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Comparing the Efficacy of Thoracic Paravertebral Block and Diclofenac to Reduce Postoperative Pain in Patients undergoing Unilateral Mastectomy: A Prospective Randomized Controlled Trial

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Background: Breast surgery is associated with postoperative pain, nausea, and chronic pain. Thoracic paravertebral block (TPVB) and diclofenac are analgesic adjuvant to manage postoperative pain.

Objectives: To compare the efficacy of TPVB and intravenous diclofenac to reduce postoperative morphine consumption after breast surgery.

Methods: Forty-four patients undergoing unilateral mastectomy under general anesthesia were randomly allocated into two groups: group PG (n=22) received TPVB using 0.25% levobupivacaine or group NG (n=22) received diclofenac 150 mg intravenously. The primary outcome was consumption of morphine during the first 24 h postoperatively. Secondary outcomes were consumption of morphine within 48 h postoperatively, numerical rating scale at 24 h and 48 h postoperatively at rest and movement, and complications during the first 24 h postoperatively

Results: Postoperative morphine consumption at 24 h was significantly lower in group NG than group PG (mean difference, MD: -3.30 mg; 95% CI: -6.56 to -0.04; *P*=0.047) and 48 h (MD: -4.10 mg; 95% CI: -7.64 to -0.56; *P*=0.024). The numeric rating scale (NRS) at rest was significantly lower in group NG than in group PG at 48 h postoperatively (MD: -0.30; 95% CI: -0.56 to -0.04; *P*=0.024). The NRS at movement was significantly lower in group NG than group PG at 24 h postoperatively (MD: -1.10 mg; 95% CI: -2.10 to -0.10; *P*=0.033). There was no complication during the first 24 h postoperatively.

Conclusion: Intraoperative intravenous diclofenac significantly decreased postoperative morphine consumption compared with thoracic paravertebral block in patients undergoing unilateral mastectomy under general anesthesia without postoperative complications.

Keywords: breast surgery, paravertebral block, postoperative pain, unilateral mastectomy

วิสัญญีสาร 2564; 47(3): 210-5. • Thai J Anesthesiol 2021; 47(3): 210-5.

Breast cancer is the most common cancer and has the highest incidence rates in women worldwide.[1] Primary breast surgery with axillary node staging or dissection is the most common surgical procedure for breast cancer.[2] Studies showed that breast surgery was associated with postoperative pain, nausea and vomiting, chronic pain, painful restricted movement, prolonged hospital stays, and additional hospital costs.[3,4]

There are many methods to reduce postoperative pain including, pharmacologic analgesics and invasive techniques, such as local anesthetics infiltration, intercostal block, thoracic epidural anesthesia, and thoracic paravertebral block (TPVB).[5,6]

TPVB is a common technique that is suitable for breast surgery. It inhibits surgical stress response, reduces the risk of recurrence or metastasis[7], postoperative nausea and vomiting (PONV),

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Received 11 Feb 2021, Revised 6 Mar 2021, Accepted 7 Mar 2021.

postoperative pain, and also prevents chronic pain.[4] Cheng et al found that TPVB decreased pain scores at rest as well as with movement up to 72 h after surgery.[5] This technique has high success rate with low serious complications.[1]

Diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), provided analgesia and, anti-inflammatory effect by inhibiting cyclooxygenase (COX) enzyme. It reduced opioid consumption and improved pain relief at rest.[8] Forget et al reported that intraoperative use of diclofenac decreased the risk of breast cancer relapse.[9] Sun et al found that perioperative intravenous (IV) flurbiprofen, a nonselective COX inhibitor, decreased the intensity and incidence of chronic pain for breast cancer.[10]

Based on the literature review, no study has compared TPVB with IV diclofenac to reduce postoperative pain for breast surgery. The aim of this study is to compare the efficacy of paravertebral block and intravenous diclofenac to reduce postoperative morphine consumption in patients undergoing unilateral mastectomy under general anesthesia.

Methods

This study was approved by the Ethics Committee in Human Research, Faculty of Medicine, Khon Kaen University (HE 591333). All patients gave written informed consent before being recruited into the study. This was a prospective, single center, randomized controlled trial conducted between May 2016 and June 2017 in patients undergoing unilateral mastectomy under general anesthesia. Inclusion criteria were patients with: (1) age 18-65 years old; (2) American Society of Anesthesiologist (ASA) classification I-III; (3) elective unilateral mastectomy; and (4) first time of mastectomy. On the other hand, patients who refused to participate; had contraindications of regional anesthesia; were allergic to local anesthetics, morphine or diclofenac; had history of chronic pain, chronic kidney disease or gastrointestinal bleeding; and retained endotracheal tube were excluded from the study. At the preoperative visit, all patients were explained by an anesthesiologist about the benefits and side effects of interventions used in this study. The patients were instructed in the use of 10-point numerical rating scale (NRS) (0 = no pain, 10 = the worst pain not imaginable) and the use of a patient controlled analgesia (PCA) device.

The sample size was calculated based on the study of Arunaku et al.[6] With type 1 error of 0.05, a power of 80%, we expected decrease at least 60% in morphine consumption, and a dropout rate of approximately 10%. Twenty-two patients were anticipated in each group with a total of 44 patients in this study.

All patients were randomly allocated into two groups by using computer generated randomization: group PG (TPVB) or group NG (diclofenac). Group PG received TPVB performed 30 minutes prior to surgery with standard monitoring (noninvasive arterial blood pressure, electrocardiography, and pulse oximetry) at the post anesthesia care unit (PACU). The patients were sedated with intravenous fentanyl 1 mcg/kg for TPVB. The TPVB technique was performed with the patient in the sitting position. The TPVB technique used was a unilateral two levels injection of 0.25% levobupivacaine with 1:200,000 epinephrine into the ipsilateral paravertebral space at T3 and T5. The spinous processes of the T3 and T5 were identified and marked. Under sterile technique, a 20-gauge Tuohy needle was inserted perpendicular to the skin 2.5 cm lateral to T3 and T5 spinous process until the tip of the needle touched the transverse process. The needle was redirected in the cephalad direction into the paravertebral space using loss of resistance technique. After negative aspiration, 5 mL of 0.25% levobupivacaine with 1:200,000 epinephrine was injected into the paravertebral space of the T3 and T5. TPVB was performed by three experienced anesthesiologists to reduce variation in the technique. Efficacy of TPVB was assessed at the dermatomes T2-T6 and tested by the pin-prick sensation at 5 min, 10 min, and 15 min after performing TPVB. Patients who failed TPVB were

excluded. All patients were monitored using noninvasive arterial blood pressure device, an electrocardiogram, and pulse oximetry at 5 min, 10 min, and 15 min after performing TPVB. Group NG received diclofenac 150 mg in normal saline 100 mL intravenously within 30 minutes after anesthetic induction.

All patients received general anesthesia with standard monitoring. The patient received IV fentanyl 1-2 mcg/kg for premedication, propofol 1.5-2 mg/kg for induction, and cisatracurium 0.2 mg/kg for intubation. Anesthesia was maintained with sevoflurane or desflurane in oxygen-air mixture adjusted to achieve 1 minimum alveolar concentration (MAC), IV fentanyl and cisatracurium. Dexamethasone 8 mg and ondansetron 8 mg were administered intravenously to prevent postoperative nausea and vomiting (PONV). Muscle relaxant was reversed with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg intravenously at the end of anesthesia. All patients were extubated after they met the fulfilled extubation criteria and transferred to the PACU. All patients were observed at the PACU for 1 hour. If the NRS was >3, intravenous morphine 3 mg was administered every 10 min until NRS was ≤3. Then the patients received IV PCA device started in the PACU. The opioid used was morphine 1 mg/mL with a 5 min dosing interval (morphine 8 mg per hour limitation). The NRS was recorded at 24 h, and 48 h postoperatively. Morphine consumption was recorded during 24 h and 48 h postoperatively. Postoperative complications due to TPVB and diclofenac including pneumothorax, accidental vascular puncture, nerve injury, high spinal block, total spinal block, Horner's syndrome and dyspepsia were recorded at 24 h postoperatively.

The surgeons, patients and anesthesiologists were not blinded to the intervention but the assessors who recorded the NRS were unaware of the patients' groups. The primary outcome was the total morphine consumption during the first 24 h postoperatively. Secondary outcomes were consumption of morphine within 48 h postoperatively, NRS at rest and movement at 24 h and 48 h postoperatively, and complications including pneumothorax, accidental vascular puncture, nerve injury, high spinal block, total spinal block, Horner's syndrome, and dyspepsia during the first 24 h postoperatively. Continuous data were presented as mean±SD and analyzed using Student's unpaired *t*-test. Categorical data were presented as number (%) and analyzed using *Chi*-square test. Value of $P<0.05$ was considered statistically significant and the data were analyzed by using the SPSS statistical software.

Results

Forty-four patients were included in this study with 22 patients in each group (Figure 1). The patients' demographics such as age, weight, height, body mass index, ASA classification, duration of surgery, and intraoperative fentanyl consumption were similar between both groups. (Table 1)

Postoperative morphine consumption was significantly lower in group NG than group PG at 24 h (mean difference, MD: -3.30 mg; 95% CI: -6.56 to -0.04; $P=0.047$), and 48 h (MD: -4.10 mg; 95% CI: -7.64 to -0.56; $P=0.024$) (Table 2). The NRS at rest was significantly lower in group NG than group PG at 48 h postoperatively (MD: -0.30; 95% CI: -0.56 to -0.04; $P=0.024$). The NRS at movement was significantly lower in group NG than group PG at 24 h postoperatively (MD: -1.10; 95% CI: -2.10 to -0.10; $P=0.033$). The mean arterial pressure and heart rate at 30 min, 60 min, 90 min, 120 min, 150 min and 180 min intraoperatively were not significantly different between both groups. No complications associated with the TPVB and diclofenac were identified during the first 24 h postoperatively.

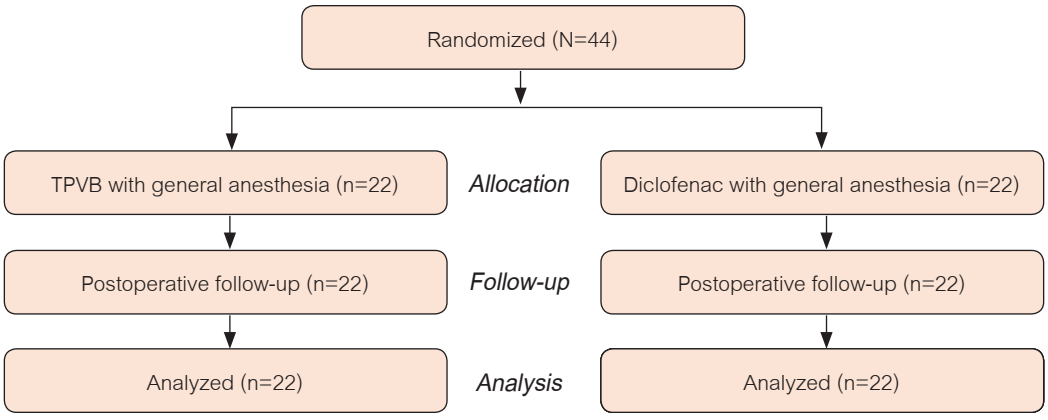

Figure 1 CONSORT diagram of the study

Table 1 Patients' demographics and clinical data

	Group PG (n=22)	Group NG (n=22)	*P*-value
Age (y)	50.4 ± 8.6	52.6 ± 8.7	0.388
Body weight (kg)	59.9 ± 8.4	56.1 ± 7.2	0.117
Height (cm)	156.6 ± 4.8	153.7 ± 5.7	0.073
Body mass index (kg/m^2)	24.4 ± 3.2	23.8 ± 3.0	0.499
ASA classification (I/II/III)	90/13/	140/8/	0.131
Duration of surgery (min)	154.1 ± 44.7	149.1 ± 62.6	0.762
Intraoperative fentanyl (mcg)	135.0 ± 32.9	125.0 ± 24.4	0.267

Data are presented as mean ± SD, number (%). *P*<0.05 is statistically significant.

ASA = American Society of Anesthesiologists.

Table 2 Postoperative morphine consumption (mg), pain score (NRS) at rest and at movement at 24 and 48 hours.

Variables	group PG (n=22)	group NG (n=22)	Mean difference, 95% CI	*P*-value
Morphine consumption				
at 24 h	9.6±5.6	6.3±5.1	-3.30 (-6.56, -0.04)	0.047
at 48 h	11.3±6.3	7.2±5.3	-4.10 (-7.64, -0.56)	0.024
Pain score at rest				
at 24 h	0.4±0.8	0.1±0.4	-0.30 (-0.69, -0.09)	0.123
at 48 h	0.3±0.6	0.001±0.0001	-0.30 (-0.56, -0.04)	0.024
Pain score at movement				
at 24 h	2.81.7±	1.71.6±	-1.10 (-2.10, -0.10)	0.033
at 48 h	2.31.4±	1.61.5±	-0.70 (-1.58, -0.18)	0.117

Data are presented as mean±SD, mean difference, and 95% CI.

P<0.05 is statistically significant.

Discussion

Our study showed that intraoperative intravenous diclofenac, compared with thoracic paravertebral block, reduced morphine consumption at the first 24 h as well as 48 h postoperatively in patients undergoing unilateral mastectomy under general anesthesia.

Previous study showed that breast surgery caused severe pain in the immediate postoperative.[11] Uncontrolled postoperative pain for breast surgery may lead to complications such as phantom breast pain, chronic pain, painful restricted movement, and prolonged hospital stay.[4,12] Das et al showed that 50%

of patients had chronic postoperative pain after breast surgery.[13] However, there are many techniques for reducing postoperative pain such as local anesthetics infiltration, intercostal block, thoracic epidural anesthesia, thoracic paravertebral block, opioids, and nonopioids including NSAIDs.[5]

TPVB is not only effective in inhibition of surgical stress response, but it also decreases analgesic consumption, prevents chronic pain, and shortens recovery time that affects ipsilateral somatic and sympathetic nerves.[13,14] Many studies showed the analgesic effect of TPVB. Schnabel et al showed a significant analgesic effect in the TPVB group at 2-24 h postoperatively.[1] Boughey et al showed that there was a significant decrease in postoperative pain up to 3 h with PVB.[2] Moller et al showed that VAS and fentanyl consumption at the PACU were significantly lower in the PVB.[15] In our study, the patients had mild pain at 24 h postoperatively (NRS 0.4±0.8 at rest, NRS 2.8±1.7 at movement). Morphine consumption at the first 24 h postoperatively was 9.6±5.6 mg, which was a small dose.

There are many approaches for TPVB such as single injection, multiple injection, and continuous TPVB catheter.[14] Pusch et al showed that a single injection was easier than multiple injections and took shorter duration to perform.[16] Das et al found that multiple paravertebral blocks increased the duration and efficacy of analgesia with higher complications.[13] Abdel-halim et al found that paravertebral catheter provided long lasting analgesia but complications with paravertebral catheter were intrapleural catheter placement and subarachnoid or epidural injection.[14] In our study, two injections of paravertebral blocks were performed, minimizing the possibility of an inadequate block.

Many local anesthetic agents have been used for regional anesthesia, such as bupivacaine, levobupivacaine, and ropivacaine with or without epinephrine.[2] In our study, we chose a total volume of 10 mL of 0.25% levobupivacaine with 1:200,000 epinephrine to increase the duration and decrease the systemic toxicity. Several methods have been described for TPVB such as loss of resistance by air or saline, nerve stimulator, and ultrasound guidance.[13]

TPVB may lead to adverse effects including inadvertent vascular puncture, hypotension, hematoma, signs of epidural or intrathecal spread, pleural puncture, and pneumothorax.[1,17] In our study, there is no incidence of complications during the first 24 h postoperatively.

Diclofenac is an NSAID. The mechanism of action involves an inhibition of the cyclooxygenase pathways and prostaglandin synthesis.[10] Many studies found the effect of NSAID to reduce opioid consumption and improve postoperative pain.Legeby et al found that the addition of diclofenac to paracetamol decreased opioid consumption during the first 6 h and improved pain relief at rest during the first 20 h postoperatively.[8] Sharma et al found that intravenous ketorolac reduced morphine consumption in patients undergoing transverse rectus abdominis myocutaneous (TRAM) flap for breast reconstruction.[18] Hynninen et al found that diclofenac reduced analgesic requirement postoperatively in cardiac surgery.[19] In our study, the patients had mild pain at 24 h postoperatively (NRS 0.1±0.4 at rest, NRS 1.7±1.6 at movement) and pain-free at rest at 48 h postoperatively. Morphine consumption at the first 24 h and 48 h postoperatively was 6.3±5.1 and 7.2±5.3 mg, respectively.

Diclofenac may lead to side effects such as an increased risk of hematoma, dyspepsia, and gastrointestinal bleeding. Legeby et al found that postoperative bleeding was higher with a diclofenac group.[8] Sharma et al found that intravenous ketorolac did not increase the risk of hematoma.[18] In our study, no patient was re-operated for hematoma or bleeding. It should be administered for a short period and not exceed 150 mg daily to reduce the risk of complications.

Our study, showed that morphine consumptions at the first 24 h and 48 h postoperatively were lower in group NG compared with group TPVB. This may be due to the analgesia of TPVB at dermatome T2-T6 did not cover the pain in extensive breast surgery such as axillary staging or dissection. Boughey JC et al showed that PVB was a significant decrease in pain score at 1 h and 3 h postoperatively in patients undergoing segmental mastectomy, but no significant difference for more extensive surgery.[2] The NRS at 24 h at movement

and 48 h at rest postoperatively were significantly lower in group NG than group TPVB. The intraoperative fentanyl consumption, mean arterial pressure (MAP) and heart rate were not significantly different between both groups.

There are many options for perioperative pain management in breast surgery. Opioids are commonly used for moderate to severe pain but can also cause side effects such as respiratory depression, nausea, and constipation. Multimodal analgesia is also required to manage postoperative pain. IV diclofenac may be an alternative to opioid for major unilateral breast surgery.

There are a few limitations in this study. TPVB in dermatome T2-T6 might be insufficient in patients undergoing extensive breast surgery such as axillary nodes dissection requires analgesia at dermatome T1-T6.

Conclusion

Intraoperative IV diclofenac significantly decreased postoperative morphine consumption compared with TPVB in patients undergoing unilateral mastectomy under general anesthesia without postoperative complications.

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