Two Doses of Oral Sustained-Release Tramadol Do Not Reduce Pain or Morphine Consumption After Modified Radical Mastectomy : A Randomized, Double Blind, Placebo-Controlled Trial

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Abstract

Background : Tramadol is a weak opioid agonist with antinociceptive effects through its action on the μ-receptor and by inhibiting the neuronal re-uptake of both noradrenaline and serotonin. Tramadol is commonly used for treatment of mild to moderate post-operative pain. An oral form of sustained-release tramadol (SR) was recently formulated for reducing the administration frequency from qid to bid.

Objective : To evaluate the analgesic efficacy and safety of two doses of oral tramadol SR for the treatment of pain after modified radical mastectomy.

Study design : Randomized, double blind, placebo-controlled trial.

Method : Fifty women were randomly allocated to receive either tramadol SR 100 mg (group T), or placebo tablet (group P) orally approximately 1 hour before surgery with a repeat dose administered 12 hours later by nurses not apprised of the patient groupings. All patients received the standard general anesthesia. Post-operatively, nurses in the research team assessed pain using a visual analog scale 0-100 mm at rest (rVAS) and during arm movements (mVAS) at admission to postanesthesia care unit (PACU) (T_0) and 2 (T_2), 6 (T_6), 12 (T_{12}) and 24 (T_{24}) hours after surgery. Rescue analgesia was provided for 24 hours *via* a morphine-loaded patient-controlled analgesia (PCA) device at 1 mg bolus with a 5-minute lockout interval. Cumulative morphine consumption and adverse events were recorded.

Results : Twenty-five patients with comparable baseline characteristics from each group were studied. The proportions of patients with VAS > 30 (both rVAS and mVAS) at each measurement period were not significantly different between the groups except for the mVAS at T_{24}, where the proportion in group T was higher than group P (48% *vs* 20%, 95% CI of difference: -53%, -3%, p = 0.04). The median morphine consumption in both groups at T_2, T_6, T_{12} and T_{24} were comparable. No serious adverse effects were observed; however, patients in group T reported nausea and vomiting more than group P (56% *vs* 24%, p = 0.02).

Conclusion : Two doses of oral tramadol SR 100 mg had no effect on post-operative pain scores and morphine consumption in patients who underwent modified radical mastectomy. In fact, more patients in the tramadol group reported nausea and vomiting than the placebo group.

Key word : Sustained-release tramadol, Mastectomy, Post-operative pain, Morphine

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Breast cancer accounts for about 8.3 per cent of all cancers in Northeast Thailand[1]. Patients undergoing total mastectomy with axial lymph node dissection have reported moderate pain in the postanesthesia care unit (PACU)[2,3] notwithstanding, they recover sufficiently from surgery to ambulate or return home the same day[4]. Ambulation required a continuous blood level of analgesia, which was accomplished by diverse routes, each having disadvantages-such as the high cost of using PCA or requiring frequent administration. Many patients, therefore, suffered during the interval between doses. Long-acting, low-dose, oral morphine (MST) has been used to bridge the gap with some success[5]. However, despite measures taken to ensure the safety of this preparation, manufacturers have not recommended it for perioperative use since 1984[6].

Tramadol is a weak opioid agonist with antinociceptive effects *via* its action on μ-receptors and by inhibiting neuronal re-uptake of both noradrenaline and serotonin[7,8]. Unlike conventional opioids, tramadol has not been associated with clinically significant respiratory depression even in children[9, 10], so has appeared as an analgesic for various mild to moderately painful conditions. A previous study found 37.4 per cent of patients in a university hospital received tramadol for post-operative pain control in the first 24 h[11]. Recently, an oral form of sustained-release tramadol (SR) was formulated for reducing frequency from qid, in the original preparations, to bid. Tramadol SR is slowly absorbed with a peak effect of 4.9 h and duration of 12 h[12].

Even though the preparation of tramadol SR is different from the original, most studies have focused on treatment of chronic pain despite the 3 per cent of recipients given it for post-operative pain[13]. Oral tramadol was reported as effective as intramuscular morphine for pain-relief after inguinal hernia surgery [14] and tramadol given before surgery reduced post-operative tramadol consumption[15]. The reported rate of adverse effects of tramadol SR was 6.5 per cent[13], less than the original preparation[16]. The current study evaluated the analgesic efficacy and safety of two doses of oral tramadol SR for treatment of pain after modified radical mastectomy. A fixed dose of 200 mg tramadol per day was chosen because most patients with moderate pain experienced sufficient relief at this dosage[12].

METHOD

Participants

The Ethics Committee of the Faculty of Medicine approved the study and informed consent was obtained from all participants. Women with ASA physical status I-II, who underwent modified radical mastectomy, were enrolled in the study. Age and weight ranged from 18 to 75 years and 40 and 75 kg, respectively. During a pre-operative interview, patients

were instructed on how to use both the PCA device and the 100-mm VAS scale (0 = No pain, 100 = Worst pain imaginable). Exclusion criteria included 1) inability to use the PCA device or the VAS instrument, 2) allergy to tramadol, or 3) substance abuse.

Interventions

By using simple randomization, patients were allocated to receive either oral tramadol SR (100 mg), or a placebo tablet approximately 1 h before surgery and again 12 h later. No additional oral preanesthetic medication was prescribed. In the operating room, anesthesia was induced with 3 to 5 mg/kg thiopentone, 1 to 2 μg/kg fentanyl, 0.1 to 0.15 diazepam mg/kg, and maintained with 70 per cent nitrous oxide in oxygen, up to 2 per cent sevoflurane, and supplemented with 0.5 to 1 μg/kg/dose fentanyl according to the judgment of the anesthetist. All patients were monitored in the PACU for 2 h. Analgesia, if inadequate, was provided by iv morphine using a PCA device (Baxter) set at 1 mg bolus with a 5-minute lockout-interval, without basal infusion. PCA was used continuously in the surgical ward for 24 h. After the PCA was discontinued, all patients received paracetamol tablets (1,000 mg) for analgesia as needed. For treatment of nausea and vomiting, 10 mg of metoclopramide was administered intravenously, on demand.

Outcomes and assessments

Nurses in the study team, not apprised of the patient groupings, carried out the assessment of pain both at rest (rVAS) and during arm movement (mVAS), at admission to the PACU (T_0) and at hour 2 (T_2), 6 (T_6), 12 (T_{12}) and 24 (T_{24}). Cumulative morphine consumption was recorded from the PCA pump at hour 2 (T_2), 6 (T_6), 12 (T_{12}) and 24 (T_{24}). Adverse events were recorded. Assessments were not performed between 22:00 and 06:00.

Statistical methods

The authors estimated the sample size required for testing the hypothesis that post-operative pain would be less in the tramadol than in the placebo group. A 50 per cent difference in the proportion of patients with the mVAS > 30 mm at T_6 was defined as clinically relevant and based on the pilot study that the proportion was 80 per cent. Therefore, a sample size of 23 patients per group was required to give 80 per cent power and a type I error of 0.05.

Descriptive statistics were used to describe demographics and clinical variables. The Z-test was used to compare the proportion of patients with VAS > 30 mm. Since the VAS score and morphine consumption did not follow a normal distribution, these parameters were analyzed by the Mann-Whitney *U* test and reported as the median with an interquatile range. The χ^2-test was used for the analysis of adverse events. A $p < 0.05$ was considered statistically significant.

RESULTS

From February 2001 to November 2002, 50 patients, with comparable baseline characteristics, fulfilling the inclusion criteria were enrolled in the study, 25 in each group (Table 1). No patients dropped out before the end of the study.

Two patients in group P and 3 in group T were not assessed for VAS at T_0 because of drowsiness. One patient in group P was not assessed at T_2 for the same reason. As per the protocol, two patients in group P and 4 in group T were not assessed at T_{12}.

The proportion of patients with VAS > 30 mm at each time of assessment was not different be-

Table 1. Patients demographic.

Baseline characteristics	Tramadol (T) (n = 25)	Placebo (P) (n = 25)
Age (yr)	44.8 ± 10.9	49.6 ± 9.4
Weight (kg)	56.9 ± 10.9	58.4 ± 9.3
Duration of surgery (min)	136.8 ± 41.3	142.2 ± 54.6
ASA Physical status I/ II	17/8	20/5
Total dose of Fentanyl during anesthesia (μg)	115.0 ± 33.7	116 ± 38.1

Data were presented as the mean ± SD and number for physical status.

tween the two groups (Fig. 1, 2), except for the mVAS at T_{24} when group T was greater than group P (48% *vs* 20%, p = 0.04). The proportion of patients with mVAS > 30 mm at T_6, the primary outcome, was not different (56% *vs* 60%, 95% CI of difference: -31%, 23%, p = 0.77).

The median rVAS of the two groups were similar (Fig. 3). The median rVAS decreased with time to below 30 mm after T_6. There was no correlation between the median rVAS at T_6 and age, body weight, intra-operative use of fentanyl and duration of anesthesia, respectively. The median mVAS of the two groups were similar (Fig. 4), except for the mVAS at T_{24} in group T, which was greater than group P (10 mm *vs* 25 mm, p = 0.04)

Cumulative morphine consumption was not different between the groups (Fig. 5). The incidence of nausea and vomiting was higher in group T than P (56% *vs* 24%, p = 0.02). Two patients from group T had headache and dizziness and one in group P had a minor skin rash.

DISCUSSION

In the present study, two doses of 100 mg oral tramadol SR failed to provide adequate analgesia after modified radical mastectomy. Several factors may explain the finding.

The median rVAS, pain intensity, upon admission to the PACU, in the placebo group was 53 mm. This was classified as moderate to severe pain,

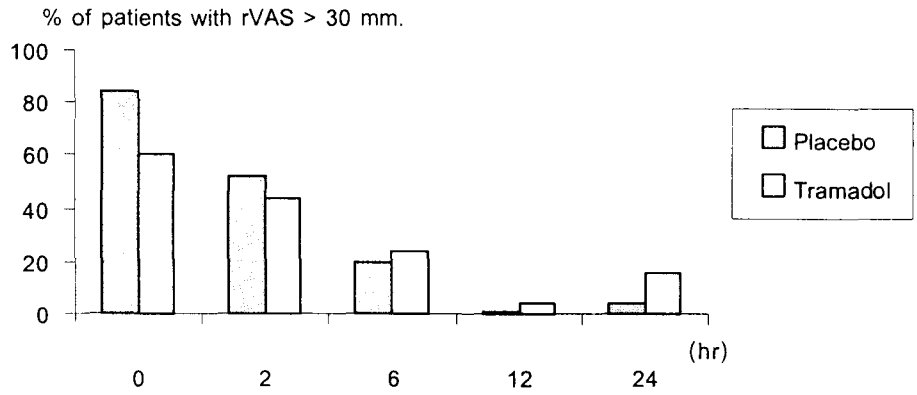

Fig. 1. The proportion of patients with rVAS > 30 mm.

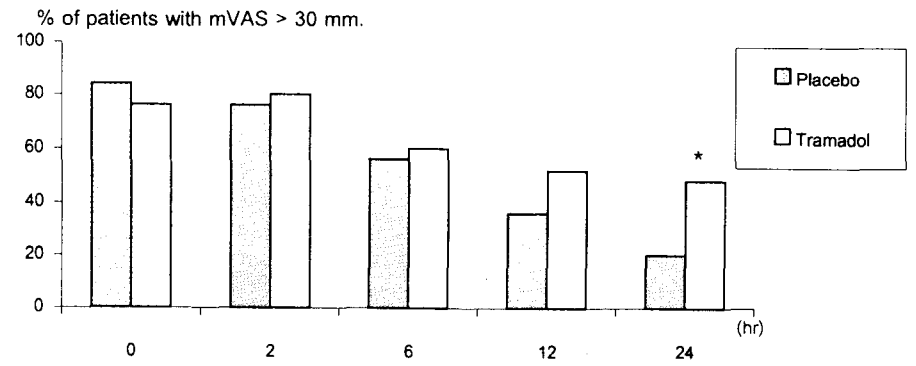

Fig. 2. The proportion of patients with mVAS > 30 mm.

*** p = 0.04 (Z test for proportion).**

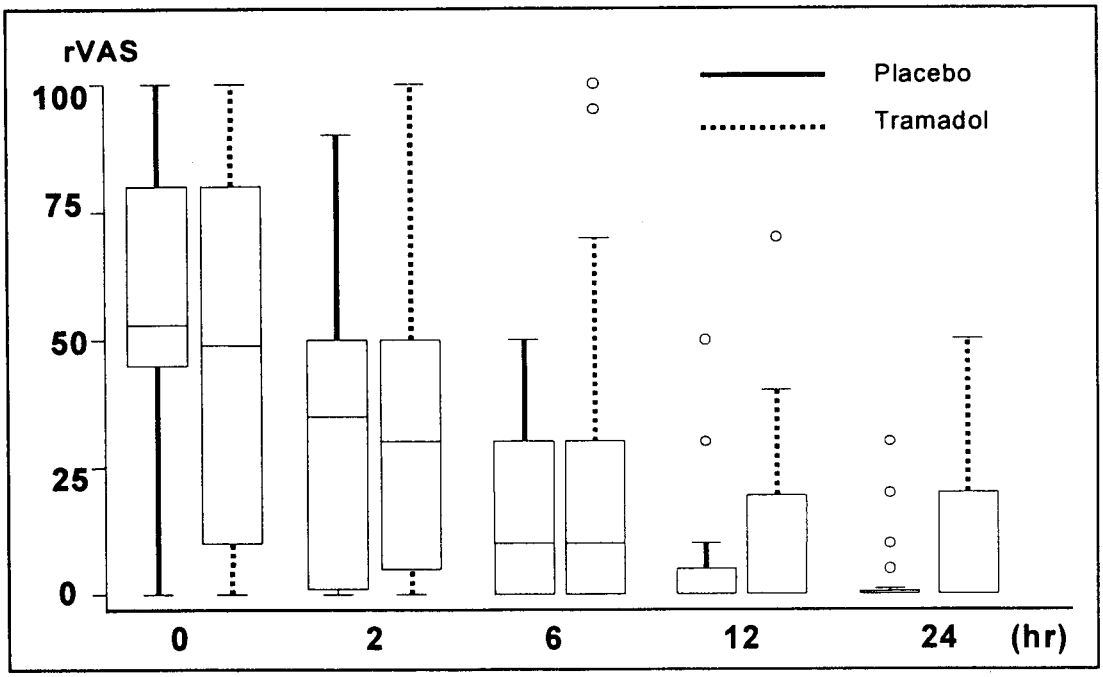

Fig. 3. The rVAS, median (interquatile range).

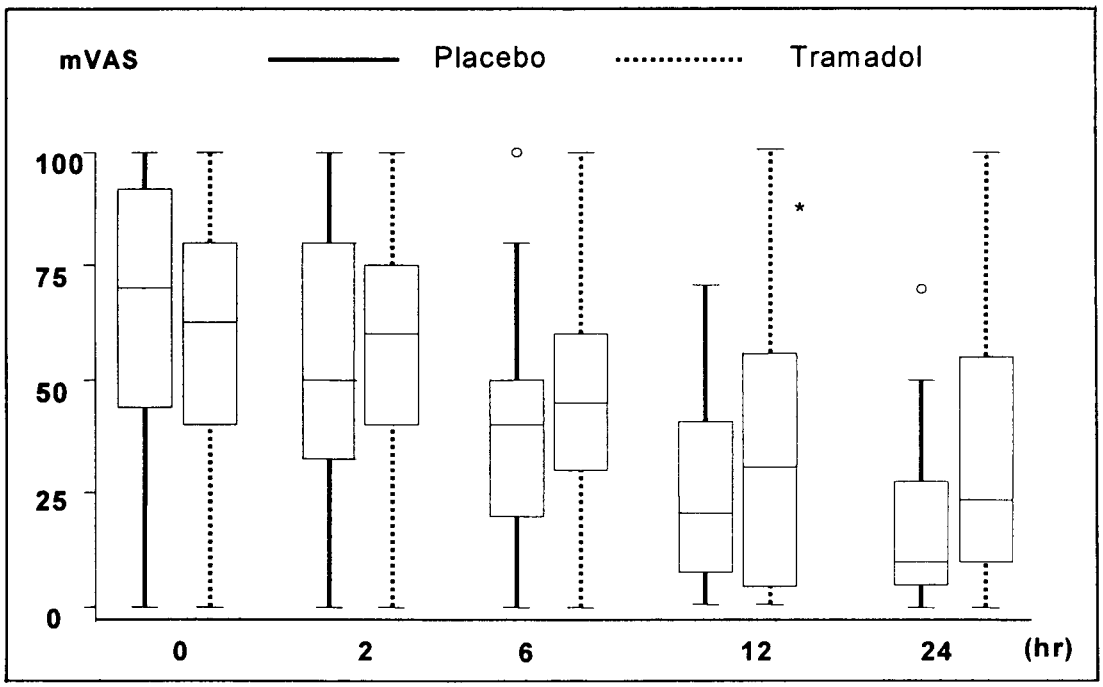

Fig. 4. The mVAS, median (interquatile range).

* Mann-Whitney *U* test.

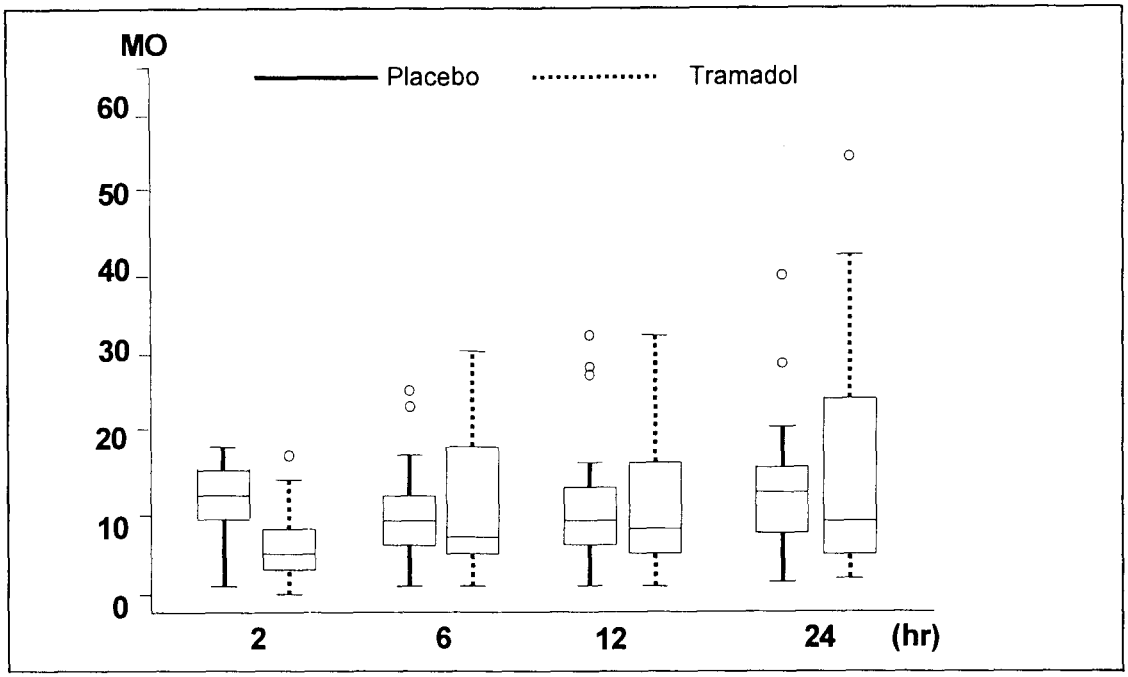

Fig. 5. The cumulative morphine consumption, median (interquatile range).

MO = morphine in mg

requiring a strong opioid, however, intensity at 2 h decreased to moderate (35 mm) as observed by Dirks J et al[3].

The median cumulative dose of morphine at 24 h, for rescue of pain in the present study, was 10 mg compared to the 29 mg at 4 h in the study by Dirks et al[3]. Evidently, the small dose of morphine resulted in high median mVAS and slowly decreased mVAS over time. The body weight (average two-fold greater) in the study by Dirks et al might explain the higher morphine consumption as might racial, cultural and educational differences. Adam et al[2] reported low cumulative dose morphine with similar pain scores as in the present study.

A dosage of 100 mg tramadol SR may be inadequate for the severe pain experienced after modified radical mastectomy. Stubhaug et al[17] reported 100 mg oral tramadol in patients with VAS ≥ 60 mm had an inferior analgesic effect to acetaminophen plus codeine. A meta-analysis by Moore et al[18] indicated oral tramadol had a dose response: at 150 mg, it had an NNT of 2.4 compared to 4.8 for 100 mg. The authors only used 100 mg/tablet of tramadol SR. Increasing the dose to 150 mg by dividing a 100 mg tablet in half would have disrupted the sustained-release property of undamaged tablets. The combination of tramadol with other analgesics such as acetaminophen may be useful for increasing overall analgesic efficacy[19]. The present results are in contrast to those of Shunshine et al[20] who reported 75 mg of oral tramadol had an analgesic effect superior to 650 mg of acetaminophen plus 100 mg of propoxyphene. It is debatable whether tramadol SR had an analgesic duration of 12 h considering the median mVAS at 24 h in the tramadol group was higher than the placebo group, while the median rVAS in both groups was comparable.

The authors found the incidence of nausea and vomiting (56%) to be as high as previous studies (range, 48 to 84%)[21-23]. Chan et al[23] found that middle-aged women and breast surgery were associated with a higher incidence of nausea and vomiting and that the peak incidence was between 2 and 6 h after surgery. Anesthesia administration techniques also affected the incidence of nausea and vomiting. The authors used a technique similar to that used by Chan et al except for sevoflurane instead of isoflurane. In contrast to the very low incidence of nausea and

vomiting after breast surgery (8.5%) reported by Dirks et al[3], perhaps the result of a different technique, except for the use of morphine for rescue analgesia after surgery, indicates the use of morphine by PCA pump had little effect on post-operative nausea and vomiting.

Tramadol was highly associated with nausea and vomiting. The authors considered this effect, however some have reported that tramadol SR has an incidence of nausea and vomiting between 3.4 and 16.6 and 1.1 and 9.8 per cent, respectively[12,13]. The incidence was low when compared to the 33 per cent for the original preparation[17], however, patients with chronic pain conditions in those studies would have less nausea and vomiting than the post-operative patients. A previous study also showed that oral administration of tramadol had a lower incidence of nausea and vomiting than intravenous administration [7] and tramadol had less effect on gastric emptying time when compared to morphine[24]. In the present study, patients with nausea and vomiting were treated with metoclopramide on request.

SUMMARY

Two doses of oral tramadol SR 100-mg compared to a placebo had no effect on post-operative pain scores and morphine consumption in patients undergoing modified radical mastectomy. Patients in the tramadol group actually reported more nausea and vomiting than the placebo group. To increase the efficacy of tramadol SR, the use of a higher dosage or combination with other analgesics should be considered.

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การให้ทรามาลรีทาร์ดรับประทาน 2 ครั้งไม่สามารถลดอาการปวดหลังผ่าตัดมะเร็งเต้านม: การศึกษาทางคลินิกชนิดสุ่มปกปิดสองฝ่ายและใช้ยาหลอก

สมบูรณ์ เทียนทอง, พบ, วิมลรัตน์ กฤษณะประกรกิจ, พบ*, วรนุช แต้ศิริ, วทบ*, นวลจันทร์ ธานินทร์สุรัตน์, วทบ**, ศิริพร อุดสาหพานิช, วทบ**, จงสุข ใกล้จันอัด, วทบ**

บทนำ : Tramadol เป็น opioid ออกฤทธิ์แบบ agonist ที่ μ–receptor และยังมีฤทธิ์ระงับปวด โดยการยับยั้งการ re–uptake ของ noradrenaline และ serotonin รวมทั้งกระตุ้นการหลั่งของ serotonin ได้ด้วย จึงมีการใช้ยา tramadol ในการระงับปวดอย่างแพร่หลาย ปัจจุบันมีการผลิตยา tramadol ชนิดรับประทานในรูป sustained–release (tramadol SR) ซึ่งออกฤทธิ์ได้นาน 12 ชั่วโมง เพื่อให้การระงับปวดอยู่ได้นานขึ้นกว่าแบบเดิมซึ่งออกฤทธิ์เพียง 4–6 ชั่วโมง แต่ยารูปแบบใหม่ยังมีการนำมาใช้ระงับปวดหลังผ่าตัดน้อย

วัตถุประสงค์ : เพื่อศึกษาผลของการให้ยา tramadol SR รับประทาน 2 ครั้ง เพื่อระงับปวดหลังผ่าตัดมะเร็งเต้านมวิธี modified radical mastectomy

รูปแบบการศึกษา : Randomized, double–blind, placebo–controlled trial

วิธีการศึกษา : ศึกษาในผู้หญิง 50 ราย โดยกลุ่มทดลอง (กลุ่ม T) ได้รับ tramadol SR (100 มก) ส่วนกลุ่มควบคุม (กลุ่ม P) ได้ placebo รับประทานประมาณ 1 ชั่วโมงก่อนการวางยาสลบและได้รับยาเดิมอีกครั้งหนึ่งหลังจากได้รับยาครั้งแรก 12 ชั่วโมง ในระหว่างการศึกษา ถ้าผู้ป่วยที่มีอาการปวดจะได้รับยาระงับปวด morphine เพิ่มทางอุปกรณ์ PCA โดยประเมินอาการปวดขณะผู้ป่วยนอนพัก (rVAS) และขณะขยับแขนข้างที่ผ่าตัดเต้านม (mVAS) ด้วย visual analog scale 0–100 mm ที่เวลาแรกรับในห้องพักฟื้น (T0) และที่ 2 (T_2), 6 (T_6), 12 (T_{12}) และ 24 (T_{24}) ชั่วโมงหลังผ่าตัดโดยพยาบาลในทีมงานวิจัย ซึ่งไม่ทราบว่าผู้ป่วยได้รับยาอะไร บันทึกปริมาณ morphine ที่ใช้ในแต่ละช่วงเวลา และอาการแทรกซ้อนที่พบ

ผลการศึกษา : ผู้ป่วยทั้งสองกลุ่มจำนวนกลุ่มละ 25 ราย มีความคล้ายคลึงกันในด้านของ อายุ น้ำหนักตัว ASA physical status, ระยะเวลาผ่าตัดและปริมาณยาระงับปวด fentanyl ที่ได้รับระหว่างผ่าตัด ผลการศึกษาพบว่าสัดส่วนของผู้ป่วยที่มีระดับความปวด VAS > 30 mm ทั้ง rVAS และ mVAS ตามเวลาที่กำหนดของทั้งสองกลุ่มไม่ต่างกัน ยกเว้นที่ T_{24} ซึ่งสัดส่วนผู้ป่วยในกลุ่ม T มี mVAS >30 สูงกว่ากลุ่ม P (48% vs 20%, 95% CI of difference: –53%, –3%, p = 0.04) ปริมาณ morphine ที่ใช้สะสมในแต่ละช่วงเวลาของทั้งสองกลุ่มไม่พบความแตกต่างเช่นเดียวกัน แต่พบอาการคลื่นไส้อาเจียนในผู้ป่วยกลุ่ม T มากกว่ากลุ่ม P (56% vs 24%, p = 0.02)

สรุป : การให้ยา tramadol SR 100 มก รับประทาน 2 ครั้ง ในผู้ป่วยผ่าตัด modified radical mastectomy ไม่สามารถลดอาการปวดหลังผ่าตัด และปริมาณการใช้ morphine ลงได้เมื่อเทียบกับยาหลอก อีกทั้งพบอาการคลื่นไส้อาเจียนร่วมด้วยในอัตราที่สูงกว่า

คำสำคัญ : ทรามาลรีทาร์ด, การผ่าตัดเต้านม, อาการปวดหลังผ่าตัด, มอร์ฟีน

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