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Short communication

Comparison of the analgesic efficacy of preemptive and preventive tramadol after lumpectomy

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Abstract:
The aim of this study was to investigate the analgesic efficacy of tramadol administrated preemptively or preventively in the earlier period of lumpectomy. Four hundred American Society of Anesthesiologists (ASA) physical status I–II patients, undergoing lumpectomy, were screened and 317 were randomly assigned into one of two groups. In the preemptive tramadol (n = 158) group, patients received an *iv* injection of tramadol 100 mg 15 min before operation. The preventive group (n = 159) received the same dose of tramadol 15 min before the end of the operation. Pain intensity at rest, overall satisfaction score, morphine consumption and side effects were recorded. A total of 299 patients completed the study. Preemptive and preventive subjects experienced similar analgesic effect and feeling of satisfaction at the first 24 h after surgeries. The similar amount of additional morphine was consumed [4.6 mg (95% CI 1.5–7.2) *vs.* 4.1 mg (95% CI 1.2–6.3), p = 0.811]. No intergroup difference was observed in the incidence of side effects. In conclusion, preemptive and preventive administration of tramadol expressed analgesia of similar efficacy up to 24 h after lumpectomy. The additional morphine requirement, the overall satisfaction and the frequency of side effects all did not display significant difference between the two groups. This implies that the administration of tramadol either before the start or before the end of the surgical procedures all can produce effective postoperative analgesia.

Key words:
postoperative pain, postoperative analgesia, opioids, tramadol, lumpectomy

Introduction

When the area of the lumpectomy "wakes up" after the anesthesia, it can recover some of its senses, which can cause mild discomfort in the breast, and the pain increases slowly and can linger for a long time [20]. Generally, benign breast masses were excised under local anesthesia in the day-surgical department with less treatment of the pain from breast incision. While several investigators were concerned with the postoperative pain management after breast surgeries, they merely focused on the nerve blocking methods [1, 5]. In contrast to this, little information is available about the bolus injection of analgesics intravenously (*iv*) referring to post-surgical analgesia in breast masses excision.

Preemptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries [11]. This can effectively prevent earlier onset of the pain than that of the preventive administration of the drugs after surgical procedures, but it was controversial whether preemptive or preventive analgesia should be used to describe the difference between the two analgesic techniques [6, 9, 16]. Nevertheless, we still adopted the concepts of preemptive analgesia delivering drugs before operation and preventive analgesia delivering drugs intraoperatively in the present study and compared the analgesic efficacy of tramadol administrated preemptively or preventively after benign breast masses excision.

Tramadol is a synthetic, centrally acting opioid analgesic with a potent opioid metabolite [19]. It produces less respiratory depression than other opioids and has no significant cardiac effects. Parenteral and oral tramadol has been proven effective and well tolerated in the management of moderate to severe acute postoperative pain in adults [18]. Preemptive administration of tramadol with a single dose in postoperative pain management was evaluated for efficacy in the earlier period after surgeries [13, 15]. In addition, intraoperative administration of tramadol (preventive) was assessed and no significant differences were found compared with the preemptive group regarding pain intensity and frequency of side effects [23].

Thus, we purpose that the preemptive and preventive bolus injection of tramadol both might produce effective analgesia after surgical procedures. The aim of this study was to objectively compare the analgesic efficacy of the two drug-delivering techniques with the 100-mm Chiroscience gauge of visual analog scale (VAS) after the clinicopathologic process of lumpectomy.

Materials and Methods

Participants and ethics

With the Hospital Ethics Examining Committee of Human Research approval 400 ASA physical status I–II patients who underwent elective lumpectomy were screened, and 317 of them were enrolled in this randomized, follow-up, double-blind and controlled study. All participants signed an informed consent and a full explanation was given about tramadol, the general anesthesia and the linear VAS of pain and satisfaction.

Exclusion criteria

Patients were excluded from the study if one or more of the following criteria were met: 1) Allergy to opioids, a history of the use of centrally-acting drugs of any sort, chronic pain and psychiatric disease records; 2) Participants younger than 18 years or older than 65 years or pregnancy; 3) Those who were not willing to or could not finish the whole study at any time; 4) The post-anesthetic care unit (PACU) assessing score was under 6 on a scale of 10 (measuring somnolence, respiration, movement, color, and blood pressure on 0–2 scales), and arterial oxygen saturation measured by pulse oximetry (SaO_2) was 92% or lower (supplemental oxygen was permitted); 5) Using or used in the past 14 days of the monoamine oxidase inhibitors; 6) Alcohol addictive or narcotinum dependent patients were excluded for their influence on the analgesic efficacy of the study substances.

Study design

All enrolled patients were randomly assigned into one of two groups according to SNOSE way [7] for bolus injection of the drug: preemptive tramadol group (tramadol hydrochloride 100 mg, T1) and preventive tramadol group (tramadol hydrochloride 100 mg, T2). Tramadol in the T1 group was injected in the volume

of 10 ml 15 min before the operation and the same volume of saline before the end of operation. In the T2 group, 10 ml of saline was injected 15 min before the operation and the same volume of tramadol 15 min before the end of the operation. The randomized envelopes were maintained in opaque until 15 min before the operation started. All research staff, data collection doctors and nurses, and drug delivery personnel were kept away from the contents of the syringe except for the drug numbers, No. 1 or No. 2 (differing in drug allocation each time), until the end of the whole study. The corresponding drug name and number were sealed in an envelope and kept in the Science & Education Department of our hospital (NMCHCH). Each syringe was filled with tramadol hydrochloride from similar ampoule with the same volume.

Baseline measurements of pain were recorded immediately prior to transfer to the surgical wards. The study drug was administered as a 10 ml bolus over 20–30 s, followed by a continuous follow-up up to 24 h. Additional drugs were not allowed except for morphine delivered *via* an intravenous patient-controlled analgesic (PCA) pump (with a bolus of morphine 0.04 mg/kg, a lockout interval of 30 min) as rescue drug for uncontrolled pain. Ondansetron 0.15 mg/kg was administrated prophylactically, but patients still could receive metoclopramide 10 mg *iv* every 6 h administered at the discretion of the nursing staff. Diphenhydramine 25 mg *iv* was delivered for treating pruritus. Patients received supplemental oxygen therapy *via* nasal tube (40% O_2 2–4 l/min) after their return to the surgical wards to remain the SaO_2 above 92%.

The parameters monitored during the whole study from before operation to the end of the study included the measurement of: heart rate by 3-lead electrocardiograph, respiratory rate, noninvasive systolic and diastolic blood pressure, mean arterial pressure and fingertip pulse oximetry (Nihon Kohden, TL-201T, Tokyo, Japan).

Anesthesia and perioperative management

Total intravenous anesthesia (TIVA) was performed in each patient. Sufentanil 0.20 μg/kg, midazolam 0.05 mg/kg and propofol 1.5–2.0 mg/kg were slowly injected *iv* for induction. The maintenance anesthetics were: propofol infused intraoperatively at a rate of 30–50 μg/kg/min, and remifentanil at a rate of 0.15 μg/kg/min. During the whole process of anesthesia, spontaneous respiration was maintained, and artificial support was given timely if only the respiratory rate was lower than 8 times per minute which was defined as the respiration depression. The pumping of propofol was stopped at about 10 min before the end of the operation, and remifentanil was stopped at approximately 5 min before the end of the surgery. No neuromuscular relaxants were used.

All the participants underwent a mono-lateral single incision for the breast masses excision.

A catheter was inserted in a right or left antecubital vein for fluid and drug administration. Intra- and post--operative fluid management included replacement of preexisting fluid deficits, normal losses (maintenance requirements), and surgical wound losses including blood loss, and the amount of urine collected *via* an indwelling urinary catheter, hemodynamic variables and hemoglobin concentration were measured. No additional drugs were administrated perioperatively except for the routine administration of atropine sulfate 8.0 μg/kg and phenobarbital sodium 1.5 mg /kg used intramuscularly 30 min prior to surgery.

Postoperative measures

During the whole process of study, the patient-derived VAS scores of pain at rest and satisfaction, and vital signs were recorded hourly from 1 h until 12 h after the surgical procedures and six-hourly up to the 24th h. Additional morphine consumption was calculated automatically by the PCA pump after pressing the delivery button each time, and the total morphine usage was recorded finally. An overall maximal pain intensity to each patient, namely the most severe affliction of pain the patient felt at the end of the 24-h study, was scored. Finally, the occurrence of the side effects throughout the study was recorded by the follow-up physicians.

Primary outcome

The VAS ratings of pain at rest were measured with the 100-mm chiroscience gauge as reported previously [22], as the primary outcome, i.e. subjective pain intensity score was established based on a 0–100 mm linear VAS (0 = no pain; 100 = worst pain imaginable). A VAS pain score of less than or equal to 30 was considered to represent effective analgesia. Patients were explained to understand that one end of the scale

represented no impact of pain at all and the other end was representative of extreme or severe impact of it.

Secondary outcomes

The following measures were selected as the secondary outcomes:

1. Overall subjective feeling of satisfaction, a 1–100 mm linear VAS used (1 = sad; 100 = happy);
2. Morphine consumption in two groups was calculated and expressed with median and corresponding 95% confidence interval (95% CI);
3. Incidence of side effects.

Statistical analysis

Analyses were performed using GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA, USA). Values are expressed as the mean, median, standard deviation (SD), 95% CI or numbers. The demographic data and background characteristics (age, weight, height), the ASA physical status and morphine consumption were compared with two-way analysis of variance (ANOVA). The effects of the study drugs on patient's self-rated VAS of pain and satisfaction were analyzed by two-way ANOVA with repeated measures. The ANOVA tests were always followed by the Bonferroni *post-hoc* tests. Finally, a Chi-square t-test was performed to compare side effects among groups. Statistical significance was accepted at the level of $p \leq 0.05$.

Results

Figure 1 shows the most common reasons for exclusion among the 400 patients who were screened but not enrolled, and the 317 patients who were randomly assigned to the two groups and followed up. Finally, 148 patients in preemptive tramadol group and 151 patients in preventive tramadol group completed the whole study.

The demographic, background, surgical, anesthesia and intraoperative management data, baseline vital signs (all were within the physiological ranges throughout the anesthesia and surgical process) were not significantly different between the two groups (Tab. 1).

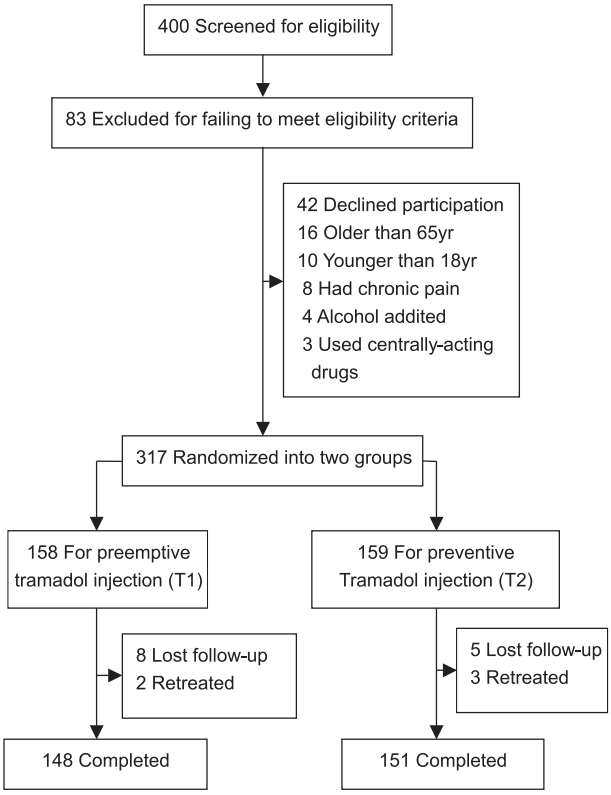

Fig. 1. Screening, enrollment and randomization. Patients might have had more than one reason for exclusion. All exclusion criteria are listed in Methods

Tab. 1. Baseline characteristics of the patients

	T1 (n = 158)	T2 (n = 159)
Age (yr)	32 ± 11	34 ± 13
Weight (kg)	58 ± 9	61 ± 13
Height (cm)	158 ± 8	157 ± 5
ASA physical status I/II (n)	154/4	157/2

Data are the mean ± SD or numbers. There were no significant differences between the two groups

Preemptive tramadol group expressed similar VAS scorings of pain at rest during the whole follow-up period compared with the preventive tramadol group (Fig. 2), the average scoring was 2.6 ± 0.7 in the T1 group *vs.* 2.4 ± 0.8 (× 10 mm) in the T2 group (Fig. 2). At the end of the study, the overall intensity of pain was evaluated. No significant difference was observed between the two groups (Fig. 3). In addition, the over-

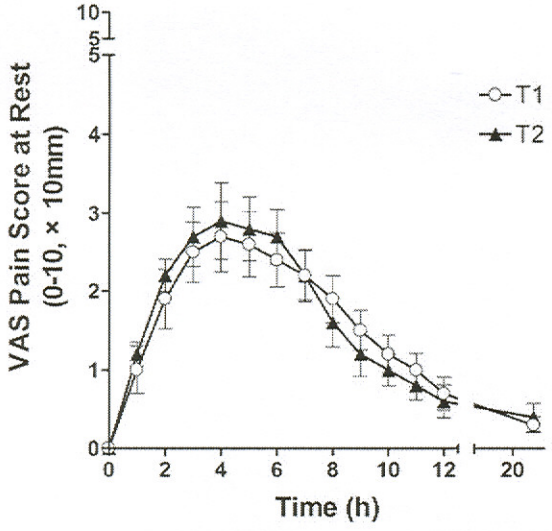

Fig. 2. Subjective VAS pain scorings at rest. Pain at rest in the two groups expressed no significant difference during the first 24 h after operation. Scores at 0 h represent the baseline ratings of pain. Data are presented as the mean ± SD of the pain score

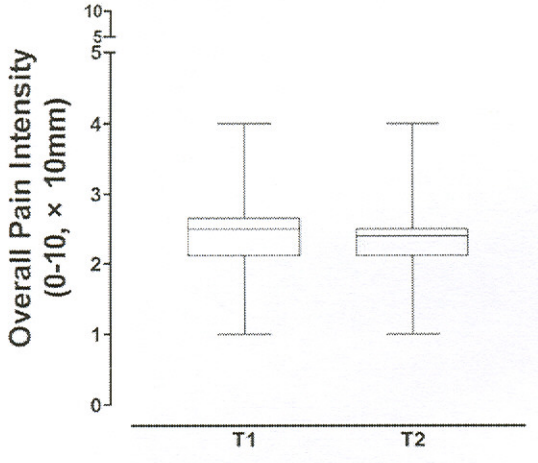

Fig. 3. Overall intensity of pain. The overall pain intensity was evaluated at the end of the study, and two groups expressed similar pain intensity, but they were still in the range of effective analgesia, i.e. the scorings were below 3 on the VAS

all intensity of pain was still in the range of effective analgesia 2.29 ± 0.09 *vs.* 2.37 ± 0.07 (× 10 mm) in preemptive and preventive groups, respectively, i.e. the scorings were below 30 on the linear VAS (p = 0.548, Fig. 3).

Additional morphine was delivered timely if the patients were under inefficient analgesia and the total morphine consumption was calculated. Preemptive

Tab. 2. Total morphine consumption and overall satisfaction

	T1 (n = 148)	T2 (n = 151)	p-value
Additional total morphine consumption (mg)*	4.6 (1.5–7.2)	4.1 (1.2–6.3)	0.811
Overall VAS satisfaction scorings (1–100 mm)**	54.6 ± 15	56.8 ± 12	0.852

* Denotes the median and 95% confidence interval (95% CI) of morphine consumption. ** Denotes data presented as the mean ± SD

Tab. 3. Incidence of side effects

Side effect	T1 (n = 148)	T2 (n = 151)	p-value
Nausea	32 (25%)	27 (18%)	0.490
Vomiting	9 (6%)	12 (8%)	0.357
Dry mouth	26 (18%)	31 (21%)	0.536
Dizziness	21 (14%)	17 (11%)	0.494
Drowsiness	30 (20%)	25 (17%)	0.533
Pruritus (Itching)	12 (8%)	18 (12%)	0.223
Sweating	6 (4%)	5 (3%)	0.573
Constipation	1 (7‰)	1 (7‰)	1.000
Urinary retention	0	2 (1%)	–
Respiratory depression	0	0	–
Miosis	0	0	–
Memory and cognitive impairment	0	0	–

Data are the number of patients and the rate of the % or ‰

patients required the same volume of morphine additionally as the preventive patients (p = 0.811, Tab. 2). Patients in the two groups experienced similar feeling of the overall satisfaction (p = 0.852, Tab. 2).

The incidence of different side effects was expressed in Table 3. The total incidence of side effects in the two groups was similar, and no statistically significant difference was observed (Tab. 3).

Discussion

The results of this study demonstrate that both preemptive and preventive bolus injection of tramadol expressed similar analgesic effect up to 24 h after

breast masses excision. In line with this, the overall pain intensity in the two study groups showed significant alleviation and both were within the range of effective analgesia. The effective pain relief was accompanied by the same morphine requirements, and the two groups of patients experienced similar feeling of overall satisfaction. In addition, no significant difference was observed in the incidence of side effects between them.

There are conflicting results concerning preemptive and preventive administration of different groups of analgesics. Preemptive low-dose ketamine is able to produce an adequate postoperative analgesia and increases the analgesic effect of tramadol in patients who underwent laparoscopic cholecystectomy [12]. Premedication of meloxicam provided a better postoperative analgesia than placebo after abdominal hysterectomy [2]. In addition, investigations of the effect of preemptive tramadol on postoperative pain were evaluated and showed interesting and meaningful results, no matter which delivery manner was used, either intramuscularly or intraarticularly or intravenously, the premedication of tramadol produced effective pain relief [4, 8, 17, 21].

Preventive analgesia was considered to be a suitable definition of both the preoperative and intraoperative administration of drugs for preventing the pain before its onset after surgical procedures [9, 16]. In the present study, we delivered tramadol 15 min before operation or 15 min before the end of the operation, namely preemptively and preventively, which produced nearly the same effect on relieving the pain from the incision of lumpectomy. Furthermore, the additional morphine requirement, overall satisfaction and side effects were similar in the two interventional groups. These data indicate that preemptive and preventive tramadol both were effective and equal in analgesia in such surgical context.

In general, it was considered that preemptive analgesia was more effective than the preventive one. The main reasons for such recognition were based on the theories that preoperative medication could block the nociceptive input, increase threshold for nociception, and decrease nociceptor receptor activation before the incisional injuries [10]. On the other hand, the intraoperative medication could merely produce limited analgesic effect because it could not totally interrupt the ongoing nociceptive input, and this sometimes was used just an adjunctive manner to the anesthesia, thus its analgesic role after operation was narrow [3]. Although such contrasting viewpoints appeared, our data strongly advised that preemptive and preventive administration of analgesics, at least of tramadol, were effective ways of treating pain from the breast masses excision.

Mc Quay reported that total consumption of analgesics was a better parameter than time to first analgesic request to demonstrate the preemptive effect [14]. In the present study, patients were allowed to be given additional morphine as the rescue drug for inefficient analgesia. No intergroup difference was observed in the total amount of morphine requirement in the 24 h study period in both groups.

While previous studies demonstrated effective analgesia with the premedication of tramadol and butorphanol, in general, such therapies were mainly based on the conditions that the preemptive delivery of the drugs was followed by continuous infusion plus PCA [23]. In our study, a single bolus injection of tramadol was used to elucidate whether a single injection of tramadol preemptively or preventively would produce effective analgesia and to compare the analgesic efficacy of the two drug-delivering manners. The present data are expectedly interesting because they show that both procedures are similar in producing pain relief effect.

The incidence of side effects did not significantly differ between the two groups. Although ondansetron was administrated prophylactically to prevent the nausea and vomiting, they were still recorded but this could not influence the whole study design for its equal delivery to the two groups.

In conclusion, preemptive and preventive delivery of tramadol expressed analgesia of similar efficacy up to 24 h after lumpectomy. The additional morphine requirement, the overall satisfaction and the incidence of side effects all did not display statistically significant difference between the two groups. This implies that the administration of tramadol either before the start or before the end of the surgical procedures both can produce effective postoperative analgesia in the context of lumpectomy.

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