parturients undergoing cesarean section under spinal anesthesia was not reduced postoperative pain when compared with placebo [31].

Table 1 Clinical trials of dextromethorphan

Ref.	Patients (n)	Time given	Dose	Route	Operation	Comments
9	90 (30/30/30)	30 min before incision, after gallbladder removal	40 mg	IM	LC	No DM-related side effects 0-2 h.
10	60 (30/30)	30 min before anesthetic induction, postoperative	5 mg/kg	IV	Major abdominal surgery	Post group consumed more morphine but pre and post group had similar morphine-related side effects
11	60 (20/20/20)	30 min before incision, 30 min before the end of surgery	120 mg	IM	Upper abdominal surgery	Other side effects were of minor intensity
12	30 (15/15)	90 min before surgery	90 mg	PO	LC	DM group reduced post-operative analgesic used and improved well-being.
13	100 (25/25/25/25)	30 min before surgery	40 mg ± lidocaine 3 mg/kg	IM	LC	VAS sig. reduced at 2 h, but not at 1 h and 4 h. No DM-related side effects 0-48 h.
14	83 (22/20/21/20)	30 min before surgery	40 mg ± tenoxicam 40 mg	IM	LC	VAS sig. reduced at 1 h and 2 h, but not at 4 h. No DM-related side effects 0-2 h.

Table 1 Clinical trials of dextromethorphan (continue)

Ref.	Patients (n)	Time given	Dose	Route	Operation	Comments
15	60 (15/15/15/ 15)	30 min before surgery	10, 20, 40 mg	IM	Upper abdominal surgery	No DM-related side effects 0-48 h.
16	56 (34/22)	2 h before surgery, then 8 and 16 h later	200 mg (3 times)	PO	Knee surgery	Sig more nausea in DM group, $p < 0.05$
17	75 (18/17/20/ 20)	90 min before surgery	90 mg ± epidural lidocaine	PO	Hernia repair, knee surgery	Patients received either LA or GA. Lower incidence of side effects in DM group.
18	53 (16/17/20)	90 min before surgery	60, 90 mg with epidural lidocaine	PO	Hernia repair, knee surgery	Low pain score VAS $\leq$ 30
19	47 (24/23)	90 min before surgery, then 3 times a day for two days	40 mg (8 times)	PO	TAH	Less morphine and paracetamol requirement after surgery in DM group
20	50 (25/25)	1 h before surgery	150 mg	PO	TAH	Low pain score VAS $\leq$ 30
21	72 (25/24/23)	90 min before surgery	60, 90 mg	PO	Bone and soft tissue surgery	Patients in DM60 and DM90 groups similarly experienced 50-80% less pain
22	56 (29/27)	90 min before surgery	90 mg	PO	Bone and soft tissue surgery	Significance 0-48 h not reported significantly nore side effects in placebo group.

Table 1 Clinical trials of dextromethorphan (continue)

Ref.	Patients (n)	Time given	Dose	Route	Operation	Comments
23	113 (29/27/28/ 29)	90 min before surgery and next 2 post-operative days	90 mg with IV PCA or 90 mg with PCEA	PO	Bone and soft tissue surgery	Patients received either PCEA or IV PCA.
24	90 (30/30/30)	30 min before surgery	40 mg with TEA	IM	Colonic surgery	Possible synergistic interaction with local anesthetics and opioids.
25	36 (12/12/12)	60 min before surgery	30, 45 mg	PO	Tonsillectomy	Reduced pain for 7 days after tonsillectomy
26	60 (30/30)	30 min before surgery	40 mg	IM	Hemorrhoidec-tomy	No other side effects reported.
27	60 (30/30)	30 min before surgery	40 mg	IM	Modified radical mastectomy	No DM-related side effects 0-2 h.
28	53 (27/26)	One on the night before, one with premedicant and 8, 6, and 24 h after operation	27 mg (5 times)	PO	TAH	Low pain score VAS $\leq$ 30
29	57 (19/19/19)	1 h before surgery	0.5 and 1.0 mg/kg	PO	Adenotonsillec-tomy	0.5 mg/kg and 1.0 mg/kg dose calculated from mean body weight
30	37 (18/19)	The night before and 1 h before surgery	60 mg (twice)	PO	Laparotomy	A four-point rating scale used for pain assessment, data not shown.
31	120 (20/20/20/ 20/20/20)	1 h before and 6, and 12 h after surgery	60 mg (3 times)	PO	Cesarean section	Fixed dose of DM in a variety of intrathecal morphine doses

Abbreviation: ± = with or without, GA = general anesthesia, h = hour(s) IM = intramuscular injection, IV = intravenous injection, kg = kilogram, LA = local anesthesia, LC = laparoscopic cholecystectomy, min = minute, mg = milligram, PCA = patient-controlled analgesia, PCEA = patient-controlled epidural analgesia, PO = orally, Ref. = references, sig = significant, TAH = total abdominal hysterectomy, TEA = thoracic epidural analgesia, VAS = visual analog pain score

Clinical studies of etoricoxib and postoperative pain

Chang, *et al* [34] demonstrated postoperative analgesic efficacy of etoricoxib 120 mg in a postoperative dental pain model, extraction of two or more third molars. This model is well validated and accepted for assessing the efficacy of analgesic medications. They found that etoricoxib 120 mg provided superior overall efficacy compared with oxycodone/acetaminophen 10/650 mg, which is a potent analgesic used for relief of moderate to moderately severe pain, and was associated with significant fewer side effects

Liu and colleagues [35] showed that a single dose of preoperative etoricoxib 120 mg decreased the use of fentanyl needed postoperatively and improved the pain scores after minor gynecological surgery without significant side effects.

For moderate to severe pain from hip and knee replacement [36], etoricoxib 120 mg once daily also provided analgesia that was similar to controlled-release naproxen sodium 1.1 gm on day 1 and superior to placebo with reduced supplement opioid used over 7 days [36].

Table 2 Clinical trials of etoricoxib

Ref.	Patients (n)	Time given	Dose (milligram)	Type of operation
34	225 (100/100/25)	After operation finished	120	Extraction of third molars
35	40 (20/20)	30-60 minutes before surgery	120	Termination of pregnancy
36	228 (75/80/73)	First dose within 24-72 hours after surgery and continue once daily for next 6 days	120	Hip and knee replacement

CHAPTER II
RESEARCH METHODOLOGY

2.1 Research questions

Since the concept of "multimodal analgesia" suggests that combinations of several analgesics of different classes and different sites of analgesic administration rather than single analgesic or single technique provide superior pain relief with reduced analgesic-related side effects, combination of etoricoxib and dextromethorphan which relieve pain with different mechanisms in the pain pathway should provide more analgesic efficacy than either etoricoxib or dextromethorphan alone.

2.1.1 Primary research question

- Are there any differences in postoperative analgesic efficacy among the patients taking oral dextromethorphan (DM), etoricoxib, and their combination before undergoing laparoscopic surgery?

2.1.2 Secondary research questions

- Are there any differences in the incidence of adverse effects among the patients taking preoperative DM, etoricoxib, and their combination?

- Are there any differences in the incidence of shoulder pain among the patients taking preoperative DM, etoricoxib, and their combination?

2.2 Objectives

According to the research questions, a clinical trial was conducted to find the answers with these following objectives.

1. To compare the postoperative analgesic efficacy after laparoscopic surgery between the patients taking preoperative oral DM, etoricoxib, and their combination.

2. To compare the incidence of adverse effects among the patients taking preoperative DM, etoricoxib, and their combination.

3. To estimate the overall incidence of shoulder pain.

4. To compare the incidence of shoulder pain among the patients taking preoperative DM, etoricoxib, and their combination.

2.3 Hypothesis

2.3.1 Research hypothesis

After laparoscopic surgery, a combination of oral DM and etoricoxib given preoperatively should demonstrate superior efficacy (measured by patient-controlled analgesia (PCA) morphine consumption) than either drug alone and cause fewer side effects.

2.3.2 Statistical hypothesis

Null hypothesis

After laparoscopy with surgical procedures, postoperative morphine consumption via PCA in patients taking preoperative oral DM, oral etoricoxib and their combination are equal.

$H_0 : \mu_1 = \mu_2 = \mu_3$

where μ_1, μ_2, μ_3 = the mean of morphine used during 24 hours after surgery in DM, etorocoxib and DM/etoricoxib group respectively.

Alternative hypothesis

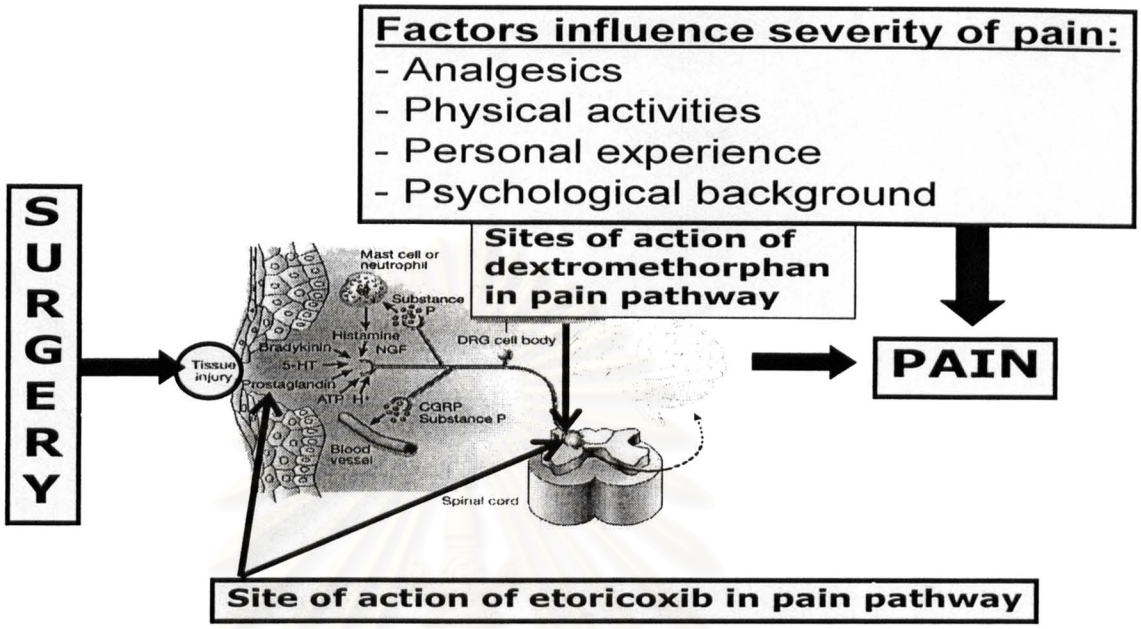
After laparoscopy with surgical procedures, morphine consumption via PCA in patients taking preoperative oral dextromethorphan, oral etoricoxib and their combination, at least one group is different.

H_1 : At least one inequality, $\mu_1 \neq \mu_2$ or $\mu_1 \neq \mu_3$ or $\mu_2 \neq \mu_3$

where μ_1, μ_2, μ_3 = the mean of morphine used for 24 hours after surgery in DM, etorocoxib and DM/etoricoxib group respectively.

2.4 Conceptual framework

Figure 1 Proposed conceptual framework



2.5 Operational definition

Some technical terms need to be explained more in details in the part of operation definition.

American Society of Anesthesiologists (ASA) physical status is a classification of patients preoperatively according to their health [54].

Class I normal healthy patient

Class II mild systemic disease – no functional limitation

Class III severe systemic disease – definite functional limitation

Class IV severe systemic disease that is a constant threat to life

Class V moribund patient unlikely to survive 24 hours with or without operation

Verbal numerical rating score (NRS) of pain intensity [55] is a range of 0 to 10 score while 0 is no pain at all and 10 is unbearable pain.

Respiratory depression is a condition which respiratory rate is below 10/min.

Sedation score: the degree of sedation will be classified as a scale 0 to 2; 0 = alert, 1 = drowsy but rousable to voice, and 2 = very drowsy, rousable to shaking.

Severity of nausea and vomiting:

mild	if	the patient reported the symptom on questioning
moderate	if	the symptom needs treatment and is effective
severe	if	treatment is necessary and is not completely satisfactory

Patient-controlled analgesia (PCA) machine is a device that allows patients to self-administered analgesic medication by triggering the button. The machine is programmed to deliver a specific dose, interval between doses, and the maximum amount of analgesic in a given period.

2.6 Research design

The study had been conducted as a prospective double-blinded, randomized (1:1), controlled, parallel group trial. The patients and outcome assessors were masked of the medications given.

2.7 Research methodology

2.7.1 Population and sample

Target population

Patients undergoing laparoscopy with surgical procedure under general anesthesia (GA)

Sample population

Patients scheduled for elective laparoscopy with surgical procedure under GA at King Chulalongkorn Memorial Hospital who met the eligible criteria.

2.7.2 Inclusion criteria

Patients who were 18-65 years of age with ASA physical status I-II scheduled for elective laparoscopy with surgical procedure under GA; cholecystectomy, laparoscopically assisted vaginal hysterectomy (LAVH), ovarian surgery, other pelvic organ surgery.

2.7.3 Exclusion criteria

For patient's safety, the following patients were excluded: a patient who was pregnant, was allergic to dextromethorphan, morphine, and etoricoxib, had renal

insufficiency, evidence of peptic ulcer, coronary artery disease, poorly controlled hypertension, and taken the following medications: amiodarone, quinidine, fluoxetine, amitriptyline, nortriptyline, and monoamine oxidase inhibitors.

To prevent confounding factors, patients who refused to participate the study, were unable to express verbal NRS, were unable to use PCA equipment, had persistent preoperative pain, and had taken any analgesics within 48 hours preoperatively were also excluded.

2.7.4 Sample size estimation

Since the primary outcome is the mean of total postoperative analgesic required during 24 hours, sample size estimation is based on comparison of more than two independent means using Cohen's *f* (effect size) [56] as follows:

$$\text{Cohen's } f = \sqrt{\frac{\sum_{j=1}^{k}\sum(\mu_j - \mu)^2}{k\sigma^2_{error}}}$$

where μ_j = population mean of the total morphine used in group j (j = 1, 2, 3),

μ = grand mean of the total morphine used,

k = number of groups, and

σ^2_{error} = error variance of the mean within group variance.

From the value of *f* (effect size), sample size can be estimated using the Cohen's table.

Data from a pilot study in 12 patients were used to calculate the sample size. To compare the estimated mean total morphine used during 24 hours after surgery in DM, etorocoxib and DM/etoricoxib group at 2-sided type I error of 5%, power of 90% and 20% drop out rate, each group required 22 subjects.

2.7.5 Randomization and concealment

All consecutive patients who met the inclusion criteria and agreed to participate in the study were recruited. Simple randomization technique using randomization table was used. Treatment allocation was concealed in separate sealed opaque envelops.

2.7.6 Intervention

Before the study, eligible patients were instructed on the method of pain assessment by NRS and how to use PCA equipment. They were randomly allocated to orally administer one of the three following medications: dextromethorphan 60 mg (D

group), etoricoxib 120 mg (E group) or combination of dextromethorphan 60 mg and etoricoxib 120 mg (DE group). These medications were prepared in identical capsules. The patients received the assigned medication(s) 90 minutes before conducting GA. They were also unaware of the assigned medication. Placebo was not used as a control group. If a placebo control group was employed in this study, it would be predicted that patients in the control group would receive morphine PCA to relieve their pain more than the other treatment groups. It might induce more unnecessary side effects of morphine to these patients. For this reason, it might be unethical.

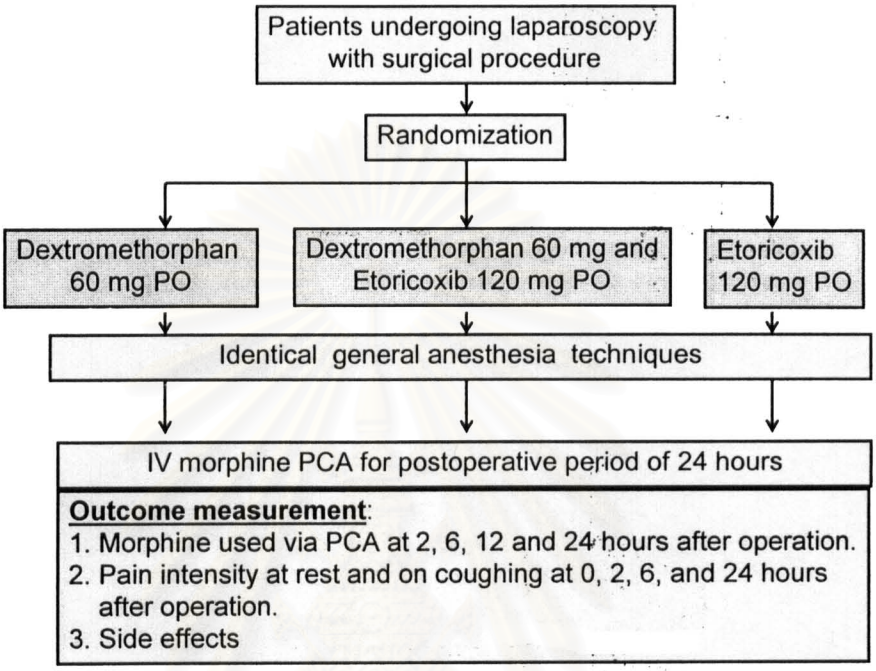
All patients did not receive any premedication. The anesthesiologist who conducts GA was blinded to the study drugs. Anesthesia was induced with fentanyl (1 mcg/kg) and thiopental (3-5 mg/kg). Endotracheal intubation was facilitated by succinylcholine (1-2 mg/kg). Anesthesia was maintained with 67% nitrous oxide in oxygen, isoflurane 1-2% via a semiclosed carbon dioxide absorption circle system. Muscle relaxation was maintained with atracurium. Additional fentanyl (1 mcg/kg) might be given to provide adequate depth of anesthesia. Standard monitors were used. After surgery, residual neuromuscular blockade was antagonized with neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). The endotracheal tube was removed when adequate spontaneous breathing was established. Patients were taken to the postanesthesia care unit (PACU).

In the PACU, with the patient's first requirement of pain medication, time and NRS were recorded by a nurse anesthetist or an anesthesiologist who was involved further in the study. Then they received PCA with IV morphine. PCA was set to deliver 1.0 mg of morphine with a lock-out interval of 6 minutes after 3 mg of loading dose every 5 minutes to a maximum of 9 mg, and no continuous infusion. PCA was discontinued at 24 hours after the operation and patients were able to subsequently receive oral paracetamol 0.5-1 gm or tramadol 50 mg IV every 4 hours or IV morphine 4 mg as needed as a non-study analgesic. Metoclopramide 10 mg was given intravenously every 6 hours as needed for relieving nausea and/or vomiting.

At any time during the trial, if a patient complained of intolerable pain, this would have been discussed between the patient and the principal investigator. Additional IV morphine 3 mg was given and 1 mg titrating until patient was comfortable. Time and the

amount of morphine used were recorded. The amount of extra-morphine given within 24 hours after surgery was recorded for statistical analysis.

Figure 2 Flow of study design



2.7.7 Outcome measurement

Primary outcome variables

1. Postoperative analgesic requirement:

PCA offers a valuable method for measuring the amount of rescue analgesic required to treat postoperative pain, and thus can be used as **an indirect assessment of pain** [57].

Analgesic consumption during the postoperative period was assessed by recording the total amount of morphine consumed from PCA and additional injection within the first 24 hours. However, the amount of morphine delivered during 2, 6, 12, and 24 hours was also recorded to determine trend of response.

2. Pain intensity:

Pain intensity, at rest and with movement, was assessed at 0, 2, 6, and 24 hours postoperatively using verbal NRS. This scale allows patients to classify the severity of pain from 0 to 10. A score of 0 means no pain and a score of 10 means the most excruciating pain one can imagine. **Assessment of pain intensity was carried out to**

monitor the adequacy of analgesic consumption which was the major outcome in this study. NRS at 12 hours after the surgery, however, was not assessed since this time mostly was the sleeping period of the patients.

Secondary outcome variables

Side effects:

The side effects of IV morphine PCA are nausea, vomiting, drowsy, and very uncommon respiratory depression. The side effects of DM are nausea, vomiting, and dizziness. All of these side effects were determined by a nurse anesthetist blinded to the study medication. Nausea, and vomiting were rated as mild (if the patient reported the symptom on questioning), moderate (if the symptom needed treatment and was effective), and severe (if treatment was necessary but was not completely satisfactory). A respiratory rate below 10/min was regarded as respiratory depression. The degree of sedation was classified as a scale 0 to 2; 0 = alert, 1 = drowsy but rousable to voice, and 2 = very drowsy, rousable to shaking. Dizziness was observed as present or absent.

2.7.8 Data collection

a) Demographic data and baseline characteristics:

These following data were recorded by the same investigator who conducted anesthesia.

- age (years)
- gender (male:female)
- weight (kilograms)
- height (centimeters)
- duration of surgery (minutes)
- type of laparoscopic surgery: cholecystectomy, ovarian surgery, LAVH, other pelvic organ surgery.

b) Outcomes

These following data were recorded from each patient by an assessor who did not know which study medication assigned to the patients.

Primary outcome:

- cumulative IV morphine PCA consumption (milligram) at 24 hours after surgery

Secondary outcomes:

- cumulative IV morphine PCA consumption (milligram) at 2, 6, and 12 hours after surgery
- verbal numerical rating pain scale (NRS, 0-10) at rest and on coughing at 0, 2, 6 and 24 hours after surgery

c) Adverse events

- shoulder pain [yes/ no]
- nausea (no, mild, moderate, severe)
- vomiting (no, mild, moderate, severe)
- sedation score (0-2)
- dizziness [yes/ no]
- respiratory depression [yes/ no]
- others [yes/ no] (identify.....)

2.7.9 Data analysis

The difference in total morphine consumption during 24 hours after surgery between 3 treatment groups was compared using one-way ANOVA and Scheffe's test was used for multiple comparisons. Accumulation of morphine consumption at 2, 6, 12, and 24 hours after surgery was compared among three treatment groups using analysis of repeated measures.

Pain score at 0, 2, 6, and 24 hours after surgery in the three treatment groups was compared using Kruskal-Wallis test and Dunn procedure was applied for multiple comparisons.

Regarding shoulder pain (yes, no) and side effects i.e., severity of nausea and vomiting (mild, moderate, severe), sedation score (0, 1, 2), respiratory depression (yes, no), dizziness (yes, no), and others (yes, no), chi-square test or Fisher's exact test was employed for comparison between three treatment groups.

If there is a clinically significant difference in potential confounders i.e., type of surgery and duration of surgery, between three treatment groups, these confounders will

be adjusted in statistical analysis. That is, to compare total morphine consumption during 24 hours after surgery between three treatment groups, a multiple linear regression will be employed to adjust for plausible confounders.

All statistical data analysis was performed using SPSS version 11.5. Two-sided *P*-value of less than 0.05 was considered statistically significant.

Table 3 Data analysis of demographic data and baseline characteristics

Age	Mean (SD)
Gender	Frequency (%)
Weight	Mean (SD)
Height	Mean (SD)
Duration of surgery	Mean (SD)
Type of surgery	Frequency (%)

Table 4 Data analysis of outcomes and adverse events

Variables	Scale	Statistical analysis
Total morphine consumption during 24 hours after surgery	Continuous	One-way ANOVA (Scheffe's test for multiple comparison)
Morphine consumption at 2, 6, 12 and 24 hours after surgery	Continuous	Analysis of repeated measure data
NRS at 0, 2, 6, and 24 hours after surgery	Ordinal	Non-parametric Kruskal-Wallis test (Dunn procedure for multiple comparison)
Shoulder pain	Binary	Chi-square test or Fisher's exact test
Side effects: - Severity of nausea and vomiting - Sedation score	 Ordinal Ordinal	Non-parametric Kruskal-Wallis test (Dunn procedure for multiple comparison)
Side effects: - Respiratory depression - Dizziness - Others	 Binary Binary Binary	Chi-square test or Fisher's exact test

2.7.10 Ethical consideration

This study was conducted in accordance with the ethical principles stated in the most recent version on the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Faculty of Medicine, Chulalongkorn University.

Prior to recruitment in the study, patients were thoroughly informed about the objectives and methods of the study, treatment outcomes and anticipating side effects, and the patient's right to refuse to participate in or to withdraw from the study at anytime without any interference on their further standard treatment. Any adverse effects that might occur were treated until subside with free of charge. The patients had to sign an

informed consent form before they entered the study. (For consent form, see appendix 1 and 2.) All data were used for study purpose only and were kept confidentially.

DM and etoricoxib are registered by Thai FDA as indications of antitussis and analgesic respectively. From previous studies these medications were used with minimal side effects. For three treatment groups, they received on-demand intravenous morphine through PCA machine, which is generally accepted as one of very potent analgesics, as a rescue medication for their postoperative pain. The patients had been explained how to use a PCA equipment and were encouraged to request for rescue medication at anytime after surgery.

2.7.11 Limitation

The study was carried out in the patients who underwent laparoscopic surgery. It might not be generalized to the patients having different type of surgery.

2.7.12 Implication

The efficacy of orally administered dextromethorphan, an NMDA antagonist, and etoricoxib was confirmed as medications for postoperative pain control. Reduction of pain and analgesic consumption especially opioid might lead to decrease the incidence and/or severity of certain dose-dependent side effects. Dextromethorphan is not expensive and has mild adverse effects. Combination of dextromethorphan with traditional pain regimens may be interesting in term of economic consideration. Etoricoxib is rather expensive. However, if using it can reduce or replace postoperative opioid treatment, it is probably useful. Cost-effectiveness analysis should be conducted to confirm this issue.

CHAPTER III

RESULTS

3.1 Basic characteristics of patients and baseline data

Sixty six patients were included in the study. Two patients in the dextromethorphan group (D group) were excluded because laparotomy was decided to perform instead of laparoscopic surgery, leaving 20 cases for analysis of efficacy outcome and adverse events. Three patients in the etoricoxib group (E group) were excluded due to receiving another source of analgesics, leaving 19 cases for analysis of efficacy and safety outcome. Two patients in the combination of drugs group (DE group) were excluded because laparotomy was decided to perform instead of laparoscopic surgery, leaving 20 cases for efficacy and safety analysis.

Table 5 displayed baseline data i.e., age (years), gender, weight (kilograms), height (centimeters), duration of surgery (minutes), and type of surgery in each treatment group. Demographics and baseline data were similar among the study groups except body weight. Mean body weight of the D group was lower than the other two groups.

Table 5 Demographic data and baseline characteristics

	Mean (SD) or Number		
	Dextromethorphan n = 22	Etoricoxib n = 22	Both n = 22
Age (yr)	43 (12)	41 (11)	42 (11)
Gender (male:female)	4:18	2:20	3:19
Weight (kg)	54.8 (8.3)	60.4 (13.8)	59.7 (8.6)
Height (cm)	158 (7)	158 (7)	160 (8)
Duration of surgery (min)	99 (26)	113 (37)	104 (45)
Type of surgery			
- Cholecystectomy	10	9	9
- Ovarian surgery	9	11	10
- LAVH	1	2	1

LAVH: laparoscopically assisted vaginal hysterectomy

3.2 Primary outcome analysis

Total morphine consumption during 24 hours after surgery

Mean (SD) total morphine consumption during 24 hours after surgery in D group, E group, and DE group were 14.6 (12.1), 13.3 (11.4), and 10.9 (6.5) mg respectively. Median (interquartile range [IQR]) of total morphine consumption during 24 hours after surgery in D group, E group, and DE group were 9.0 (18.8), 9.0 (12.0), and 10.5 (9.5) mg respectively. Due to non-normal distribution of the total morphine consumption in each group, Kruskal Wallis test was employed instead of 1-way ANOVA (figure 3). It revealed that there was no statistically significant difference in mean total morphine consumption during 24 hours after surgery ($p = 0.989$) (table 6).

As a supporting analysis, the total morphine consumption was log10 transformed (figure 4) to create normally distributed data for further analysis with 1-way ANOVA. ANOVA also showed no statistical difference in mean log10 of total morphine consumption during 24 hours after surgery ($p = 0.768$) (table 6).

Beside log 10 transformation, the total morphine consumption was natural log transformed (figure 5), square root transformed (figure 6) and 1/morphine used 24 hours transformed (figure 7). The transformed data showed non-normal distribution.

Figure 3 Distribution of total morphine consumption during 24 hours after surgery

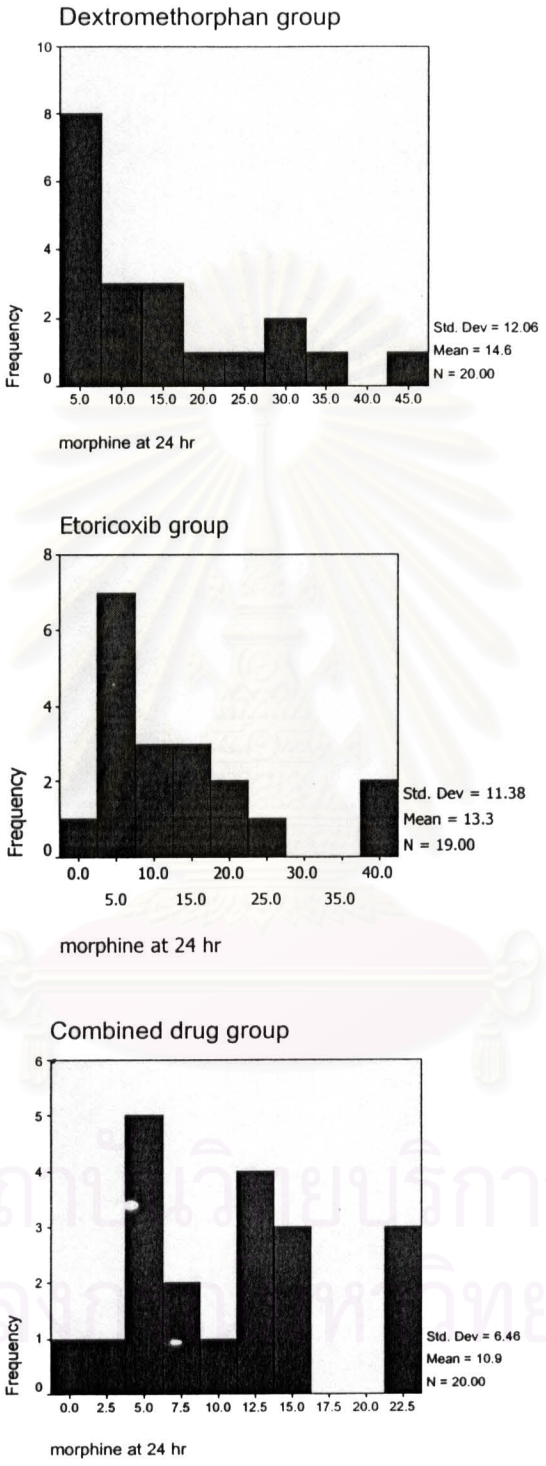
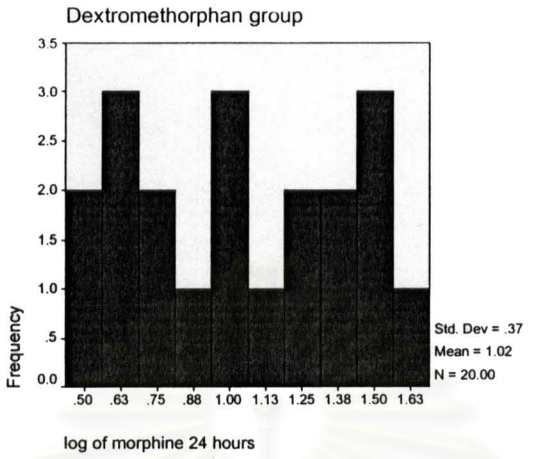
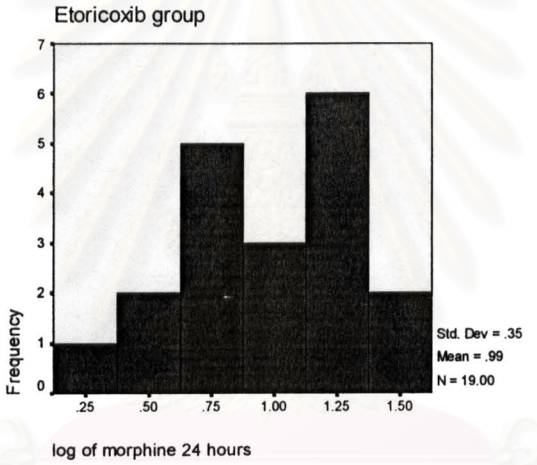


Figure 4 Distribution of log10 of total morphine consumption during 24 hours after surgery





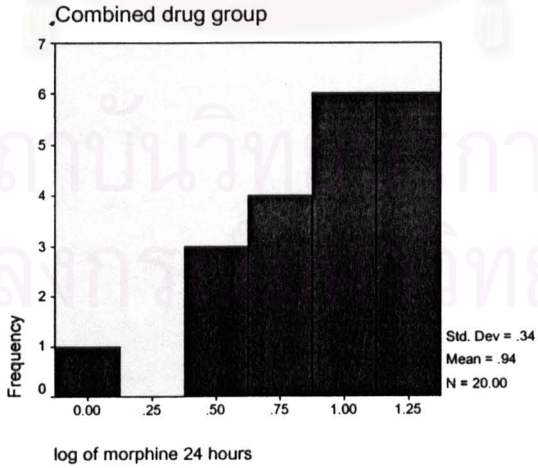


Figure 5 Distribution of natural log of total morphine consumption during 24 hours after surgery

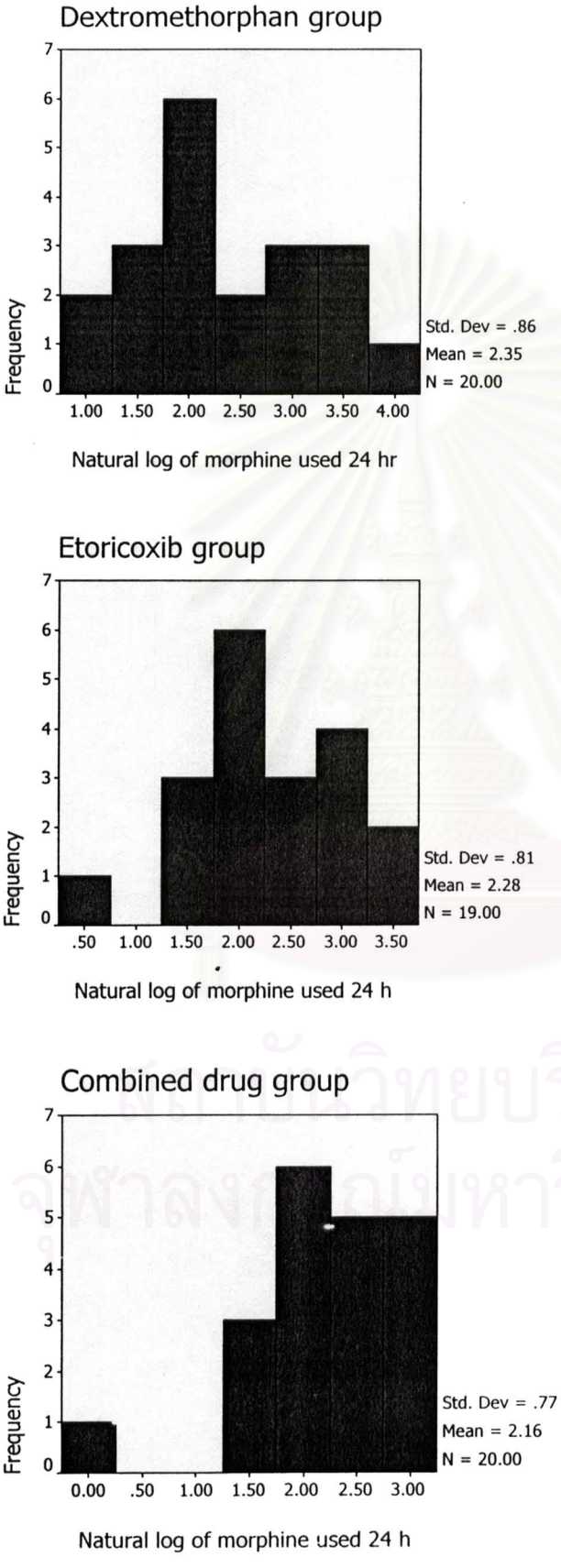
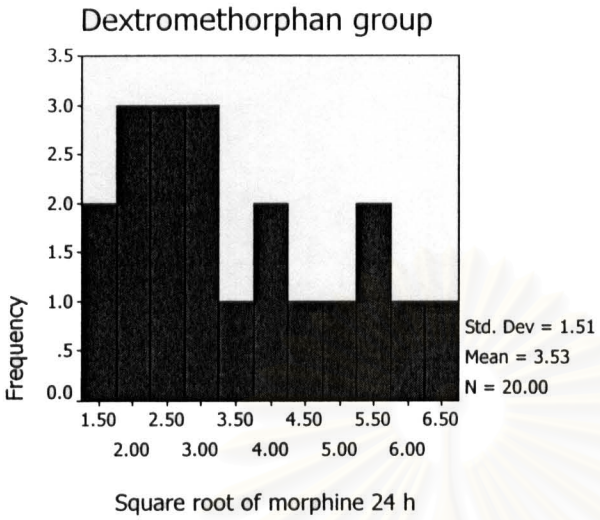
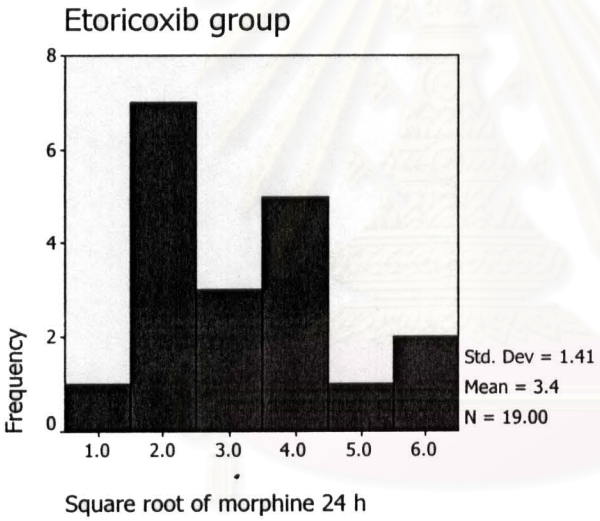


Figure 6 Distribution of square root of total morphine consumption during 24 hours after surgery





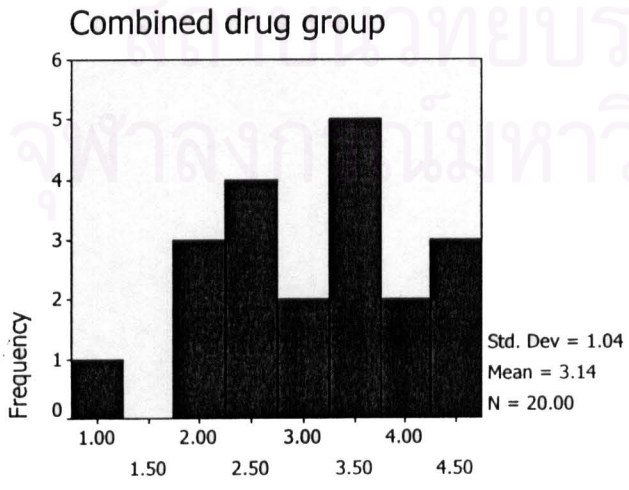
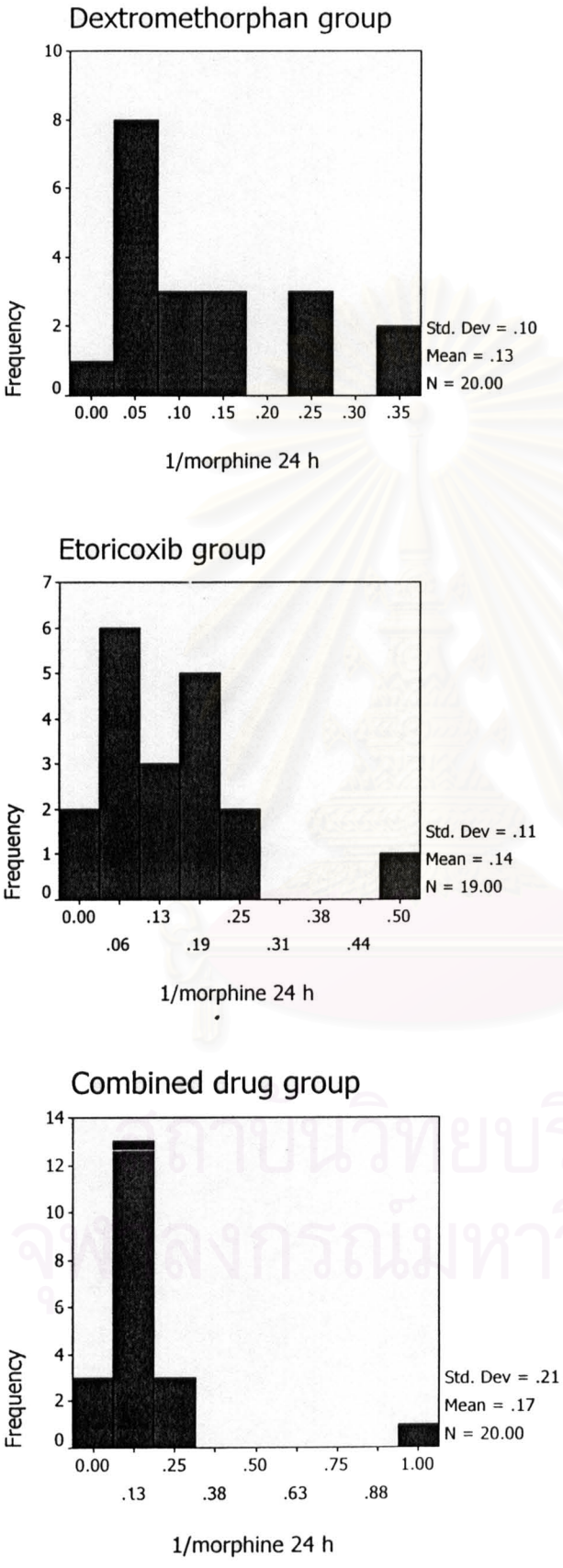


Figure 7 Distribution of 1/ total morphine consumption during 24 hours after surgery



Total morphine consumption per body weight during 24 hours after surgery

According to demographics, mean body weight of the D group was fewer than the other two groups. As body weight is considered to influence upon usage of postoperative morphine, mean total morphine consumption per body weight during 24 hours after surgery was calculated and analyzed using nonparametric Kruskal Wallis test due to non-normal distribution (figure 8). It revealed that there was no statistically significant difference in mean total morphine consumption per body weight during 24 hours after surgery ($p = 0.654$). Mean (SD) total morphine consumption during 24 hours after surgery in D group, E group, and DE group were 0.26 (0.21), 0.21 (0.17), and 0.18 (0.10) mg respectively. Median (interquartile range [IQR]) of total morphine consumption during 24 hours after surgery in D group, E group, and DE group were 0.20 (0.31), 0.16 (0.18), and 0.16 (0.13) mg respectively.

To confirm Kruskal-Wallis result, total morphine consumption per body weight was log10 transformed to obtain normally distributed data for 1-way ANOVA (figure 9). ANOVA showed no statistical difference in mean log10 of total morphine consumption per body weight during 24 hours after surgery ($p = 0.490$) (table 6).

For numerical pain rating scale (NRS) at rest and on coughing at different time, there was no statistically significant difference among the study groups. The maximum pain intensity occurred immediately after surgery and tended to decline as time went by (table 6)

Beside log 10 transformation, the total morphine consumption 24 hours after surgery/ body weight was natural log transformed (figure 10), square root transformed (figure 11) and 1/morphine used 24 hours transformed (figure 12). The transformed data showed non-normal distribution.

Figure 8 Distribution of total morphine consumption per body weight during 24 hours after surgery

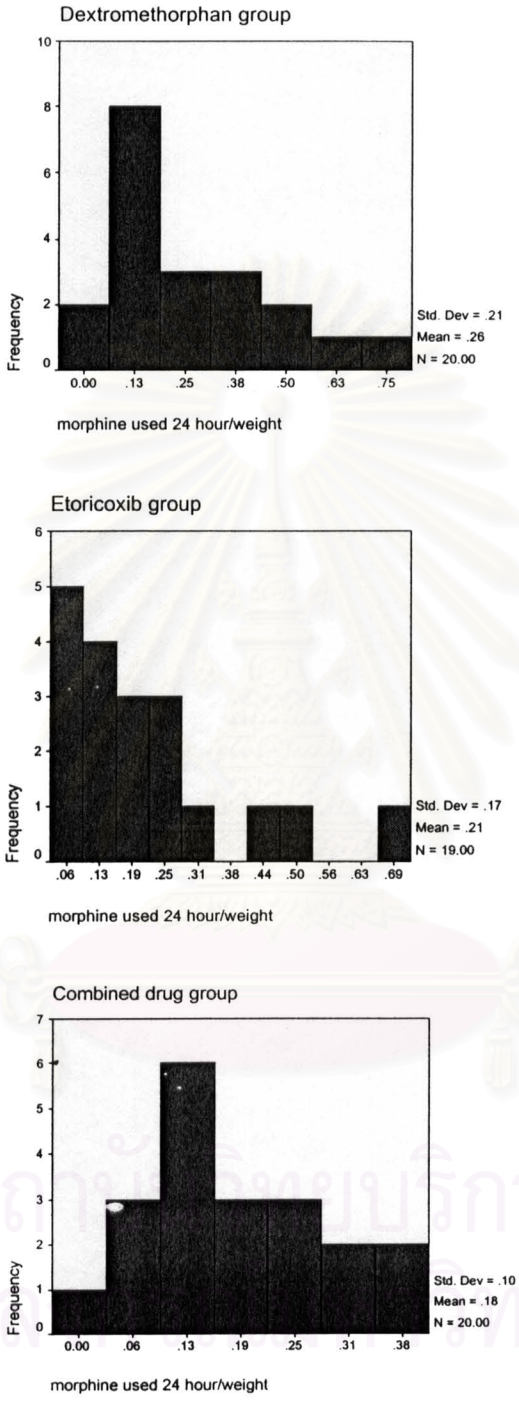
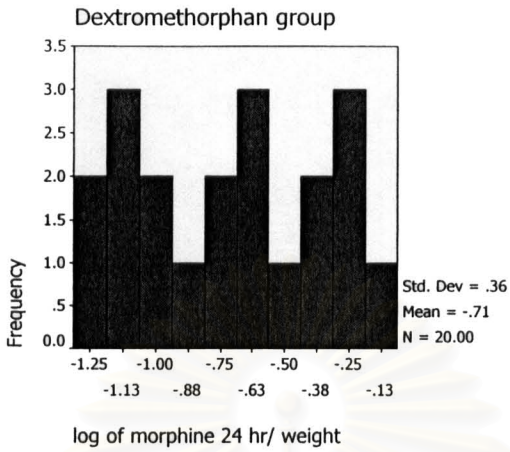
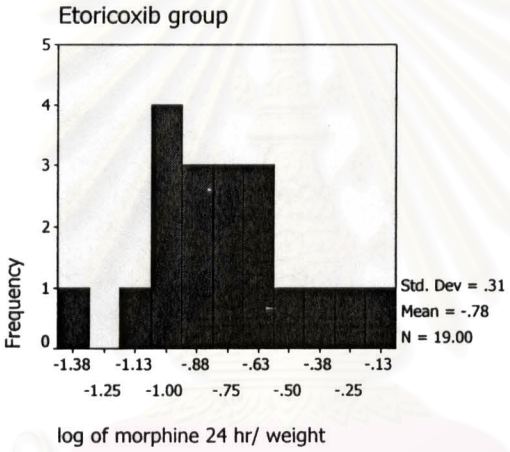


Figure 9 Distribution of log10 of total morphine consumption per body weight during 24 hours after surgery





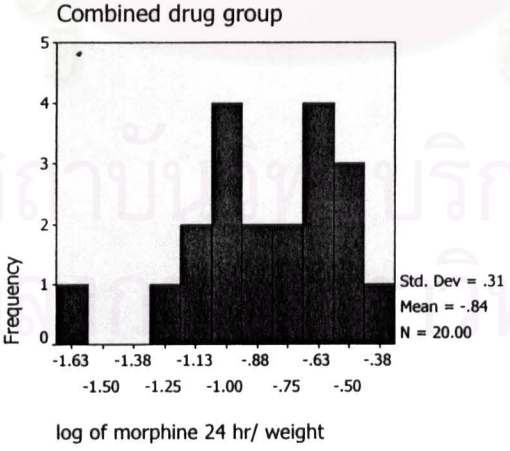
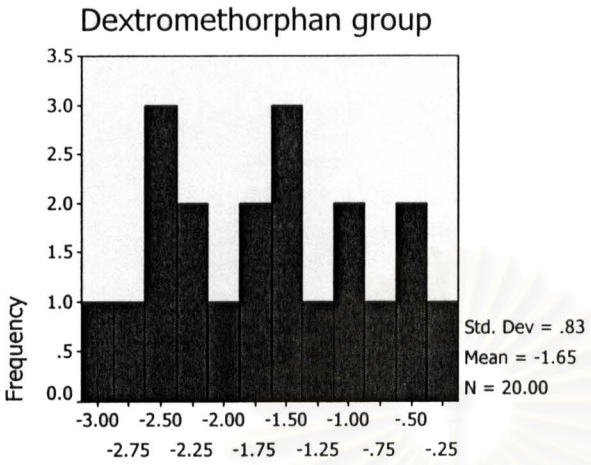
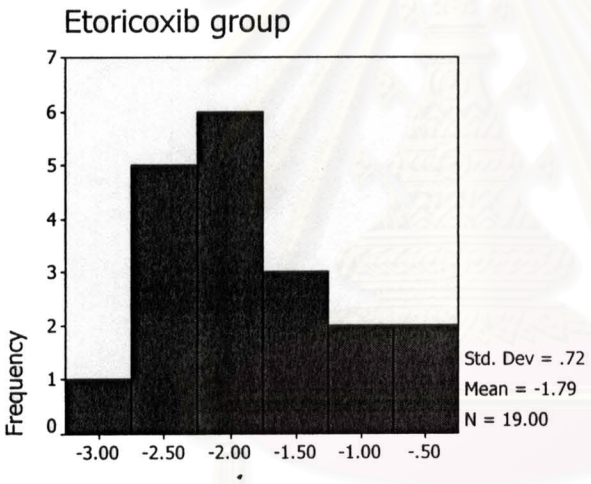


Figure 10 Distribution of natural log of total morphine consumption per body weight during 24 hours after surgery





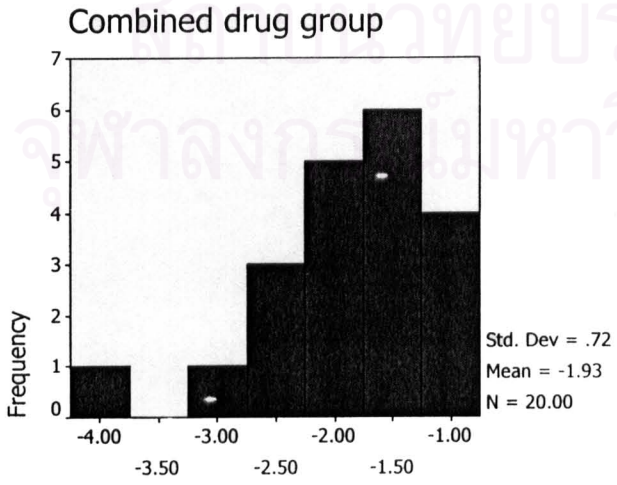
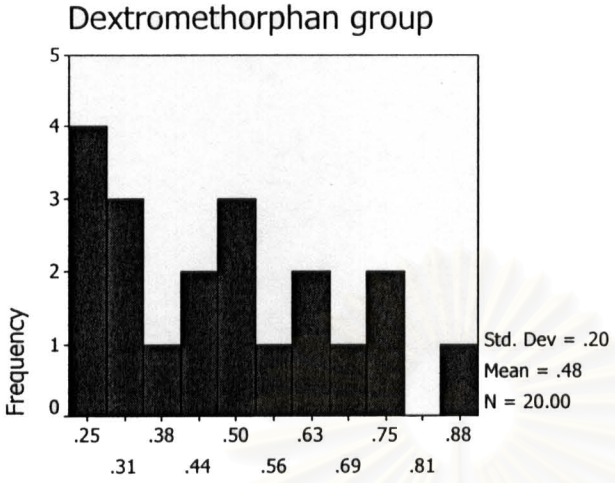
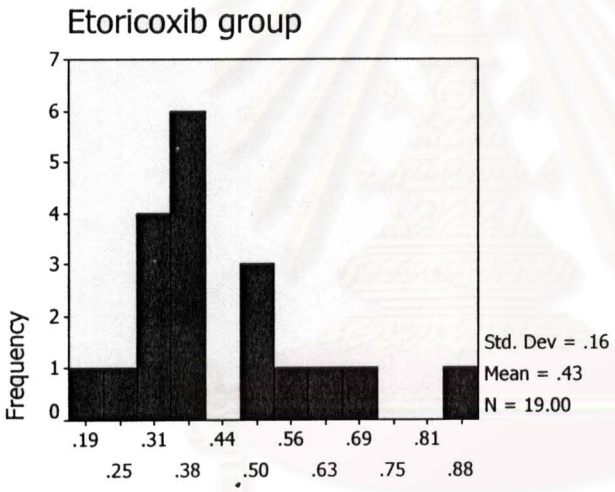


Figure 11 Distribution of square root of total morphine consumption per body weight during 24 hours after surgery





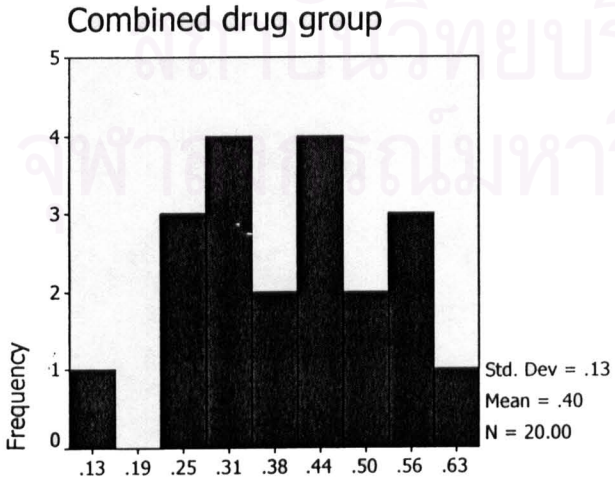
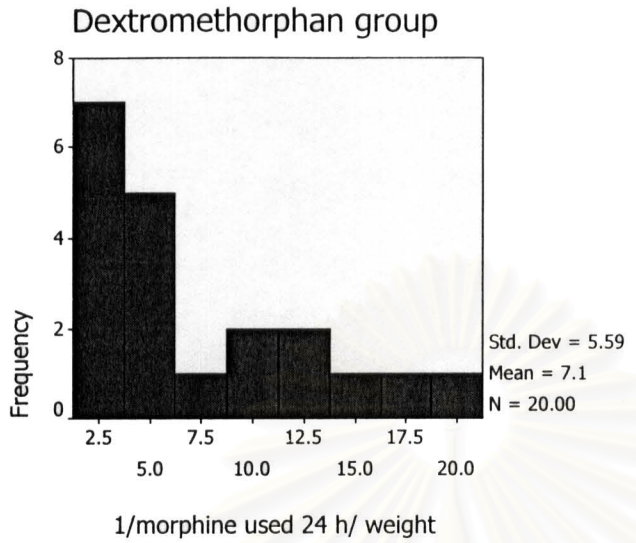
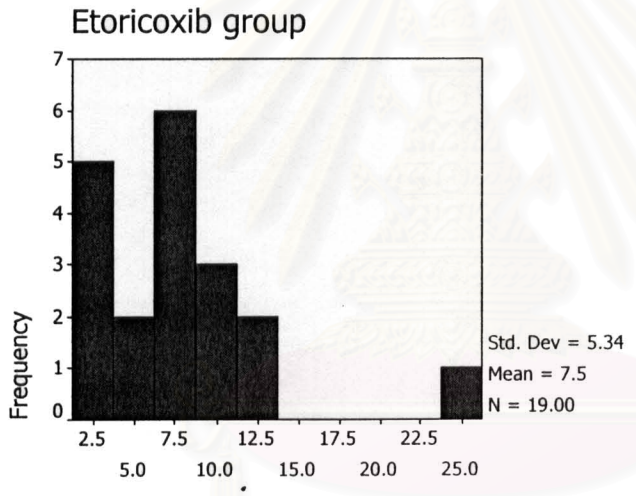


Figure 12 Distribution of 1/ total morphine consumption per body weight during 24 hours after surgery





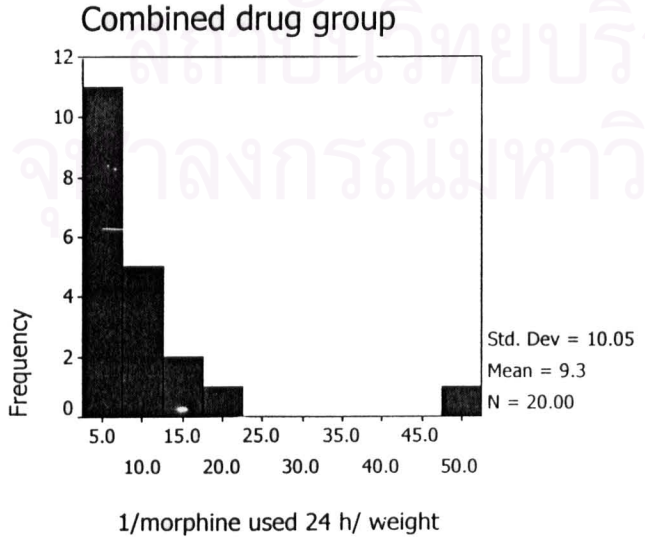


Table 6 Efficacy outcomes

	Mean (SD)			P value
	Dextromethorphan (n = 20)	Etoricoxib (n = 19)	Both (n = 20)	
Total morphine used (mg) after surgery at				
- 2nd hour	6.4 (4.9)	5.9 (3.5)	5.5 (3.1)	0.915#
- 6th hour	8.9 (6.7)	9.0 (6.8)	8.1 (5.1)	0.964#
- 12th hour	11.0 (9.0)	10.6 (9.1)	9.3 (5.2)	0.989#
- 24th hour	14.6 (12.1)	13.3 (11.4)	10.9 (6.5)	0.858#
Log10 of total morphine used at24 hours after surgery	1.02 (0.37)	0.99 (0.35)	0.94 (0.34)	0.768@
Total morphine used per body weight at 24 hours after surgery (mg/kg)	0.26 (0.21)	0.21 (0.17)	0.18 (0.10)	0.654#
Log10 of total morphine used per body weight at 24 hours after surgery	-0.71 (0.36)	-0.78 (0.31)	-0.84 (0.31)	0.490@
NRS at rest at				
- 0 hour after surgery	4.2 (3.1)	3.7 (2.4)	4.4 (3.1)	0.769#
- 2 hours after surgery	1.9 (2.3)	2.5 (2.5)	1.6 (1.9)	0.494#
- 6 hours after surgery	1.3 (1.8)	1.6 (2.1)	2.0 (3.0)	0.871#
- 24 hours after surgery	1.0 (1.5)	0.5 (0.9)	0.7 (1.0)	0.517#
NRS on coughing at				
- 0 hour after surgery	4.8 (3.0)	4.5 (2.6)	5.0 (3.1)	0.851#
- 2 hours after surgery	3.6 (2.6)	3.6 (2.3)	3.2 (2.5)	0.802#
- 6 hours after surgery	2.9 (2.2)	3.0 (2.1)	3.5 (3.2)	0.921#
- 24 hours after surgery	2.8 (2.2)	2.0 (1.7)	2.1 (1.7)	0.509#

Kruskal Wallis test, @ Oneway ANOVA

NRS: numerical pain rating scale

3.3 Secondary outcomes analysis

Chi-square test was employed to test the difference in shoulder pain and dizziness (yes, no) between three treatment groups whereas Kruskal-Wallis test for nausea, vomiting (no, mild, moderate, severe), and sedation (0-2).

Twenty seven patients (43.5%) developed shoulder pain within 24 hours after the operation in the study. The incidence of shoulder pain was not statistically significant difference among the study groups ($p = 0.664$) which was 45.0%, 36.4%, and 50.0% in D, E, and DE group respectively (table 7). There was no statistical difference in the adverse events in terms of nausea and vomiting ($p = 0.819$ and 0.066 respectively) (table 7). The incidence of zero score of sedation (no sedation) was lower in D group (65.0%) while that of E and DE group were 95.5% and 80.0% respectively. However, there was no statistically significant difference ($p = 0.063$) (table 7). The incidence of dizziness in D group, E group, and DE group was 45.0%, 9.1%, and 30.0% respectively. They were statistically different with p value 0.032 (table 7). No respiratory depression was detected in the study.

Table 7 Adverse events

Adverse events	Number (%)			P value
	Dextromethorphan (n = 22)	Etoricoxib (n = 22)	Both (n = 22)	
Shoulder pain	9 (40.9%)	8 (36.4%)	10 (45.5%)	0.664#
Nausea				0.819@
- no	6 (27.3%)	9 (40.9%)	7 (31.8%)	
- mild	7 (31.8%)	6 (27.3%)	8 (36.4%)	
- moderate	5 (22.7%)	4 (18.2%)	4 (18.2%)	
- severe	4 (18.2%)	3 (13.6%)	3 (13.6%)	
Vomiting				0.066@
- no	5 (22.7%)	11 (50.0%)	11 (50.0%)	
- mild	7 (31.8%)	7 (31.8%)	7 (31.8%)	
- moderate	7 (31.8%)	2 (9.1%)	1 (4.5%)	
- severe	3 (13.6%)	2 (9.1%)	3 (13.6%)	
Sedation score				0.063@
- 0	13 (59.1%)	21 (95.5%)	16 (72.7%)	
- 1	9 (40.9%)	1 (4.5%)	6 (27.3%)	
Respiratory depression	0	0	0	
Dizziness	9 (40.9%)	2 (9.1%)	6 (27.3%)	0.032#

Pearson's chi-square test

@ Kruskal-Wallis test

CHAPTER IV
DISCUSSION

The present study showed that patients undergoing laparoscopic surgery under general anesthesia and receiving preoperative dextromethorphan (DM) 60 mg, etoricoxib 120 mg or their combination required postoperative 24-hour intravenous (IV) morphine patient-controlled analgesia (PCA) without statistically significant difference. Mean body weight of patients in DM group, however, was less than that of the other two groups. It is a fact that body weight is a factor influenced the amount of analgesic requirement. Then mean total morphine consumption per body weight during 24 hours after surgery was calculated. It also revealed that analgesic used per weight in all groups were not statistically significant difference.

According to non-normally distributed data of morphine consumption 24 hours after surgery and morphine consumption 24 hours per body weight after surgery, several transformation methods of the data which were log 10, natural log, square root, 1/x transformation, to demonstrate normal distribution of the data were employed. Unfortunately, no normally distributed data was showed. Non-parametric Kruskal-Wallis test was finally used for statistical analysis of the primary outcome data.

Up to date there was no clinical trial comparing analgesic efficacy between DM and cyclooxygenase-2 (COX-2) inhibitors as well as their combination like the present study. However, there were two clinical trials comparing postoperative analgesic efficacy between placebo, DM, non-steroidal anti-inflammatory agents (NSAID's), and their combination. The results of these two trials were in the opposite ways. One study compared postoperative pethidine requirement between DM, tenoxicam, and their combination [14]. Surprisingly patients in tenoxicam group used postoperative pethidine less than the control group without statistical difference while patients in DM group and combined drug group consumed less pethidine significantly. The other work by Ilkjaer *et al* [58] showed an opposite result. They conducted a trial in elective termination of pregnancy. Their patients received placebo, ibuprofen 400 mg, oral DM 120 mg, or their combination. No analgesic effect of oral DM was demonstrated while patients taking ibuprofen requested less morphine during the first two hours postoperatively.

The amount of postoperative morphine supplement of DM group was similar to that of etoricoxib group in the present study. Analgesic efficacy in acute pain management of etoricoxib 120 mg was supported by several clinical trails [34, 35, 36, 59, 60] Meanwhile that of DM was inconclusive [61, 62]. Several controlled trials demonstrated that administration of DM to surgical patients significantly prolonged first analgesic request and significantly decreased in supplemental opioid consumption. Some studies, however, did not confirm these positive results [8, 29, 30, 31] The results of the present study probably implied that both oral DM 60 mg and etoricoxib 120 mg provided similar analgesic property or equipotent analgesia. However, the next clinical research with equivalence trial design might be necessary to confirm this implication.

The dose of oral DM 60 mg was chosen in this study because previous studies looking for the effect of lower-dose DM regimens on postoperative pain and analgesic use were inconclusive. A clinical trial in laparoscopic cholcystectomy (LC) setting [12] prescribing oral DM 90 mg revealed reduction of postoperative analgesic used. However, another study using 60 mg and 90 mg of oral DM [18, 21] in bone and soft tissue malignancy operation, herniorplasty, and knee surgery which had more tissue injury than LC, demonstrated similar analgesic efficacy between DM 60 and 90 mg. Preoperative IM DM 10, 20, and 40 mg were studied in patients undergoing upper abdominal surgery. Postoperative analgesic efficacy was dose-related which 10 mg of DM was not superior to placebo while 40 mg of DM had more efficacy than DM 20 mg [15]. In one study, pain scores and analgesic use after abdominal hysterectomy were reduced by oral DM 40 mg given preoperatively and then at 8-hour intervals for 48 hours [19], but not by oral DM 27 mg given preoperatively and 8, 16, and 24 hours postoperatively in another study [28].

One strategy for relieving postoperative pain is to prevent or minimize central sensitization [63, 64]. Central sensitization mainly results from activation of NMDA receptors in the central nervous system triggered by long-lasting nociceptive afferent input. Hence, NMDA antagonist may prevent the induction of central sensitization [65].

The antitussive effect of a single oral dose of DM 60 mg lasts 6-8 hours [5]. With respect to pharmacological property of DM, its duration of analgesic efficacy should not last more than 8 hours. At 12 and 24 hours after surgery, there still was the analgesic

effect of etoricoxib 120 mg. Therefore the patients in DM group should require postoperative morphine more than the other two groups. But in the present study, accumulation of IV morphine PCA used at 12 and 24 hours postoperative in all groups were not statistically significant difference. The possible explanation was that the development of central sensitization in the spinal cord induced by nociceptive stimulation of surgery was blocked or modulated by DM acting on N-methyl-D-aspartate (NMDA) receptors.

The concept of multimodal analgesia suggests that combinations of several analgesics of different classes and different sites of analgesic administration rather than single analgesic or single technique provide superior pain relief with reduced analgesic-related side effects [37, 38]. The use of multimodal analgesia decreases pain scores and/or the requirement for postoperative analgesics in different surgical procedures [39, 40, 41]. Unfortunately, the present study neither revealed additive nor synergistic effect when both of them were administered together. Since pain intensity after laparoscopic surgery was considered to be moderate, either etoricoxib or DM alone could provide adequate analgesia. Their combination under the concept of multimodal analgesia might not offer more benefit. However, the present study also applied the concept of multimodal analgesia to every patient by prescribing the study drugs together with morphine which relieved pain by another different mechanism.

In the present study, the average maximum pain intensity on coughing, approximately 4/10, occurred immediately after surgery and tended to decline to mild intensity beyond six hours after surgery. The result was similar to time course of pain after LC which was reviewed by Bisgaard and colleagues [46]. Pain intensity peak was within the first 4-8 postoperative hours. Visual analogue pain scores are usually in the range of 40/100 mm within the first 24 hours.

The overall incidence of shoulder pain in the present study was 40.9% in which between 35% [47] and 58% [66] from other reports. The incidence of shoulder pain was not statistically significant difference among the study groups. Shoulder pain is probably minor on the first day but it can increase and becomes significant on the following day [67].

Regarding adverse events in terms of nausea, vomiting, and sedation, there was no statistically significant difference. However, the incidence of dizziness in DM group was higher than the others. Like other reports, the adverse events occurred were mild in severity.

One limitation of the present study was that it lacked of a control group. A placebo group could provide some useful information. If there had been a placebo group, it would have been able to demonstrate the amount of opioid reduction in the study groups. But a placebo group was not employed as a control group in the present study. The reason was that it could be predicted that the patients in placebo group would require more amount of postoperative morphine than the other groups. Although they could achieve as minimal pain as the other patients, but they probably took risk of opioid-induced side effects more than the others. It might be unethical.

There was one possible explanation why the three study groups required morphine 24 hours after surgery without statistically significant difference. When the PCA machine was turned on, the loading dose of morphine 3 mg would be delivered and if it had been necessary, another 3 mg of morphine would have been delivered every five minutes to a maximum of 9 mg. With this amount of loading morphine, it might provide adequate postoperative analgesia that the patients activated the PCA machine with very few times. The loading dose of morphine probably confounded the actual requirement of postoperative morphine.

In conclusion, DM 60 mg, etoricoxib 120 mg, and their combination as an oral medication before laparoscopic surgery did not alter the 24-hour postoperative morphine consumption significantly. NRS at rest, NRS on coughing and other adverse events were not statistically different except dizziness which was less in etoricoxib group. DM may be considered as an adjuvant of pain medications for management of postoperative pain with mild to moderate severity. Combination of DM and etoricoxib, however, does not offer more benefit than prescribing either one of them.

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Appendices

Appendix A

หนังสือให้ความยินยอมเข้าร่วมในโครงการวิจัย

ทำที่_____

วันที่_____

ข้าพเจ้า_____อายุ_____ปี อยู่บ้านเลขที่_____ซอย/ตรอก_____ถนน_____หมู่ที่_____แขวง/ตำบล_____เขต/อำเภอ_____จังหวัด_____

ขอทำหนังสือนี้ให้ไว้ต่อหัวหน้าโครงการวิจัยเพื่อเป็นหลักฐานแสดงว่า

1. ข้าพเจ้าได้รับทราบโครงการวิจัยของนายแพทย์ปิ่น ศรีประจิตติชัย (หัวหน้าผู้วิจัย) และคณะ เรื่อง **"การรับประทาน dextromethorphan และ/หรือ etoricoxib ก่อนผ่าตัดเพื่อระงับปวดหลังการผ่าตัดผ่านกล้อง"**
2. ข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยนี้ด้วยความสมัครใจ โดยมิได้มีการบังคับขู่เข็ญหรือหลอกลวงแต่ประการใด และพร้อมจะให้ความร่วมมือในการวิจัย
3. ข้าพเจ้าได้รับทราบการอธิบายจากผู้วิจัยเกี่ยวกับวัตถุประสงค์ของการวิจัย วิธีวิจัย ประสิทธิภาพ ความปลอดภัย อาการหรืออันตรายที่อาจเกิดขึ้น รวมทั้งประโยชน์ที่จะได้รับจากการวิจัยโดยละเอียดแล้วจากเอกสารการวิจัยที่แนบท้ายหนังสือให้ความยินยอมนี้
4. ข้าพเจ้าได้รับการรับรองจากผู้วิจัยว่าจะเก็บข้อมูลส่วนตัวของข้าพเจ้าเป็นความลับ จะเปิดเผยเฉพาะผลสรุปการวิจัยเท่านั้น
5. ข้าพเจ้าได้รับทราบจากผู้วิจัยว่า หากเกิดอันตรายใดๆในระหว่างการวิจัยหรือภายหลังการวิจัยอันพิสูจน์ได้จากผู้เชี่ยวชาญของสถาบันที่ควบคุมวิชาชีพนั้นๆได้ว่าเกิดขึ้นจากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการดูแลและค่าใช้จ่ายในการรักษาพยาบาลจากผู้วิจัยและ/หรือผู้สนับสนุนการวิจัย
6. ข้าพเจ้าได้รับทราบแล้วว่า ข้าพเจ้ามีสิทธิจะบอกเลิกการร่วมโครงการวิจัยนี้เมื่อใดก็ได้ และการบอกเลิกการร่วมโครงการวิจัยจะไม่มีผลกระทบต่อการได้รับบรรดาค่าใช้จ่าย ค่าชดเชยและค่าทดแทนตามข้อ 5 ทุกประการ
7. หัวหน้าวิจัยได้อธิบายเกี่ยวกับรายละเอียดต่างๆของโครงการ ตลอดจนประโยชน์ของการวิจัยรวมทั้งความเสี่ยงและอันตรายต่างๆที่อาจจะเกิดขึ้นในการเข้าร่วมโครงการนี้ให้ข้าพเจ้าทราบ และตกลงรับผิดชอบตามคำรับรองในข้อ 5 ทุกประการ

ข้าพเจ้าได้อ่านและเข้าใจข้อความตามหนังสือนี้โดยตลอดแล้ว เห็นว่าถูกต้องตามเจตนาของข้าพเจ้า จึงได้ลงลายมือชื่อไว้เป็นสำคัญพร้อมกับหัวหน้าผู้วิจัยและต่อหน้าพยาน

ลงชื่อ_____ผู้ยินยอม

(_____)

ลงชื่อ_____หัวหน้าผู้วิจัย

(_____)

ลงชื่อ_____พยาน

(_____)

ลงชื่อ_____พยาน

(_____)

หมายเหตุ

1. กรณีผู้ยินยอมตนให้ทำวิจัยไม่สามารถอ่านหนังสือได้ ให้ผู้วิจัยอ่านข้อความในหนังสือให้ความยินยอมนี้ให้แก่ผู้ยินยอมให้ทำวิจัยฟังจนเข้าใจดีแล้ว และให้ผู้ยินยอมตนให้ทำวิจัยลงนามหรือพิมพ์ลายนิ้วหัวแม่มือรับทราบในการให้ความยินยอมดังกล่าวด้วย
2. กรณีผู้ยินยอมมีอายุไม่ครบ 18 ปีบริบูรณ์ จะต้องมีผู้ปกครองตามกฎหมายเป็นผู้ให้ความยินยอมด้วย

Appendix B

ข้อมูลสำหรับผู้ป่วย

การศึกษาทางคลินิก: การรับประทาน dextromethorphan และ/หรือ etoricoxib ก่อนผ่าตัดเพื่อระงับปวดหลังการผ่าตัดผ่านกล้อง

ผู้วิจัยหลัก: นายแพทย์ปิ่น ศรีประจิตติชัย

1. เหตุผลในการศึกษาวิจัย

เด็กซ์โตรเมทรอแฟน (dextromethorphan) เป็นยาแก้ไอมากว่า 40 ปี ราคาถูก มีอาการไม่พึงประสงค์บ้างเล็กน้อย เช่น ง่วงซึม มวนท้อง มีการศึกษาวิจัยทางคลินิกจำนวนมากพบว่าเด็กซ์โตรเมทรอแฟนมีประสิทธิภาพในการบรรเทาความปวดหลังการผ่าตัดได้

อีโทริค็อกสิบ (etoricoxib) มีคุณสมบัติในการระงับปวดทั้งเรื้อรังและเฉียบพลัน มีโอกาสทำให้เกิดแผลในกระเพาะอาหารต่ำมาก และมีอาการไม่พึงประสงค์บ้างเล็กน้อย

การผ่าตัดถุงน้ำดีและการผ่าตัดทางนรีเวชผ่านกล้องเป็นการผ่าตัดวิธีใหม่ ซึ่งมีข้อดีหลายประการเมื่อเทียบกับวิธีเก่า เช่น ปวดแผลน้อยกว่า ฟื้นตัวหลังการผ่าตัดเร็วกว่า พักฟื้นในโรงพยาบาลสั้นกว่า เป็นต้น ผู้ป่วยจะปวดแผลหลังผ่าตัดประมาณ 3 วัน แต่จะปวดมากที่สุดในช่วง 24 ชั่วโมงแรกหลังผ่าตัด และมักจะได้รับมอร์ฟีนหรืออนุพันธุ์ของมอร์ฟีนแก้ปวดอันอาจจะทำให้เกิดอาการอันไม่พึงประสงค์ เช่น ง่วงซึม คลื่นไส้อาเจียน การกดการหายใจ เป็นผลให้ฟื้นตัวหลังการผ่าตัดช้ากว่าที่ควร ทั้งเด็กซ์โตรเมทรอแฟน และอีโทริค็อกสิบต่างก็มีคุณสมบัติในการระงับปวดหลังการผ่าตัด จึงอาจจะเป็นอีกทางเลือกหนึ่งในการบรรเทาความปวดหลังการผ่าตัดได้ โดยใช้ตัวใดตัวหนึ่งหรือใช้ร่วมกันทั้งสองตัวแทนที่การใช้มอร์ฟีนหรืออนุพันธุ์ของมอร์ฟีนแก้ปวด

2. วิธีการ

ในการศึกษาวิจัยนี้ ผู้ป่วยที่สมัครใจเข้าร่วมจะถูกแบ่งออกเป็น 3 กลุ่มโดยวิธีการสุ่ม คือ กลุ่มที่ได้รับเด็กซ์โตรเมทรอแฟน กลุ่มที่ได้รับอีโทริคอสิบ และกลุ่มที่ได้รับทั้งเด็กซ์โตรเมทรอแฟนและอีโทริค็อกสิบโดยผู้ป่วยจะไม่ทราบว่าตัวเองอยู่ในกลุ่มใดเพื่อป้องกันการเกิดอคติในการประเมินผล ผู้ป่วยจะได้รับ-ıประทานยาที่จะศึกษาในแคปซูลลักษณะเดียวกัน 90 นาทีก่อนเริ่มผ่าตัด

หลังการผ่าตัดผู้ป่วยจะได้รับมอร์ฟีนทางหลอดเลือดดำเพื่อบรรเทาความปวด โดยผู้ป่วยเป็นผู้ควบคุมการให้ยาด้วยตนเองผ่านทางอุปกรณ์ที่ใช้ในการควบคุมการให้มอร์ฟีนซึ่งจะถูกตั้งโปรแกรมไว้เพื่อมิให้ผู้ป่วยได้รับมอร์ฟีนมากเกินไปจนเกิดอันตราย

3. การประเมินผล

ผู้ป่วยจะได้รับการประเมินความปวดหลังผ่าตัดโดยวิสัญญีพยาบาลที่ได้รับการฝึกมา โดยจะถามเป็นคะแนนความปวดจาก 0-10 0 คะแนนแปลว่าไม่ปวดเลย ในขณะที่ 10 คะแนนเป็นความปวดที่รุนแรงมากจนไม่สามารถทนได้ โดยจะประเมินที่ 2, 6, และ 24 ชั่วโมงหลังผ่าตัด ปริมาณมอร์ฟีนที่ใช้ไปจะถูกบันทึกไว้ในเครื่องตลอด 24 ชั่วโมง และจะมีการเฝ้าระวังอาการข้างเคียงต่างๆ และให้การรักษาทันทีที่พบ

4. ประโยชน์ที่จะได้รับ

ผู้ป่วยจะได้รับการดูแลรักษาในเรื่องความปวดหลังการผ่าตัดอย่างใกล้ชิดโดยผู้ป่วยไม่ต้องเสียค่าใช้จ่ายใดๆในการรักษาอาการปวดนี้ รวมถึงค่ารักษาอาการข้างเคียงอันเกิดจากยาที่ทำการศึกษา

5. การรักษาความลับ

ข้อมูลต่างๆที่ได้จากการศึกษานี้จะใช้เพื่อวัตถุประสงค์ทางวิชาการเท่านั้น ข้อมูลทั้งหมดจะถูกเก็บเป็นความลับ การตีพิมพ์เผยแพร่ผลงานทางวิชาการจะไม่มีการระบุชื่อของผู้เข้าร่วมในโครงการ

6. สิทธิของผู้ป่วย

การเข้าร่วมในการศึกษาครั้งนี้เป็นไปโดยสมัครใจ ท่านอาจปฏิเสธที่จะเข้าร่วมโครงการหรือถอนตัวจากโครงการได้ตลอดเวลาโดยไม่กระทบต่อการดูแลรักษาท่าน

7. การลงนาม

เพื่อเข้าร่วมโครงการศึกษาวิจัยนี้ ท่านหรือผู้แทนโดยชอบด้วยกฎหมายต้องลงนามพร้อมวันที่ในใบแสดงความยินยอมเข้าร่วมโครงการศึกษาวิจัยที่แนบมาด้วยกันนี้

หากท่านมีปัญหาหรือข้อสงสัยประการใด กรุณาติดต่อ นพ. ปิ่น ศรีประจิตติชัย ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย หรือโทรศัพท์ติดต่อได้ที่ 02-256-4295 หรือ 06-310-2322

คณะกรรมการจริยธรรม คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย 02-256-4455, 02-256-4493 ต่อ 14, 15

Appendix C

Case Record Form

Patient screening form:

Inclusion criteria	Yes	No
1. Patients scheduled for elective laparoscopy with surgical procedure under general anesthesia; cholecystectomy, laparoscopically assisted vaginal hysterectomy (LAVH), ovarian surgery, other pelvic organ surgery.	☐	☐
2. Age 18-65 years.	☐	☐
3. American Society of Anesthesiologists physical status I-II	☐	☐

Exclusion criteria	Yes	No
1. pregnant	☐	☐
2. allergic to dextromethorphan	☐	☐
3. allergic to morphine	☐	☐
4. allergic to etoricoxib	☐	☐
5. renal insufficiency	☐	☐
6. evidence of peptic ulcer	☐	☐
7. coronary artery disease	☐	☐
8. poorly controlled hypertension	☐	☐
9. daily intake the following medications: amiodarone, quinidine, fluoxetine, amitriptyline, nortriptyline, and monoamine oxidase inhibitors	☐	☐
10. refute to participate the study	☐	☐
11. unable to express verbal numerical rating scale (NRS)	☐	☐
12. unable to use patient-controlled analgesia equipment	☐	☐
13. have persistent preoperative pain	☐	☐
14. daily intake or intake 48 hours preoperatively any analgesics	☐	☐

Title: Preoperative Oral Administration of Dextromethorphan and/or Etoricoxib for Pain Management after Laparoscopic Surgery.

----------Record ID ☐☐☐

Baseline data

1. Age.....years
2. Gender ☐ Male ☐ Female
3. Weight.....kilograms
4. Height.....centimeters
5. Duration of surgery.....minutes
6. Type of surgery: ☐ Cholecystectomy
   ☐ Ovarian surgery
   ☐ LAVH
   ☐ Other pelvic organ surgery
   (identify.....)

Efficacy outcomes

Outcomes	0 hour	2 hours	6 hours	12 hours	24 hours
Cumulative morphine consumption					
Numerical pain rating score					

Shoulder pain and safety outcomes

1. Shoulder pain ☐ Yes ☐ No
2. Adverse effects:
   - Nausea ☐ No ☐ mild ☐ moderate ☐ severe
   - Vomiting ☐ No ☐ mild ☐ moderate ☐ severe
   - Sedation score ☐ 0 ☐ 1 ☐ 2
   - respiratory depression ☐ Yes ☐ No
   - Dizziness ☐ Yes ☐ No
   - Others ☐ Yes (specify.....) ☐ No

VITAE

Pin Sriprajittichai was born on January 31st, 1968 in Bangkok,, Thailand. He graduated with M.D. Degree from the Faculty of Medicine, Chulalongkorn University in 1992. From 1992 to 1995, he underwent a residency training program at King Chulalongkorn Memorial Hospital and obtained a Thai Board of Anesthesiologist from the Medical Council of Thailand in 1995. In 1997, he obtained a scholarship from the Faculty of Medicine, Chulalongkorn University to be a one-year fellow in pain management at Vanderbilt University Medical Center, Nashville, Tennessee, USA.

Since 2005, he has admitted in the Master Degree in Health Development Program at the Faculty of Medicine, Chulalongkorn University. His principal research interest is postoperative pain management. During this course, he has conducted a randomized clinical trial on the efficacy of dextromethorphan, etoricoxib, and their combination for analgesia after laparoscopic surgery.

Presently, he has been working as an instructor at the Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University since 1995.