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Preemptive Analgesic Efficacy of Tramadol, Butorphanol, and Flurbiprofen in Lumpectomy: A Randomized, Controlled and Double-blind Trial

The BSAE Study Group *,†,Δ,1

BACKGROUND Preemptive medication prior surgical procedures has been proposed of the promising manner in controlling pain effectively, whereas different drugs given in this way produced varying effects in different contexts. We herein hypothesized that preoperative bolus injection of analgesics functioning through various mechanisms produced contrasting analgesic efficiency in patients undergoing lumpectomy.

METHODS After approval by the Institutional Ethical Committee, a total of 1,500 patients undergoing lumpectomy were screened and 1,336 were randomized into one of the four groups: saline, tramadol 100 mg, butorphanol 2 mg, and flurbiprofen 100 mg. All drugs were administered 15 min prior operation in 10 ml. Visual analog scale of pain at rest and during movement were rated, and analgesic indexes were calculated as the primary outcomes. Secondary outcomes include complementary morphine consumption, side effects, and overall satisfaction.

RESULTS Patients in the group of flurbiprofen experienced less intensity of pain at rest than the other three groups ($P < 0.01$), and also displayed a higher stationary analgesic index ($P < 0.05$). Besides, the pain scorings in both groups of tramadol and butorphanol showed effective analgesia began from the sixth hour after the surgery compared to the saline-delivered patients ($P < 0.05$). Correspondingly, patients treated with flurbiprofen reported less side effects than both tramadol and butorphanol, in which a lower satisfactory ratings were presented than the flurbiprofen-treated ones.

CONCLUSION Flurbiprofen has superior analgesic effect over tramadol and butorphanol in lumpectomy suggesting that conquering peripheral inflammatory responses evoked by surgical lesion is much more effective in controlling the pain than those drugs functioning through the CNS-associated mechanisms.■

*: The members of the BSAE Study Group are disclosed at the end of the paper.

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WITH 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 improves slowly and can linger for a long time (1). In general, benign breast masses were excised under local anesthesia at the day-surgical department with less treatment of the pain from breast incision. While several reports concerned the postoperative pain management after breast surgeries, their major focuses were on the nerve blocking manners (2, 3). In contrast, little information is available regarding the preemptive injection of analgesics intravenously referring to post-surgical analgesia in breast masses excision. We herein purposed that a bolus injection of the analgesics, opioids or non-opioids, would produce effective analgesia after lumpectomy.

Tramadol is a synthetic, centrally acting opioid analgesic with a potent active opioid metabolite (4). 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 (5). Preemptive administration of tramadol with a single dose in postoperative pain management was evaluated that it was effective in the earlier period of time after surgeries (6, 7). Butorphanol, a totally synthetic morphinan, is considered to be a mixed agonist-antagonist opioid analgesic (8). WHO suggests that therapeutic categories for butorphanol in humans are as an anesthesia or preanesthesia adjunct, narcotic analgesic for postoperative pain (9). It has been shown to be several advantages of few side effects, including vomiting and respiratory depression, of minimal potential for abuse and low toxicity (10, 11). Flurbiprofen axetil is a member of the phenylalkanoic acid derivative family of nonsteroidal anti-inflammatory drugs (NSAIDs), and functions by suppressing the local production of prostaglandin (12). It produced superior analgesic effect when used preemptively than postoperative administration (13, 14). As thus, the preemptive bolus injection of tramadol, butorphanol and flurbiprofen may produce effective analgesia after surgical procedures. The aim of this study was to objectively compare the analgesic efficacy of these three drugs with the 100-mm chiroscience gauge of visual analog scale (VAS) in the context of lumpectomy.

MATERIALS AND METHODS

Participants and Ethics

With the approval of the Institutional Ethics Examining Committee of Human Research, a total of 1,500 American Society of Anesthesiologists physical status I-II patients who underwent elective lumpectomy were screened, and 1,336 of them were randomized, followed-up in this double-blind and controlled study. All participants signed an approved consent and a full explanation was given about tramadol, butorphanol, flurbiprofen axetil, general anesthesia and the linear VAS scoring of pain, sedation, and satisfaction.

Exclusion Criteria

Patients were excluded from the study if one or more following criteria were met: (i) Allergy to opioids, a history of the use of centrally-acting drugs of any sort, chronic pain and psychiatric diseases records. (ii) Participants younger than 18yr，older than 65yr or pregnancy. (iii) Those who were not willing to or could not finish the whole study at any time. (iv) 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). (v) Using or used in the past 14 days of the monoamine oxidase inhibitors (MAOIs). (vi) Alcohol addictive or narcotinum dependent patients were excluded for its influence on the analgesic efficacy of the study substances. (vii) Subjects with gastrointestinal ulcers and asthma, or receiving therapy with quinolone antibiotics.

Study Design

All enrolled patients were randomly divided into one of four groups according to SNOSE way (15) for preemptive injection of the drugs, one of control group (Saline), one of tramadol group (tramadol hydrochloride 100 mg), one of butorphanol group (butorphanol tartrate 2 mg) and one of flurbiprofen group (flurbiprofen axetil 100 mg). Each drug was injected in a volume of 10 ml 15 min prior to the operation. The randomized envelopes were maintained in opaque until 15 min before the operation started. All research staff, data collectors and nurses, and drug delivery populations were kept from the contents of the brown syringe except for the drug numbers, No. 1, No.2, No.3 or No.4 for each time (different in drug allocation each time), until the end of the study. The corresponding drug name and number were sealed in an envelope and administrated by the institutional ethical department. Each syringe received saline, tramadol, butorphanol or flurbiprofen contained into similar brown ampoule with same volume. We adopted brown syringe and ampoule for keeping the contents from being recognized by the research staff due to the white emulsion of flurbiprofen axetil.

Baseline measurements of pain were recorded immediately prior to return to surgical wards. The study drugs were administered as a 10ml

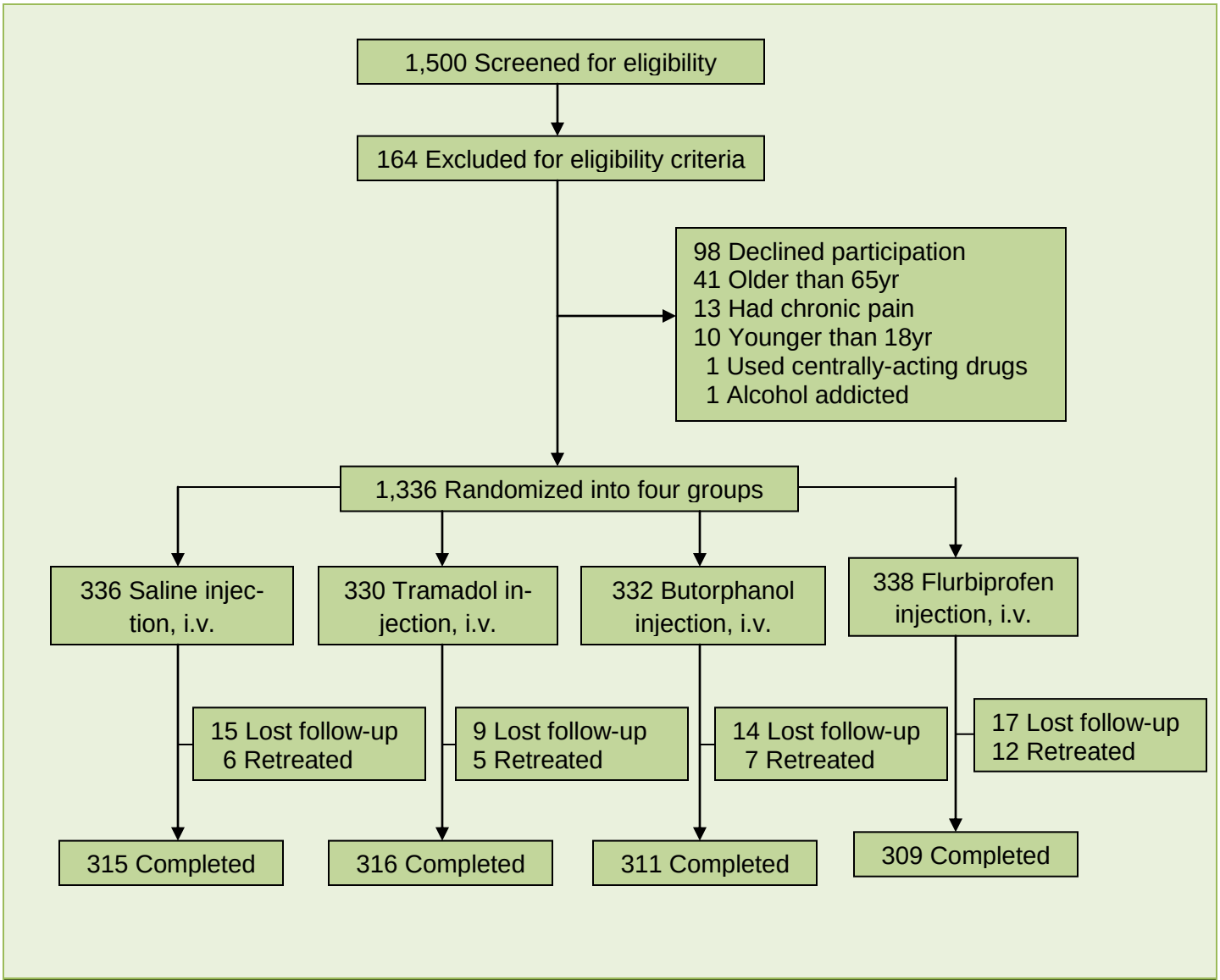

Figure 1. Flowchart for the postoperative analgesia after lumpectomy.

bolus over 20-30 sec, followed by a continuous follow-up up to 24 h. Additional drugs were not allowed except for 0.04 mg/kg morphine as rescue drug of uncontrolled pain. Ondansetron 0.15 mg/kg was administered prophylactically, but patients still could receive metoclopramide 10 mg i.v. every 6 h administered at the discretion of the nursing staff. Diphenhydramine 25 mg was delivered intravenously (i.v.) for conquering pruritus. Patients received supplemental oxygen therapy via nasal tube (40% O_2 2-4 l/min) after returning to the surgical wards to maintain SaO_2 above 92%.

The monitoring parameters during the whole 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 to each patient. Sufentanil 0.20 μg/kg, midazolam 0.05 mg/kg, and propofol 1.5-2.0 mg/kg slowly injected i.v. for induction. The maintenance of anesthetics was consisted of propofol was infused intraoperatively at a rate of 30-50 μg/kg/min, and remifentanil at a rate of 0.15 μg/kg/min. During the process of anesthesia, spontaneous respiration was maintained, and artificial support was given timely if only the respiratory rate was lower than 8 breaths per minute which was defined as the respiration depression. The pump of propofol was stopped at ~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 mono-lateral single incision. A catheter was inserted in a right or left antecubital vein for fluid and drug administration. Intra- and post-

Table 1. Base-line characteristics of the patients.

	Saline (n=336)	Tramadol (n=330)	Buborphanol (n=332)	Flurbiprofen (n=338)
Age – yr	32 ± 11	34 ± 13	32 ± 9	35 ± 15
Weight – kg	58 ± 9	61 ± 13	59 ± 9	60 ± 11
Height – cm	158 ± 8	157 ± 5	161 ± 9	158 ± 9
Education – yr	7 ± 5	7 ± 4	8 ± 5	6 ± 5
ASA physical status I/II	328/8	324/6	320/12	331/7
Intraoperative propofol – mg	155 ± 45	147 ± 58	152 ± 52	161 ± 63
Intraoperative sufentanil – μg	16 ± 5	16 ± 6	15 ± 4	16 ± 5
Intraoperative remifentanil – μg	46 ± 9	51 ± 11	48 ± 10	48 ± 9
Intraoperative midazolam – mg	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Intraoperative fluid therapy				
Crystalloids – ml	419 ± 114	421 ± 105	408 ± 121	417 ± 112
Colloids – ml	229 ± 101	211 ± 95	230 ± 114	222 ± 118
Surgical duration – min	58 ± 15	57 ± 21	61 ± 16	55 ± 18
Estimated blood loss – ml	62 ± 27	57 ± 15	66 ± 18	64 ± 21
Volumes of urine – ml	115 ± 39	127 ± 44	109 ± 48	118 ± 47
Preoperative blood pressure				
Systolic pressure – mmHg	125 ± 8	113 ± 9	118 ± 11	124 ± 13
Diastolic pressure – mmHg	73 ± 12	71 ± 14	69 ± 11	71 ± 10
Preoperative heart rate – bpm	75 ± 14	67 ± 9	78 ± 16	74 ± 11
Preoperative respiratory rate – bpm	19 ± 4	20 ± 3	18 ± 2	20 ± 4

Data are mean ± SD or numbers. No significant differences among the four groups.

operative fluid management included replacement of preexisting fluid deficits, of normal losses (maintenance requirements), and of surgical wound losses including blood loss and the amount of urine collected via an indwelling urinary catheter, of hemodynamic variables and hemoglobin concentration. 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 prior to surgery 30 min.

Postoperative Measurements

During the study, the patient-derived VAS scorings of pain at rest and during movement, and VAS ratings of 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 every 4 h after the operation, and the total morphine usage was recorded eventually. At the end of the study, an overall maximal pain intensity score and the occurrence of the side effects throughout the study were evaluated by the follow-up physicians.

Primary Outcome

The VAS of pain at rest and during movement with the 100-mm chiroscience gauge as reported previously (16) was measured as the primary outcome, i.e. subjective pain intensity ratings, based on a 0-100mm linear VAS (0 = no pain; 100 = worst pain imaginable). A VAS pain score of less than or equal to 3 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: (i) Overall subjective satisfaction, a 1-100mm linear VAS used (1 = sad; 100 = happy). (ii) Morphine consumption in four groups were calculated and expressed with median and corresponding 95% confidence interval (95% CI). (iii) 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 mean, median, standard deviation (SD), 95% CI or numbers. The demographic data and background characteristics (age, weight, baseline heart and respiratory rates, SpO_2, blood pressure and education status), the ASA physical status, the duration of surgery, the amounts of perioperative drugs administration and morphine consumption, fluids therapy and blood transfusion were compared with two-way analysis of variance (ANOVA). The effects of the study drugs on patient's self-rated VAS pain and satisfaction were analyzed using two-way

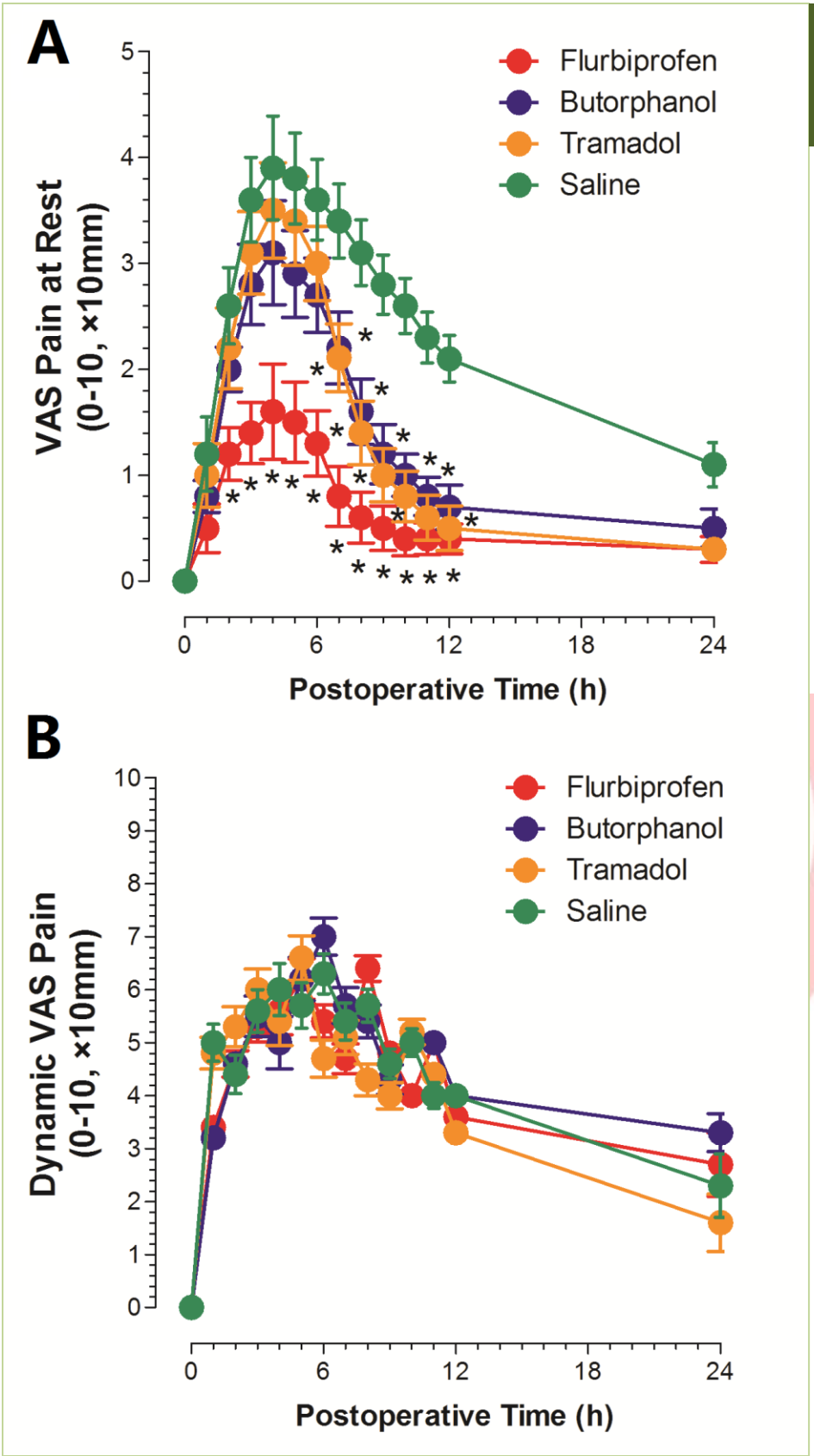

Figure 2. Analgesic scorings in patients at rest and during movement.

Preemptive administration of tramadol, butorphanol, and flurbiprofen in patients undergoing lumpectomy produced different effects on conquering postoperative pain. Flurbiprofen displayed significant lower VAS scorings of pain at rest than the other three groups (*P < 0.05 versus Saline; Panel A). Of interest, tramadol and butorphanol expressed significant analgesia since the 6th h after the surgical procedures, and during the first six hours, both of them had little effects on the pain relief after lumpectomy (*P < 0.05 versus Saline; Panel A). However, all three drug-treated groups displayed almost same pain scorings during movement (Panel B). Data were presented with mean ± SD.

ANOVA with repeated measures. Finally, a Chi-square t-test was performed to compare side effects among groups. Statistical significance was accepted at the level of $P < 0.05$.

RESULTS

Participants

The flowchart in Figure 1 shows the most common reasons for exclusion for the 1,500 patients who were screened but not randomized and the follow-up for the 1,336 patients who were randomly assigned to the four groups. Finally, 315 patients in saline, 316 patients in the group of tramadol, 311 subjects in the group of butorphanol, and 309 subjects in the group of flurbiprofen axetil completed the study.

Baseline Characteristics

The demographic, background, surgical, anesthesia and intraoperative management data, baseline vital signs all were within the physiological ranges throughout the anesthesia and surgical process and were no significant difference amongst the four groups (Table 1).

Flurbiprofen Axetil Expressed the Most Significant Analgesic Effect at Rest

Preemptive flurbiprofen axetil evidenced significant lower VAS scorings of pain at rest during the whole follow-up period than the other three groups ($P < 0.05$, Figure 2A). The average scoring was 1.1 ± 0.5 in the group of flurbiprofen versus 4.2 ± 1.3 in the Saline patients, and versus 2.3 ± 0.8 and 2.1 ± 0.9 in the groups of tramadol and butorphanol, respectively (Figure 2A). Of interest, tramadol and

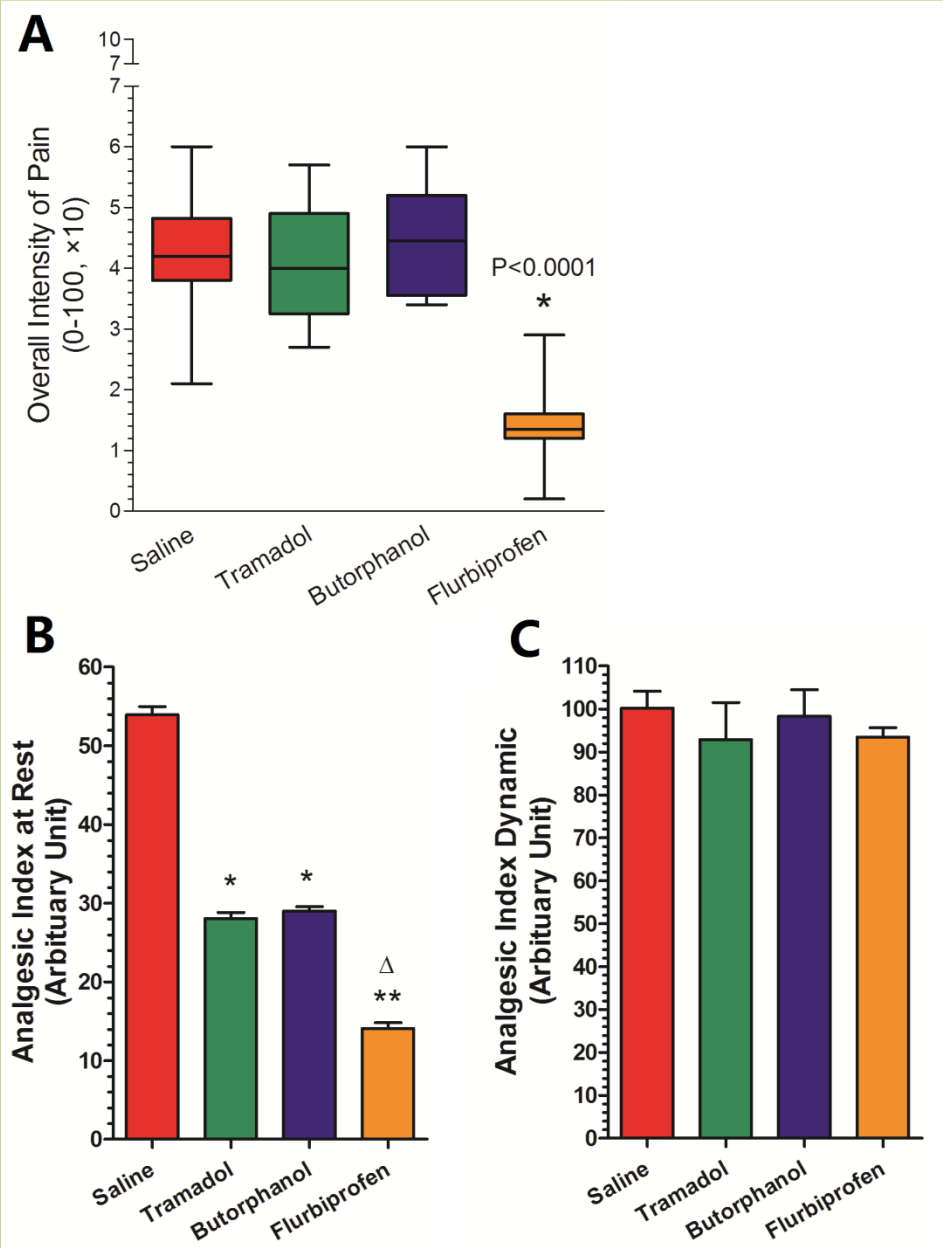

Figure 3. Overall analgesic ratings and analgesic indexes.

At the end of the study, the overall intensity of pain was evaluated, and flurbiprofen expressed the lowest scoring (*P < 0.0001), which was followed by the tramadol and butorphanol groups evidenced relative lower scorings compared with the saline group (Panel A). Although the three study drugs produced different analgesic effects after lumpectomy individually at different time points, the overall intensity of pain also showed big difference (Panel A). In addition, the area under the curve (AUC) of the analgesic scorings as the index of pain control was calculated, and the results showed that all three interventions had lower analgesic indexes at rest, and flurbiprofen showed the most significant analgesia (**P < 0.01 versus Saline, $^{\Delta}$P < 0.05 versus both Tramadol and Butorphanol, *P < 0.05 versus Saline; Panel B), but the dynamic analgesic indexes showed no significant difference among the four groups (Panel C). Data were presented with mean ± SD.

butorphanol expressed significant analgesia since the 6th h after the surgical procedures, and during the first six hours, both of them had little effects on the pain relief after lumpectomy (Figure 2A). However, all three drug-treated groups displayed almost same analgesic effects during movement (Figure 2B).

In addition, the overall intensity of pain was evaluated at the end of the study, and flurbiprofen axetil expressed the lowest scoring ($P < 0.0001$), which was followed by the tramadol and butorphanol groups evidenced relative lower scorings compared with the saline group ($P < 0.05$, Figure 3A). Although the three study drugs produced different analgesic effects after lumpectomy individually at different time points, the overall intensity of pain also showed big difference (Figure 3A). Besides, we calculated the area under the curve (AUC) of the analgesic scorings as the index of pain control, and the results showed that all three interventions had lower analgesic indexes at rest, and flurbiprofen showed the most significant analgesia depicted as the analgesic index ($P < 0.01$, Figure 3B), but the dynamic analgesic indexes showed no significant difference among the four groups (Figure 3C).

Additional Morphine Requirement and Overall Satisfaction

Additional morphine was delivered timely if the patients were under insufficient analgesia and the total morphine consumption was calculated. flurbiprofen axetil-treated subjects consumed the least morphine than saline ones ($P < 0.01$, Table 2), and the tramadol and butorphanol patients required relatively more morphine than flurbiprofen ones ($P < 0.05$, Table 2).

Patients' overall feeling of satisfaction was best in the group of flurbiprofen than the other three groups ($P < 0.01$, Table 2), and tramadol and butor-phanol groups showed relative higher scorings than the saline group ($P < 0.05$, Table 2).

Table 2. Total morphine consumption and overall satisfaction.

	Saline (n=315)	Tramadol (n=316)	Buborphanol (n=311)	Flurbiprofen (n=309)
Additional total morphine consumption – mg*	8.5 (4.2-12.4)	4.6 (1.5-7.2) †‡	4.1 (1.2-6.3) †‡	1.1 (0.7-2.5) †
Overall VAS satisfaction scorings (1-100mm)**	24.1 ± 9	54.6 ± 15 †‡	56.8 ± 12 †‡	70.7 ±11.5 †

* Denotes the median and 95% confidence interval (95% CI) of morphine consumption.
** Denotes data are mean ± SD.
† Denotes compared with the group of Saline (P<0.01).
‡ Denotes compared with the group of Flurbiprofen (P<0.01).

Table 3. Incidence of side effects.

Side effect	Saline (n=315)	Tramadol (n=316)	Bbutorphanol (n=311)	Flurbiprofen (n=309)
Nausea	36 (11)	32 (10)	27 (9)	11 (4)
Vomiting	11 (3)	9 (3)	12 (4)	4 (1)
Dry mouth	44 (14)	26 (8)	31 (10)	14 (5)
Dizziness	27 (9)	21 (7)	17 (5)	7 (2)
Drowsiness	24 (8)	30 (9)	25 (8)	6 (2)
Pruritus (Itching)	9 (3)	12 (4)	18 (6)	3 (1)
Sweating	8 (2)	6 (2)	14 (5)	2 (0.6)
Constipation	4 (1)	1 (0.3)	1 (0.3)	2 (0.6)
Urinary retention	1 (0.3)	1 (0.3)	2 (0.6)	0
Respiratory depression	1 (0.3)	1 (0.3)	0	0
Miosis	0	0	0	0
Memory and cognitive impairment	0	0	0	0

Data are number of patients and %.

Side Effects

The incidence of different side effects was expressed in table 3. The total incidence of side effects in the group of flurbiprofen was the lowest (P < 0.01, Table 3), and no significant difference was observed among the other three groups.

DISCUSSION

The results of this study demonstrate that tramadol and butorphanol expressed similar analgesic manner with bolus injection preemptively after breast masses excision, i.e. the effective analgesia started from the 6th h and almost no pain relief role in the early 6 hours after the surgical procedures. In contrast, flurbiprofen axetil produced more effective analgesia since from the end of the operation to up to 24 h post surgical procedures. Although so, the overall pain intensity in the three study drug groups evidenced significant alleviation. Consistent with the analgesic data, the additional morphine requirement was saline > tramadol > butorphanol > flurbiprofen, on the contrary, the overall scoring of satisfaction was flurbiprofen > butorphanol > tramadol > saline. Finally, the incidence of side effects in flurbiprofen was the lowest than the other three groups.

To our knowledge, this is the first time to find that the analgesic effect of tramadol and butorphanol expressed nearly parallel manner after surgeries, and even more interesting thing is the later-occurring analgesia at least 6 hours after operation. While previous studies displayed effective analgesia of the premedication of tramadol and butorphanol, in general, such therapies mainly based on the conditions as that the preemptive delivery of the drugs followed by continuous infusion or patient-controlled analgesia (PCA) (17). In our study, the single bolus injection prior operation demonstrated an easy-to-conduct analgesic regimen

with emphasis on the short-durational surgeries.

Our data depicted a functional situation in which flurbiprofen, a nonsteroidal anti-inflammatory drug (NSAID) taking function through inhibiting cyclooxygenase (COX), mainly plays the role peripherally especially at the injury-induced inflammatory sites as in this study context – lumpectomy. Contrarily, both centrally-functioning drugs, tramadol and butorphanol, did not show high analgesic indexes. All these tell us a fact that peripheral inflammatory responses resulted from regional lesion is superior to the central sensitization suggesting the local inflammatory "soup" at the peripheral injured sites was the major contributor to such kind of pain condition rather than the central involvement which generally is the key composition of the large surgical wound-associated pain.

In addition, centrally-functioning medications showed more incidences of central nervous system (CNS)-related side effects such as sedation and drowsing make these drugs unwanted by patients than the peripherally-functioning ones, of which showed much less undesirable side effects. In some patients, they even preferred to have pain than experience the sufferings of side effects.

In sum, flurbiprofen has superior analgesic effect over tramadol and butorphanol in locally-restricted injury like lumpectomy suggesting that conquering peripheral inflammatory responses evoked by surgical lesion is much more effective in controlling the pain than those drugs functioning through the CNS-associated mechanisms. Our findings and conclusions only derived from lumpectomy-related analgesic context. Whether such analgesic regimen also plays an effective role or not in other types of surgeries needs further investigation.■

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Conflict of Interests

None

APPENDIX 1

Members of the Breast Surgery Analgesia Evaluation (BSAE) group:

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