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Short communication

Preoperative tramadol combined with postoperative small-dose tramadol infusion after total abdominal hysterectomy: a double-blind, randomized, controlled trial

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Abstract:
This double blind, randomized, controlled trial investigated whether a single preoperative intravenous (*iv*) dose of tramadol (100 mg) given 30 min before abdominal hysterectomy resulted in improved analgesic efficacy, reduced postoperative morphine patient-controlled analgesia (PCA) use and reduced side effects when combined with a postoperative small-dose tramadol infusion. Two-hundred twenty-four patients undergoing elective abdominal hysterectomy were randomly allocated to one of two groups: the tramadol group (n = 113) received *iv* tramadol (100 mg) 30 min before surgery, and the control group (n = 111) received an equivalent volume of normal saline. Upon awakening from general anesthesia, all patients received a loading dose of 0.5 mg/kg of tramadol and a small-dose infusion of tramadol (0.1 mg/kg/h) for 48 h. In addition, all patients were connected to morphine PCA delivering a morphine bolus of 0.02 mg/kg with a 6-min lock-out. Data on pain intensity at rest and during movement, morphine consumption, side-effects and overall patient satisfaction were recorded. A total of 189 patients completed the study. Preemptive tramadol was associated with superior analgesia at rest and with movement in the first 24 h after surgery ($p < 0.01$), a longer interval to first morphine PCA request ($p = 0.019$), and reduced morphine PCA use ($p = 0.017$). The tramadol group had reduced nausea ($p = 0.015$), dizziness ($p = 0.001$) and drowsiness ($p = 0.0001$), while other side-effects were similar. In conclusion, a single dose of *iv* tramadol (100 mg) 30 min prior to abdominal hysterectomy improves analgesia, and reduces morphine PCA requirements, nausea, dizziness and drowsiness when combined with a postoperative small-dose tramadol infusion and morphine PCA when compared to the same analgesic regimen that omitted the preemptive tramadol.

Key words:
postoperative pain, patient-controlled analgesia, tramadol, hysterectomy

Introduction

In many institutions, intravenous (*iv*) morphine patient-controlled analgesia (PCA) is a standard in postoperative pain management after major surgery such as an abdominal hysterectomy. However, morphine-associated side-effects are considered major concerns in morphine PCA mono-therapy [9]. Combining different analgesic drugs with actions at different pharmacological sites is likely to produce more effective pain relief, reduced morphine consumption with fewer side-effects and a better feeling of satisfaction [10].

Although tramadol is considered a synthetic, centrally acting opioid analgesic with a potent opioid metabolite [21], its analgesic effects have also been shown to be associated with the serotonergic system *via* inhibition of serotonin (5-hydroxytryptamine, 5-HT)-type 2C receptor (5-HT2CR) function [8, 26]. Tramadol produces less respiratory depression than other opioids and has no significant cardiac effects. Parenteral and oral tramadol have been proven to be effective and well-tolerated in the management of moderate to severe acute postoperative pain in adults [19].

A previous study showed that premedication with a single dose of tramadol was no more effective than intraoperative delivery in early postoperative pain management after lumpectomy [20]. While a preemptive strategy did not show additional benefit after superficial surgical procedures, it may be hypothesized that premedication with tramadol may be effective in other surgical settings where postoperative pain is likely to be greater. Furthermore, small-dose infusions of tramadol combined with morphine PCA had superior analgesic effects when compared with morphine alone [13, 23]. We hypothesized that tramadol premedication combined with small-dose infusion and adjunctive *iv* morphine PCA would be more effective for postoperative pain therapy after total abdominal hysterectomy than the same postoperative regimen that omitted tramadol premedication.

Materials and Methods

After approval by the Hospital Ethics Examining Committee of Human Research, 224 American Society of Anesthesiologists (ASA) physical status I–II patients undergoing elective abdominal hysterectomy gave written consent to be randomized in this double-blind, placebo-controlled study. All surgery was done by the same group of surgeons. Explanation was provided about the general anesthesia technique, tramadol, morphine, the use of the *iv* PCA and the linear visual analogue scoring (VAS) of pain, sedation and satisfaction.

Exclusion criteria included allergy to opioids, prior use of centrally acting drugs of any sort (including sleeping tablets like benzodiazepine, antidepressants of any kind, etc., and monoamine oxidase inhibitors), chronic pain, psychiatric illness, past history of substance abuse, age < 18 or > 65 years, refusal of continuing the study, a Post-Anesthesia Care Unit (PACU) assessing score of under 6 on a scale of 10 (measuring somnolence, respiration, movement, color, and blood pressure on 0–2 scales), and arterial oxygen saturation (SaO_2) measured by pulse oximetry that was 92% or lower (supplemental oxygen was permitted).

Preoperative routine administration of drugs in our institution includes atropine sulfate (8.0 μg/kg) to reduce airway secretions and phenobarbital sodium (1.5 mg/kg) as a short-term sedative for all patients 30 min prior to surgery, given by the nurse in the surgical ward.

Patients were randomly assigned into one of two groups by means of a computer-generated, random-number list for postoperative pain management: the *control* group (normal saline premedication combined with postoperative tramadol infusion and morphine PCA) and the *tramadol* group (tramadol premedication combined with the same postoperative analgesia as the control group). Patients, all trial investigators and those involved with data collection were blinded from the group allocation by means of sealed opaque envelopes containing the allocation. Each syringe contained tramadol or saline with the same volume prepared by a physician who was not a member of the study.

Baseline measurement of pain was recorded immediately prior to the tramadol loading dose delivered before infusion began in the PACU. Premedication with tramadol (100 mg) in 10 ml or equal volume of saline was injected *iv* 30 min before the operation over 15 min. After surgical procedures and in the PACU, a loading dose of tramadol (0.5 mg/kg) was administered over 20–30 s, followed by a continuous *iv* infusion at a rate of 0.1 mg/kg/h for 48 h. Morphine PCA with a bolus of 0.02 mg/kg, a lockout interval of 6 min, and no background infusion was started during the 48 h period of study. All patients received metoclopramide (30 mg, *iv*) that was administrated prophylactically. Diphenhydramine (25 mg, *iv*) was delivered for treating pruritus. Patients received supplemental nasal oxygen therapy (O_2 2–4 l/min) after returning to the surgical ward to maintain the SaO_2 above 92%. Flurbiprofen Axetil (100 mg, *iv*) was permitted in treating inadequate pain relief at the patient's request.

The monitoring parameters during the whole study from before the operation to the end of the study included the measurement of heart rate by a 3-lead elec-

trocardiograph, respiratory rate, systolic and diastolic blood pressure, mean arterial pressure and fingertip pulse oximetry.

A standard general anesthetic technique was used, which included midazolam (0.05 mg/kg), fentanyl (1.5 μg/kg) and propofol (1.5–2.0 mg/kg) for induction. Suxamethonium chloride (1.0 mg/kg) was used to facilitate endotracheal intubation. Maintenance of anesthesia was performed with low flow oxygen (0.5–1.0 l/min) plus 0.7–1.5% isoflurane. Administration of fentanyl (50 μg) occurred at time intervals of 45 min or earlier if a raised intraoperative heart rate or blood pressure suggested light planes of anesthesia. Such administrations were recorded. Additionally, vecuronium was infused constantly at a rate of 3 μg/kg /min to facilitate artificial ventilation and abdominal muscle relaxation. Depth of anesthesia was monitored with the Bispectral Index (BIS) monitor (Aspect A-2000 Bispectral Index Monitor, Paterson, NJ, USA), with the BIS level maintained under 50. The infusion of vecuronium was stopped approximately 10 min before the end of the operation, and isoflurane was stopped approximately 5 min before the end of the surgery and replaced with 100% oxygen. Neuromuscular blockade was not reversed pharmaceutically and the patients were tracheally extubated according to the standard train-of-four and clinical criteria in PACU.

All of the participants underwent a low abdomen vertical incision for hysterectomy and unilateral salpingo-oophorectomy.

During the 48 h data collection period, vital signs and the VAS pain scores at rest and during movement were recorded hourly for 12 h, and then every four hours afterwards. Overall satisfaction with the analgesia and modified sedation rating were assessed, and total morphine usage was recorded at the end of the study. The VAS was measured using a linear 100-mm gauge (VAS, 0 = no pain; 100 = worst pain imaginable). Movement VAS was evaluated by patients performing an isometric muscle contraction or by moving the respective joints. A VAS pain score of less than or equal to 30 was considered to represent effective analgesia. VAS pain scores were the primary study outcome.

The following measures were selected as the secondary outcomes:

1) Morphine PCA consumption.

2) Overall subjective feeling of satisfaction with the analgesia; a 1–100 mm linear VAS was used (1 = sad; 100 = happy).

3) Sedation rating using a 1–10 cm linear scale (1 = fully awake; 10 = heavily sedated or asleep), as described elsewhere [24]. This was used due to its greater sensitivity than the Ramsay Sedation Scale (RSS) [16]. The overall sedation ratings were assessed by the study investigators at the end of the trial by evaluating the time point values obtained during the study period at intervals of 4 h.

4) Incidence of side effects as follows: nausea (investigated at four-hour intervals with the 0–10 cm VAS scale, as described elsewhere [3]), vomiting, dizziness and drowsiness (followed-up at a four-hour interval; dizziness was assessed according to means of the Audiology & Speech Associates [2], and drowsiness was evaluated according to the description of Hiromi using facial images [7]), dry mouth, sweating, urinary retention (incomplete emptying of the bladder or cessation of urination), pruritus (itching), myosis (the diameter of the pupil was equal or less than 2.5 mm or less than 21% of the iris diameter as measured with a pupillometer), constipation (having a bowel movement fewer than three times per week and with stools that were usually hard, dry, small in size, and difficult to eliminate), and respiratory depression and memory/cognitive impairment (assessed by recalling previous matters and answering questions raised by investigators). A ventilatory frequency of less than 8 tpm was defined as respiratory depression. This was recorded with a monitor, indicated with an alarm, and reversed with the opioid antagonist naloxone (0.5–1.0 mg *iv*) plus high-volume (8–10 l/min) oxygen.

5) Other, including urinary catheterization > 24 h, time to ambulation and total hospital stay.

Statistical analysis

Analyses were performed using GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA, USA). Values are expressed as the mean, standard deviation (SD), median, and interquartile range of numbers. A pre-study power table where δ (the mean difference in pain relief recorded in a pilot study, *i.e.,* a difference of 44 percent), two-sided $\alpha = 0.05$, one-sided $\beta = 0.10$, power of test = 0.90, and expected SD = 10 resulted in the need for a minimum of 108 subjects in each group to detect this difference. We increased the sample size to 150 to account for potential missing data and drop-outs during the study period.

All categorical data were analyzed with a Chi-square test or Fisher's exact test. The difference in the

demographic data, background characteristics, and the VAS ratings of satisfaction and sedation were compared with the Student's *t* test. Continuous variables like the global ratings of VAS pain, satisfaction and sedation, and the overall consumption of morphine and tramadol were summarized by calculating the median and interquartile interval, and compared using the Mann-Whitney test. The effect of the PCA on the patient's self-rated VAS of pain was analyzed with one-way analysis of variance (ANOVA). The ANOVA tests were always followed by the Bonferroni *post hoc* tests. All reported p values are two-sided, and a p value of equal to or less than 0.05 was considered to indicate statistical significance.

Tab. 1. Baseline characteristics of the patients

	S + T + M (n = 111)	T + T + M (n = 113)
Age – year	44 ± 9	43 ± 6
Weight – kg	59 ± 8	58 ± 7
Height – cm	157 ± 5	160 ± 6
ASA physical status I/II	81/14	86/8
Preoperative blood pressure		
Systolic pressure – mmHg	114 ± 8	118 ± 12
Diastolic pressure – mmHg	75 ± 10	80 ± 6
Preoperative heart rate – bpm	71 ± 6	76 ± 9
Preoperative respiratory rate – breaths/min	19 ± 4	18 ± 3

Data are the mean ± SD or numbers. Bpm: beats per minute. No significant difference between the two groups. Those excluded after randomization were still analyzed in the baseline characteristics

Results

Figure 1 shows the most common reasons for exclusion for the 300 patients who were screened but not enrolled, and the 224 patients who were randomly assigned to the two groups and followed-up on. The intent-to-treat number of patients was 112 to each group, and 224 eligible patients were randomized. Ninety-five patients in the control group and 94 patients in the intervention group completed the study. Eight patients were withdrawn from the trial because three suffered postoperative abdominal bleeding and underwent abdominal laparotomy, and five withdrew their consent for various reasons. Furthermore, the data of 17 patients was sufficiently incomplete that withdrawal was required, and in 9 cases, analgesic infusion devices were not continued in accordance with the study protocol.

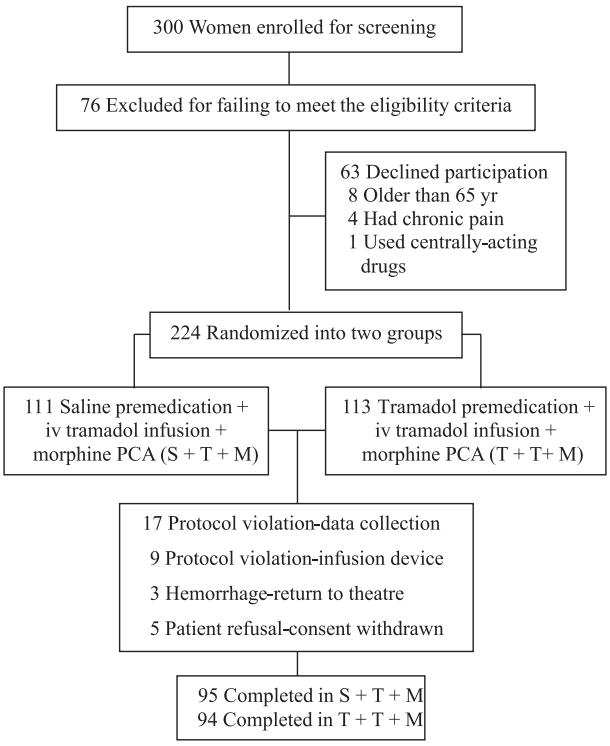

Fig. 1. Flowchart of screening, enrollment and randomization. Patients may have had more than one reason for exclusion. The full exclusion criteria are listed in the methods

The demographics and baseline vital signs of the study groups were not significantly different (Tab. 1).

VAS scorings of pain at rest and during movement were lower in the tramadol preemptive group than in the saline control group, particularly in the first 24 h after surgery ($p < 0.01$) (Figs. 2 and 3). Sedative ratings are presented in Figure 4 and show that tramadol premedication had a relatively higher score than the control group in the early 12 h after the follow-up begun, but no statistically significant difference was found between the two groups.

Table 2 summarizes the analgesic requirement and other parameters. In the saline group, the time interval of first morphine required was much shorter than in the tramadol group ($p = 0.019$), and the total morphine consumption was more than doubled in the control group ($p = 0.017$).

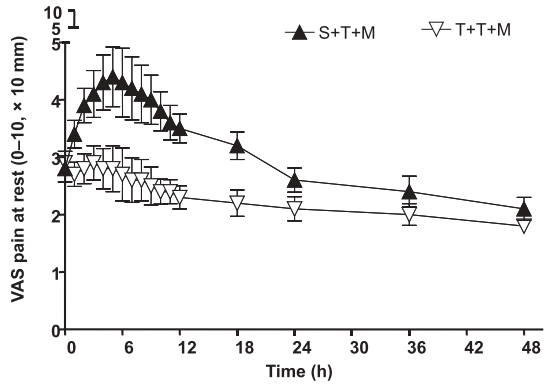

Fig. 2. Subjective scorings of VAS pain at rest. Pain at rest in both groups expressed significant differences during the earlier 24 h after operation ($p < 0.01$), and preemptive tramadol showed a more stable role in pain relief. Scores at 0 h represent the baseline ratings of pain. Data are presented as the mean ± SD of the pain

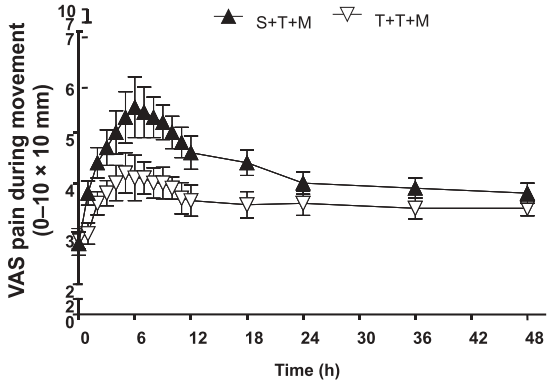

Fig. 3. Subjective ratings of VAS pain during movement. Pain during movement in the two groups expressed significant differences during the earlier 24 h after operation ($p < 0.01$), and the premedication of tramadol presented a more stable role in dynamic pain relief. Scores at 0 h represent the baseline ratings of pain. Data are presented as the mean ± SD of the pain

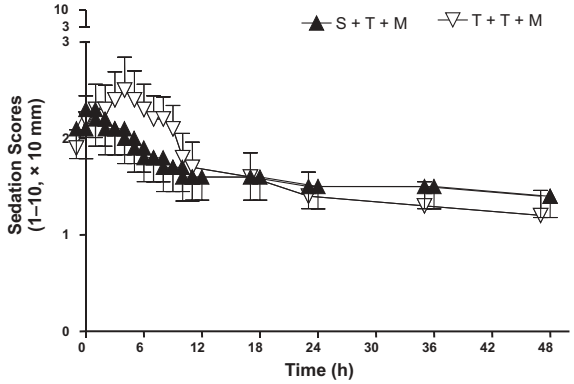

Fig. 4. Sedation scores. Tramadol premedication had a relatively higher score than the control group in the early 12 h after the follow-up began, but no statistically significant difference was observed. Scores at 0 h represent the baseline ratings of sedation. Data are presented as the mean ± SD of the sedation

Tab. 2. Total analgesic consumption and overall conditions for the patients

	S + T + M (n = 95)	T + T + M (n = 94)	p-value
Time interval of first morphine required – h*	5.3 (3.1–8.2)	8.1 (5.7–12.4)	0.019
Total morphine consumption – mg*	48.6 (32.2–63.9)	22.5 (14.3–35.3)	0.017
Total intraoperative fentanyl – mg*	150 (132–246)	145 (128–253)	0.87
Overall pain intensity (VAS, 1–100 mm)*	42 (35–54)	33 (22–41)	0.012
Overall sedation (VAS, 1–10 cm)*	2.3 (1.1–3.8)	2.6 (1.3–4.2)	0.68
Overall satisfaction with analgesia (VAS, 1–100 mm)*	63 (47–80)	75 (56–88)	0.015
Urinary indwelling catheter > 24 h	18 (19%)	16 (17%)	0.73
First time left from bed – day	2.5 ± 0.5	2.3 ± 0.7	0.21
Hospitalization time – day	6.5 ± 2	6.7 ± 2	0.91

Data are the mean ± SD or numbers (%). * Denotes the median and interquartile interval of first morphine requirement and morphine consumption, and were compared with the Mann-Whitney test

Tab. 3. Incidence of side effects

Side effect	S + T + M (n = 95)	T + T + M (n = 94)	p-value
Nausea	39 (41%)	23 (24%)	0.015
Vomiting	25 (26%)	18 (19%)	0.24
Dizziness	36 (38%)	16 (17%)	0.001
Drowsiness	47 (49%)	21 (22%)	0.0001
Dry mouth	11 (12%)	8 (8%)	0.48
Sweating	19 (20%)	11 (12%)	0.12
Pruritus	32 (34%)	21 (22%)	0.083
Myosis*	3 (3%)	2 (2%)	1.0
Constipation	19 (20%)	12 (13%)	0.18
Respiratory depression	2 (2%)	0	–
Urinary retention	0	0	–

Data are number of patients and rate of percent of each group. No urinary retention was observed because all the participants were treated with a urinary indwelling catheterization. * Denotes Fisher's exact *t* test

The incidence of different side effects is shown in Table 3, and the preemptive tramadol patients experienced relatively fewer side events than the control patients.

Discussion

The data of this study demonstrate that premedication with tramadol (100 mg) 30 min prior to surgery combined with its background infusion adjunct to morphine PCA after total abdominal hysterectomy produced superior analgesic effects when compared with the same analgesic regimen that omitted the preemptive tramadol.

Clinical trials regarding the benefits of preemptive analgesia have been contradictory. Positive results in animal models have not always been replicated in human trials [6]. Positive results in human trials regarding preemptive analgesia have been found with certain classes of analgesics. Preemptive low-dose ketamine is able to produce an adequate postoperative analgesia and increases the analgesic effect of tramadol in patients who have undergone laparoscopic cholecystectomy [14]. Regarding non-steroidal anti-inflammatory drugs, premedication with meloxicam provided a better postoperative analgesia than placebo after oral surgery [1]. Lornoxicam administered preemptively improves the quality of postoperative analgesia and leads to reduced consumption of tramadol postoperatively in patients undergoing major abdominal operations [11]. Regarding tramadol, Shen and colleagues did not find any improvement in pain relief between preoperative and intraoperative administration of tramadol in lumpectomy [20]. This is in contrast with this study, which did find that preemptive tramadol produced a significant and long-lasting benefit. In Shen's study, they investigated the preemptive effectiveness of tramadol compared with the intraoperative means without basal infusion, and this would result in a significant peak effect of drugs administered with a bolus injection. However, they merely observed the analgesic efficacy of tramadol in superficial surgeries such as lumpectomy, but in our trial, we selected patients that were to undergo hysterectomy as the study subjects, so the population difference is likely to be another reason for such different results.

Webb used an analgesic regime very similar to our trial, i.e., patients had major abdominal surgery and were given a larger tramadol loading dose (1 mg/kg) and postoperative tramadol infusion (0.2 mg/kg/h) plus morphine PCA [23]. These patients were compared with those getting morphine PCA by itself, and the study showed that the addition of tramadol infusion to morphine PCA was beneficial. However, it was not designed to show if the preemptive administration of tramadol was useful, as the loading dose was given during surgery and the control group received no tramadol at all. Therefore, we hypothesized that the preemptive plus continuous basal infusion of tramadol adjunct to morphine PCA would be effective in controlling postoperative pain. The results in our study proved this idea, and agreed with other previous reports regarding the effectiveness of preemptive tramadol on postoperative analgesia [25].

Previously, a basal infusion of tramadol at a rate of 0.2 mg/kg/h with a loading dose of 1–5 mg/kg was administrated after abdominal surgeries [5, 13, 17, 23], and Chiaretti found that tramadol efficacy seems to be better when it is administered *via* continuous infusion in children, and has fewer adverse effects [4]. Tramadol (1 mg/kg) administered after the induction of anesthesia offered equivalent postoperative pain relief and similar postoperative PCA morphine consumption compared with giving morphine (0.1 mg/kg) [22]. In the present trial, we used a relatively lower loading dose of tramadol (0.5 mg/kg) combined with the background infusion at a rate of 0.1 mg/kg/h to morphine PCA, but, interestingly, patients consumed less morphine with a relatively longer interval of the first request for morphine, experienced better analgesia and fewer side effects than the controlled subjects. These demonstrate that a dose-finding study is needed to clarify the optimal dose of tramadol in postoperative pain management in a continuous infusion manner.

The main reasons for considering whether the preemptive analgesia was effective were mainly based on the theories that preoperative medication could block the nociceptive input, increase the threshold for nociception, and decrease nociceptor receptor activation before the incisional injuries [12]. Our data showed that preemptive medication before nociceptive stimuli occur is a valid means in controlling pain in patients undergoing abdominal surgeries.

Treatment-associated side effects are an essential component in determining therapeutic success and patient satisfaction. Premedication of tramadol produced

fewer side effects, which is likely due to the lower consumption of morphine. Some previous studies have found that tramadol PCA increased the occurrence of side effects, especially in nausea and dizziness [15, 18]. These studies used tramadol with a bolus injection. In contrast, we administrated tramadol preemptively plus its basal infusion, and observed a lower incidence of side events, particularly nausea, dizziness and drowsiness. When concerned about the difference between sedation, dizziness and drowsiness, we measured these outcomes using different gauges to avoid overlaps among each other. In our trial, preemptive tramadol produced higher, but non-significant, sedative scores with less dizziness and drowsiness; this is perhaps because different scales of measurement were used in assessing these outcomes. The present management provided relatively continuous, stable and tolerable drug doses *via* a preemptive plus basal infusion manner during the entire study period. This may be the evidence that balanced and stable delivery of drugs during the whole therapeutic period is an effective and feasible means of pain management. The influence of tramadol on nausea, dizziness and drowsiness were significant compared with other side events, but the underlying mechanism is yet to be determined.

In conclusion, bolus premedication of tramadol (100 mg) combined with the postoperative continuous small-dose *iv* infusion of tramadol adjunct to standard morphine PCA after total abdominal hysterectomy highlighted a superior analgesic effect, fewer incidence of side effects, higher satisfaction ratings, and less morphine consumption than the same analgesic regimen that omitted the preemptive tramadol.

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