*Original Article*

# Efficacy of Perioperative Administration of Intravenous Parecoxib on Postoperative Morphine Consumption after Video-Assisted Thoracoscopic Surgery

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***Background***: Morphine is commonly used to relief pain after video-assisted thoracoscopic surgery (VATS), however high dose morphine is usually related with many complications. Parecoxib is a potent cyclo-oxygenase inhibitor for parenteral administration that has a role in acute pain management addition to opioid protocol.

***Objective***: To investigate the potential benefits of intravenous parecoxib for relieving postoperative pain after VATS.

***Materials and Methods***: The present study was a randomized controlled trial that assigned 22 patients undergoing VATS into two groups to received either parecoxib 40 mg as P group with 11 patients, or placebo using 2 mL of Normal Saline Solution as C group with 11 patients with an intravenous administration at 30 minutes prior to surgery and then 12 hours later. In the postoperative period, all patients received intravenous patient-controlled analgesia (PCA) with morphine. The primary outcome was the total morphine consumption for 24 hours postoperatively. The secondary outcomes were pain score at 2, 6, 12, and 24 hours postoperatively, using a numeric rating scale (NRS, 0 to 10) and the incidence of side effects.

***Results***: The total morphine consumption was significantly lower in P group (26.64±4.41 mg) than C group (39.82±3.87 mg) at 24 hours postoperatively ($p<0.001$). The NRS pain score at rest and on coughing at 24 hours postoperatively between P group compared with C group were 1.09±1.04 versus 4.45±0.69 ($p<0.001$) and 2.91±0.83 versus 5.36±0.81 ($p<0.001$), respectively. The incidences of nausea and vomiting were found in both groups at 2, 6, and 12 hours, postoperatively, but there was no statistically significant difference between both groups ($p>0.05$). Other adverse events such as sedation, pruritus, dyspepsia, headache, hypotension, and respiratory depression were not found.

***Conclusion***: Perioperative administration of parecoxib was safe and effectively decrease postoperative morphine consumption and pain score at rest and on coughing within 24 hours postoperatively after VATS.

***Keywords***: Intravenous parecoxib; Video-assisted thoracoscopic surgery; Acute postoperative pain

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Video-assisted thoracoscopic surgery (VATS) has been gradually replacing conventional thoracotomy for diagnosis and treatment of thoracic disease such as lung cancer, mediastinal mass, spontaneous pneumothorax, and emphysema thoracis. A VATS is considered minimally invasive conducted via two or three small ports in the chest with approximately 1 cm in diameter. The advantages of VATS include less postoperative pain, earlier mobilization, earlier recovery, earlier discharge, less impact on pulmonary function, and reduction of the cost of hospitalization[1,2].

Patients that underwent VATS still complain of a moderate degree of acute postoperative pain and the incidence of chronic postoperative pain has been reported similar to open thoracotomy[3,4]. Therefore, postoperative pain in patients that underwent VATS should not be undertreated and neglected as an adequate acute postoperative pain control to avoid adverse events of postoperative quality of life and morbidity.

A VATS, compared to conventional open thoracotomy, has less tissue trauma and postoperative pain score than the open technique. However, patients after VATS reported a moderated to severe degree of acute postoperative pain, which 20 to 47% of

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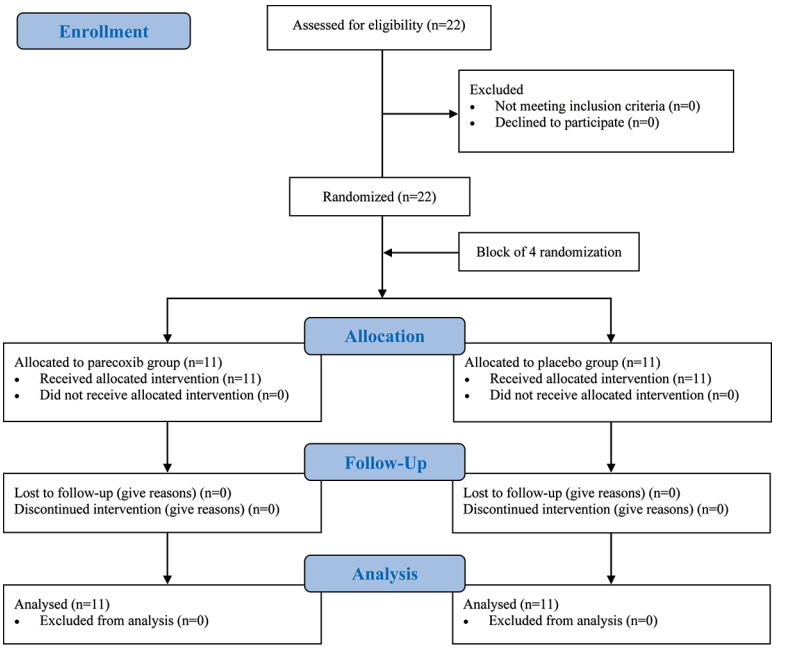


**Figure 1.** Flow diagram of the study.

the patients suffered chronic post-surgical pain[4-7]. Inadequate postoperative pain control relates to postoperative complications such respiratory complication, prolong hospital stay, and development of chronic post-surgical pain. Therefore, adequate treatment and postoperative pain control are essential in all patients undergoing VATS.

There are many techniques for postoperative pain control after VATS such as local anesthetic infiltration, peripheral nerve blockade, epidural or spinal opioids, intravenous opioids, and intravenous anti-inflammatory drugs (NSAIDs). All these techniques can be selectively used in combination as multimodal analgesia. Nowadays, intravenous opioids are common prescriptions and less invasive for administration for acute postoperative pain control in VATS. Moderate to severe degree of postoperative pain after VATS requires not only a large dose of morphine but has the inevitable side effects of opioids such as nausea, vomiting, pruritus, urinary retention, and respiratory depression[8]. Therefore, a combination of intravenous multimodal analgesia could decrease the required dose and reduce the side effect from large morphine consumption.

Reports suggested that parecoxib, a COX-2 selective inhibitor, was an effective treatment for acute postoperative pain with anti-inflammatory and analgesic effects[9-12]. Parecoxib has been shown to be effective for treatment of postoperative pain in many types of surgery[9-17], but there is no report of the effect of parecoxib in patients undergoing VATS. The authors intended to study the analgesic efficacy and side effects of intravenous parecoxib in combination with morphine for postoperative pain control in patient undergoing VATS.

## Materials and Methods

The authors conducted a double-blinded, randomized, placebo-controlled study, at the Srinagarind Hospital and the Queen Sirikit Heart Center of the Northeast, Khon Kaen University. The present study was approved by the Khon Kaen University Ethics Committee for Human Research, approval number: HE 601223, and was registered at the Thai Clinical Trials Registry (TCTR), TCTR20171213002. Data were collected between January 2017 and February 2018. All patients provided written informed consents before being enrolled into the present study. The authors followed the Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized, controlled clinical trials (Figure 1)[18].

Patients were eligible for participation if they were aged between 18 and 65 years, scheduled to undergo elective VATS, the American Society of Anesthesiologist physical status (ASA PS) I to III, and could operate a patient-controlled analgesic (PCA) device. Exclusion criteria included any known allergy

to sulfonamides or contraindication to parecoxib, preoperative opioids used, pregnancy or lactation, the New York Heart Association (NYHA) Functional Classification II to IV[19], and psychiatric patients. All patients were instructed how to operate PCA device and assess pain score by using a verbal numerical rating scale (NRS) pain score ranging from 0 (no pain) to 10 (worst pain possible).

All patients were randomly allocated into two groups to receive either parecoxib as P group or placebo as C group, by block of four randomization using a computer-generated random number (http://www.randomizer.org/). In a sealed opaque envelope, the sequential random number code was enclosed to ensure concealment of allocation. The nursing staff who were not involved in evaluating the patients, kept the randomization code. Both study solution, transparent and colorless, was prepared by another anesthesiologist. In the P group, 40 mg of parecoxib (Dynastat, Pfizer Inc, Kent, United Kingdom) was diluted into 2 mL. In the C group, 2 mL normal saline had the same appearance. For group allocation, all patients, health care providers participating in postoperative management, data collectors, and outcome adjudicators were blinded.

On the day of the surgery, standard anesthetic monitoring was done, and general anesthetic techniques was induced with fentanyl at 1 to 2 mcg/kg and propofol at 2 mg/kg. Endotracheal intubation was facilitated with cis-atracurium at 0.1 to 0.2 mg/kg, atracurium at 0.5 to 0.6 mg/kg, or rocuronium at 0.8 to 1.0 mg/kg. Anesthesia was maintained with sevoflurane in a mixture of 50% air and 50% oxygen, and total doses of 0.5 mcg/kg of fentanyl were added when necessary. Local anesthetics or any medications with a possible analgesic property were not administered during intraoperative period. Standard VATS technique was conducted by cardiovascular-thoracic surgeon at the Srinagarind Hospital and the Queen Sirikit Heart Center of the Northeast, standard intraoperative monitoring included electrocardiogram (EKG), non-invasive blood pressure (NIBP), oxygen saturation, invasive blood pressure (IBP), and arterial blood gas (ABG).

Both groups received parecoxib or normal saline as per protocol, the first dose was administered 30 minutes before skin incision and the second dose was administered 12 hours later. All patients received standard postanesthetic care unit (PACU) and postoperative pain management. They were connected to a PCA pump in PACU. The PCA solution contained morphine at 1 mg/mL. PCA mode with 1 mg per dose, a lockout interval of five minutes, and a 1-hour limit of 8 mg. Any patients with severe pain or NRS of 4 or greater, received morphine 3 mg intravenously until relieved as loading dose. No other analgesic supplements were given during the study perioded. The PCA pump was continued 24 hours postoperative and postoperative data records included cumulative morphine consumption at 24 hours, pain score at 2, 6, 12, and 24 hours, and postoperative adverse events, such as gastric discomfort, dizziness, headache, pruritus, nausea, and vomiting.

### Data collection and assessment

Baseline characteristics of the patients, including age, gender, weight, height, body mass index (BMI), ASA PS, diagnosis, type of operation, duration of operation, total intraoperative fentanyl, and postoperative blood loss were recorded. The primary outcome measure was the total cumulative morphine consumption from a PCA pump at 24 hours after surgery. The secondary outcome measures were NRS pain score at rest and on coughing at 2, 6, 12, and 24 hours after surgery, and postoperative adverse events including drowsiness, nausea, vomiting, hypotension, pruritus, gastric discomfort, headache, and respiratory depression.

### Sample size and statistical analysis

The sample size was calculated to enable detection of 20% difference of morphine consumption during 24 hours between the two groups[9]. The sample size of 11 per group was based on power 0.8 and $\alpha$=0.05. Continuous data would be presented as the mean and standard deviation (SD) or the median and interquartile range (IQR) as appropriate. Categorical data would be presented as number (%). A p-value below 0.05 was considered statistically significant. The total cumulative morphine consumption and pain intensity between groups at each time points were compared using Student t-test, Wilcoxon rank-sum test, Chi-square test or Fisher's exact test as appropriate. End point data were analyzed according to the intention-to-treat principle. Stata for Windows, version 10.0 (StataCorp LP, College Station, TX, USA) was used to analyze the data.

## Results

Twenty-two patients, divided into 11 patients in parecoxib (P group) and 11 patients in placebo (C group), were included in this study. No patient withdrew because of severe pain requiring additional analgesic beyond the PCA protocol. There was

**Table 1.** Demographic data in study population (n=22)

| Demographic data | P group (n=11); n (%) | C group (n=11); n (%) | p-value |
|---|---|---|---|
| Age (years); mean±SD | 51.6±21.9 | 41.7±15.5 | 0.234 |
| Sex: male | 7 (63.6) | 2 (18.2) | 0.080 |
| BMI (kg/m$^2$); mean±SD | 19.0±4.0 | 21.7±4.3 | 0.141 |
| ASA physical status | | | 0.149 |
| I | 1 (9.1) | 5 (45.5) | |
| II | 9 (81.8) | 6 (54.5) | |
| III | 1 (9.1) | 0 (0.0) | |
| Type of operation | | | 0.600 |
| Blebectomy | 4 (36.3) | 5 (45.4) | |
| Lung biopsy | 3 (27.3) | 1 (9.1) | |
| Wedge resection | 2 (18.2) | 4 (36.4) | |
| Lung lobectomy | 1 (9.1) | 0 (0.0) | |
| Thymectomy | 1 (9.1) | 0 (0.0) | |
| Pleurodesis | 0 (0.0) | 1 (9.1) | |
| Duration of operation (minute); mean±SD | 130.5±54.7 | 148.2±33.7 | 0.371 |
| Total intraoperative fentanyl used (mcg); mean±SD | 159.1±39.2 | 156.8±40.5 | 0.895 |
| Total blood loss (mL); median (IQR) | 50 (20 to 100) | 100 (50 to 150) | 0.367 |

BMI=body mass index; ASA=American Society of Anesthesiologist; SD=standard deviation; IQR=interquartile range

* Significant as p<0.05

**Table 2.** Postoperative cumulative morphine consumption and severity of pain (NRS 0 to 10) at rest and on coughing within 24 hours after VATS (n=22)

| | P group (n=11); mean±SD | C group (n=11); mean±SD | Mean difference | 95% CI | p-value |
|---|---|---|---|---|---|
| Total morphine consumption (mg) | 26.64±4.41 | 39.82±3.87 | –13.18 | –16.87 to –9.49 | <0.001* |

SD=standard deviation; CI=confidence interval

* Significant as p<0.05

no statistical significance of patient baseline characteristics between the groups (Table 1).

The amount of intraoperative fentanyl used was not statistically significant different in both groups at P group versus C group with 159.1±39.2 versus 156.8±40.5 mcg (p=0.895) (Table 1). Postoperative cumulative morphine consumption at 24 hours in P group was significantly lower than C group at P group versus C group for 26.64±4.41 versus 39.82±3.87 mg with a mean difference of –13.18 and a 95% CI of –16.87 to –9.49 (p<0.001) (Table 2).

Table 3 shows that the NRS pain score at rest and on coughing at 2, 6, 12, and 24 hours postoperative in P group was significantly lower than C group (p<0.01).

Nausea and vomiting were found to be the only postoperative adverse events at 2, 6, 12 hours postoperative with no statistically significant difference between the groups (p=0.125, 0.282, and 0.546, respectively) (Table 4).

## Discussion

The present study demonstrated that two dosages of perioperative parecoxib 40 mg intravenously every 12 hours could significantly reduce postoperative cumulative morphine consumption at 24 hours and postoperative pain score after VATS without serious adverse events.

It has been widely known that preemptive analgesia possibly reduces postoperative pain by reduction of nociceptive input from afferent stimuli to central nervous system. Selective COX-2 inhibitors that selectively inhibit COX-2 enzyme, are effective for the management of pain and inflammation, and reduce potential for serious gastrointestinal ulceration and bleeding compared with non-selective NSAIDs[15].

**Table 3.** Severity of pain (NRS 0 to 10) at rest and on coughing for specific time periods after VATS (n=22)

| Time | Level of activity | P group (n=11); mean±SD | C group (n=11); mean±SD | Mean difference (95% CI) | p-value |
|---|---|---|---|---|---|
| 2 hours | At rest | 3.00±1.27 | 5.64±1.03 | 2.64 (1.61 to 3.66) | 0.001* |
| | On coughing | 4.91±0.83 | 7.00±1.18 | 2.09 (1.81 to 3.00) | 0.001* |
| 6 hours | At rest | 2.55±1.21 | 5.18±0.87 | 2.63 (1.70 to 3.58) | 0.001* |
| | On coughing | 4.09±0.94 | 6.36±0.81 | 2.27 (1.49 to 3.05) | 0.001* |
| 12 hours | At rest | 2.18±0.87 | 4.82±0.60 | 2.64 (1.97 to 3.30) | 0.001* |
| | On coughing | 3.73±0.79 | 6.00±0.63 | 2.27 (1.64 to 2.90) | 0.001* |
| 24 hours | At rest | 1.09±1.04 | 4.45±0.69 | 3.36 (2.58 to 4.15) | 0.001* |
| | On coughing | 2.91±0.83 | 5.36±0.81 | 2.45 (1.73 to 3.18) | 0.001* |

SD=standard deviation; CI=confidence interval

* Significant as p<0.05

**Table 4.** Incidence of adverse events at 24 after VATS (n=22)

| Adverse effect | Time (hour) | P group (n=11); n (%) | C group (n=11); n (%) | Risk ratio (95% CI) | p-value |
|---|---|---|---|---|---|
| Nausea/vomiting | 2 | 4 (36.4) | 0 (0) | 9.00 (0.54 to 149.50) | 0.125 |
| | 6 | 2 (18.2) | 0 (0) | 5.00 (0.27 to 93.55) | 0.282 |
| | 12 | 2 (18.2) | 1 (9.1) | 2.00 (0.21 to 18.98) | 0.546 |
| | 24 | 0 (0) | 0 (0) | NA | NA |

CI=confidence interval; NA=not available

* Significant as p<0.05

Many studies reported that 40 mg intravenous parecoxib, a selective COX-2 inhibitor, every 12 hours until 24 hours is effective for postoperative pain control with less side effects[10,13-16]. Therefore, dosing of 40 mg parecoxib intravenously every 12-hour was used in the present study for postoperative pain control.

The present study showed that postoperative cumulative morphine consumption at 24 hours in P group was significantly lower than C group. Morphine consumption in P group was 26.64±4.41 mg, while C group was 39.82±3.87 mg, similar to the study of Tang et al showing postoperative morphine consumption in parecoxib group was lower than control group at 33±21 versus 54±27 mg[9]. However, his study was demonstrated in patients that underwent open lower abdominal surgery and required higher dose of morphine consumption when compared to the present study. A systematic review and meta-analysis showed that patients that received parecoxib tended to require fewer rescue analgesics after laparoscopic surgeries than placebo patients, which is the same result as in the present study[16]. A study of postoperative pain control after thoracotomy using combination of thoracic epidural analgesia and intravenous parecoxib showed no statistical significance of medications used as rescue analgesics. This might be because thoracic epidural analgesia could provide superior analgesia for postoperative pain control in thoracic surgery[20].

The present study found that NRS pain score at 2, 6, 12, and 24 hours postoperative at rest and on coughing in P group was significantly lower than C group. NRS pain score at 2, 6, 12, and 24 hours in P group were reported as a mild degree, while C group reported as a moderate to severe degree. Ling et al reported that patients that underwent thoracotomy with thoracic epidural analgesia had NRS pain score, especially on coughing, significantly lower in the parecoxib group than in the control group[20]. This suggested that parecoxib effectively controlled pain on movement.

Postoperative serious adverse events of parecoxib in 24 hours were not found in the present study similar to the study of Tang et al and Ng at et al[9,10]. The authors found only nausea and vomiting as the morphine minor adverse events of parecoxib with no statistical significance between both groups and without other adverse effects described in other report[12,16,20].

There are some limitations of the present study. Firstly, the small number of patients included in the study was underestimated from the sample size

calculation. Secondly, the present study included various types of VATS that might affect the intensity of pain score. Thirdly, there might be interobserver differences in postoperative pain assessment among attending nurses. However, the authors attempted to reduce variance by standardizing and training the nurses prior to performing the study.

## Conclusion

Perioperative administration of two dosages of parecoxib 40 mg intravenously every 12 hours could significantly reduce postoperative cumulative morphine consumption at 24 hours, and NRS pain score at rest and on coughing in 24 hours in patients undergone VATS.

## What is already known on this topic?

Previous studies have been reported that patients underwent VATS had a moderate to severe degree of acute postoperative pain and were reported with chronic post-surgical pain. Traditionally, intravenous opioids have been used for postoperative pain control with undesirable dose-related side effects. Nowadays, multimodal analgesia provides superior analgesic efficacy and reduces adverse effects over single technique for postoperative pain control. However, the benefit of intravenous parecoxib was unclear in patients undergoing VATS.

## What this study adds?

This study showed that two dosages of intravenous parecoxib in combination with morphine in patient that underwent VATS could reduce pain score and postoperative cumulative morphine consumption without serious adverse effects.


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## Conflicts of interest

The authors declare no conflict of interest.

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