Journal of Clinical Anesthesia 36 (2017) 189–193

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

Original Contribution

The effect of tramadol plus paracetamol on consumption of morphine after coronary artery bypass grafting☆,☆☆,★

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A R T I C L E I N F O

Article history:
Received 22 March 2016
Received in revised form 18 July 2016
Accepted 27 October 2016

Keywords:
Cardiac surgery
Postoperative analgesia
Tramadol
Paracetamol
Morphine

A B S T R A C T

Study of objective: To compare the effects of oral tramadol + paracetamol combination on morphine consumption following coronary artery bypass grafting (CABG) in the patient-controlled analgesia (PCA) protocol.
Design: A prospective, double-blind, randomized, clinical study.
Setting: Single-institution, tertiary hospital.
Patients: Fifty cardiac surgical patients undergoing primary CABG surgery.
Interventions: After surgery, the patients were allocated to 1 of 2 groups. Both groups received morphine according to the PCA protocol after arrival to the coronary intensive care unit (bolus 1 mg, lockout time 15 minutes). In addition to morphine administration 2 hours before operation and postoperative 2nd, 6th, 12th, 18th, 24th, 30th, 36th, 42th, and 48th hours, group T received tramadol + paracetamol (Zaldiar; 325 mg paracetamol, 37.5 mg tramadol) and group P received placebo. Sedation levels were measured with the Ramsay Sedation Scale, whereas pain was assessed with the Pain Intensity Score during mechanical ventilation and with the Numeric Rating Scale after extubation. If the Numeric Rating Scale score was ≥3 and Pain Intensity Score was ≥3, 0.05 mg/kg morphine was administered additionally.
Measurements: Preoperative patient characteristics, risk assessment, and intraoperative data were similar between the groups.
Main results: Cumulative morphine consumption, number of PCA demand, and boluses were higher in group P ($P < .01$). The amount of total morphine (in mg) used as a rescue analgesia was also higher in group P (5.06 ± 1.0), compared with group T (2.37 ± 0.52; $P < .001$). The patients who received rescue doses of morphine were 8 (32%) in group T and 18 (72%) in group P ($P < .001$). Duration of mechanical ventilation in group P was longer than group T ($P < .01$).
Conclusion: Tramadol + paracetamol combination along with PCA morphine improves analgesia and reduces morphine requirement up to 50% after CABG, compared with morphine PCA alone.

1. Introduction

In coronary artery bypass grafting (CABG), sternotomy is performed [1]. The pain after surgery is usually severe and requires medical intervention. However, the use of the analgesics is limited by their adverse effects.

Intravenous (IV) opioids, such as morphine, are the analgesics commonly used to provide postoperative pain relief after CABG surgery [1]. However, adverse effects, such as drowsiness, respiratory depression, excessive sedation, biliary spasm, depression of gastrointestinal motility, nausea and vomiting, and, particularly in elderly, confusion caused by opioids may delay patient recovery and rehabilitation [1,2].

Because of several well-known adverse effects of opioids, efforts are being made to replace existing drugs with novel ones with less adverse effects and to develop innovative approaches to reduce postoperative pain [3]. Oral analgesics after the "fast-track" cardiac anesthesia may be a good choice. A potential alternative to IV morphine is oral tramadol + paracetamol combination, used alone or in combination with mild analgesics. To avoid such situations, a better integration of opioid and nonopioid analgesics may decrease opioid-related adverse effects and result in better patient satisfaction. Both tramadol and paracetamol are considered to be lacking in such adverse effects [4].

☆ Disclosures: The study was conducted in the Department of Anesthesiology, Baskent University Istanbul Training and Medical Research Center, Istanbul, Turkey, and was supported by Başkent University Research Fund, Ankara, Turkey.
☆☆ None of the authors declare conflict of interest, as this study is not industry sponsored and none of the authors received financial support for research and analysis.
★ Presented in part at 20th Cardio-Vascular-Thoracic Anaesthesia and Intensive Care Society Congress, 17-20th April 2014, Marmaris, Turkey.
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http://dx.doi.org/10.1016/j.jclinane.2016.10.030
0952-8180/

As a result, there is an unmet need for drugs or combinations therapies without these drawbacks. Paracetamol (acetaminophen) is not an nonsteroidal anti-inflammatory drug (NSAID) and interferes neither with platelet nor with kidney functions, nor does it present common undesired adverse effects of NSAIDs [5]. In addition, tramadol is a centrally acting analgesic, which, unlike traditional opioids, does not depress respiration or provoke sedation [5-9].

In this study, we aimed to investigate the effectiveness of oral tramadol + paracetamol combination to the IV morphine consumption in an overall analgesia protocol and to determine the satisfaction levels of the patients. The second objective was to compare the results of this study including (duration of mechanical ventilation and length of cardiovascular intensive care unit [ICU] stay) with those of a standard treatment in which morphine was administered as IV patient-controlled analgesia (PCA).

2. Materials and methods

2.1. Patients

The study protocol was approved by the institutional Ethics Committee (KA13/87) and a written informed consent was obtained from each patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

This prospective, double-blind, randomized clinical study included a total of 50 adult patients scheduled to undergo elective primary CABG surgery who had an American Society of Anesthesiologists grades II to III between May 2013 and January 2014. The patients were randomized into 1 of 2 treatment groups of tramadol + paracetamol group and placebo group. Randomization was performed with closed-envelope technique. Placebo drugs prepared by hospital pharmacist who was also blind to study protocol. All patients in both groups have taken morphine with IV-PCA. All patients were blinded to their treatment group. The patients, providers, and assessors are blinded to the groups to which the patients are assigned. The hospital pharmacist and the operating room anesthetic team were only blind to the study group to which a patient is assigned. They were not blind to the study protocol.

In the preoperative visit, all patients were fully examined. Furthermore, all participants were informed about the visual analog scale (VAS) and PCA (Abbott Pain Management Provider, Class II, Type CF; Abbott Laboratories, North Chicago, IL) a day before surgery. They were also instructed about how to use PCA, when they experienced pain. The night before surgery, all patients were familiarized with the Numeric Rating Scale (NRS) and the PCA pump. All patients continued to receive cardiac drugs, until the morning of the operation.

The patients with preexisting chronic renal insufficiency (a serum creatinine level of 1.5 mg/dL), impaired hepatic function, diabetes mellitus, chronic obstructive pulmonary disease based on long-term use of bronchodilators or steroids for lung disease, stroke, a pulmonary artery pressure of more than 25 mm Hg (as indicated by a preoperative transthoracic echocardiogram), and previous sternotomy were excluded from the study.

Postoperative exclusion criteria included requiring intra-aortic balloon pump, surgical reexploration, hemodynamic instability, bleeding, and failure of the patient to properly use the PCA pump. Hemodynamic instability was defined as systolic blood pressure less than 90 mm Hg despite ongoing infusion of inotropic drugs.

After assessments for eligibility, 6 patients were excluded because of refusing to participate to the study protocol. Fifty patients were finally included in the study after the objectives of the study had been described, the confidentiality of information had been assured, and informed consents had been obtained.

2.2. Anesthetic management

Technique of anesthesia was standardized for all patients. All operations were conducted by a single surgical team and using the same standardized technique. The team in the operating room was blinded to the study protocol.

Anesthesia was induced in all patients with thiopental (4-6 mg/kg), fentanyl (8-10 μg/kg), and vecuronium (0.08 mg/kg) and was maintained with a fentanyl infusion (8 μg^{-1} kg^{-1} h^{-1}), 0.5% to 0.7% isoflurane in an oxygen-air mixture, and an IV injections of vecuronium (0.02 mg/kg every 30 minutes). Surgical approach was through a midline sternotomy, with one side of the sternum elevated using a special retractor to harvest internal thoracic artery. The internal thoracic artery pedicle was mobilized from the chest wall by cautery. Saphenous vein harvesting from the calf was accomplished by using a standard open incision. IV heparin (300 IU/kg) was administered as needed to keep the activated coagulation time longer than 480 seconds. Cardiopulmonary bypass was instituted in a standard manner by cannulating the right atrium and ascending aorta. The patients were cooled to the level of mild hypothermia (body temperature, 30°C-32°C). During cardiopulmonary bypass, hematocrit was kept between 26% and 28%; pump flow rates were kept between 2.0 and 2.5 L min^{-1} m^{-2}, and the mean arterial pressure was kept at 70 to 80 mm Hg using sodium nitroprusside or norepinephrine, as required. In all patients, myocardial preservation was achieved with antegrade crystalloid cold cardioplegia. All distal and proximal anastomoses were performed during a single cross-clamping period. Sternotomy was closed with 6 or 7 sternal wires, and the skin incision was closed with intracutaneous stitches. After the operation, patients were transferred to the cardiac ICU (CICU) where they were weaned from mechanical ventilation after the following criteria were met: hemodynamic stability, a body temperature of >36°C, chest tube output of <100 mL/h, and a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of >200.

Tracheal extubation was performed when the patient met the following criteria: hemodynamic stability, a body temperature of >36°C, urine output of >0.5 mL kg^{-1} h^{-1}, absence of residual muscle paralysis, and adequate ventilator parameters (vital capacity >12 mL/kg, respiratory rate <25 beats/min, minute ventilation >90 mL kg^{-1} min^{-1}, fraction of inspired oxygen <0.6, positive end-expiratory pressure <7.5 cmH_2O, oxygen pressure, >90 mm Hg).

Before extubation, all patients took morphine with a PCA device by their nurse according to their sedation and analgesic scores. The nurse who was assessing the patient was blinded to the technique. Randomization was done with closed-envelope technique. Immediately after extubation, all patients were allowed to use themselves morphine PCA device for 48 hours postoperatively, with initial settings for IV morphine at a bolus dose of 1 mg (1 mL), lockout time of 15 minutes, and 4-hour limit dosage of 16 mg.

Group T (n = 25) received (in addition to PCA) tramadol + paracetamol tablet (Zaldiar, Grünenthal GmbH, Zieglerstraße 6, 52078 Aachen, Germany; 325 mg paracetamol, 37.5 mg tramadol) orally, and group P (n = 25) received placebo starting after the second hour of the operation and received 4 times per day through a nasogastric tube and orally after extubation. Those who were cooperated before the extubation and had an NRS of ≥3 received a self-administered bolus dose of opioids via the PCA device. The IV-PCA opioid infusions were discontinued after 48 hours.

Table 1
Demographic characteristics of patients

	Group T (n = 25; morphine + tramadol)	Group P (n = 25; morphine + placebo)	*P*
Sex[a], n (%)			
Male	17 (68)	15 (60)	.77
Female	8 (32)	10 (40)	
Age (mo)[b], median (range)	62.60 ± 8.36	66.28 ± 7.87	.11
Weight (kg)[b], median (range)	73.12 ± 6.99	75.72 ± 7.55	.21

[a] Continuity (Yates) correction.
[b] Student *t* test.

Table 2
Risk assessment and intraoperative data

	Group T (n = 25; morphine + tramadol)	Group P (n = 25; morphine + placebo)
Hypertension (%)	17 (68)	19 (76)
Diabetes mellitus (%)	10 (40)	8 (33)
ASA (II/III)	13/12	10/15
Ejection fraction (%)	52 ± 6	48 ± 6
Coronary artery graft (no.)	3 (1-5)	3.5 (2-5)
LIMA (%)	25 (100)	25 (100)
Bypass time (min)	77 ± 22	81 ± 22
Cross-clamp time (min)	65 ± 25	69 ± 24
Total operation time (min)	265 ± 29	245 ± 35

Values are reported as mean ± SD, frequency, median (range), or number (%).
ASA = American Society of Anesthesiologists; LIMA = left internal mammary artery.

2.3. Measurements

Sedation levels were measured with the Ramsay Sedation Scale (RSS); pain was assessed with the Pain Intensity Score (PIS) during mechanical ventilation and with the NRS score after extubation. Overall effectiveness of pain relief was evaluated with a 4-stage scale ("very good," "good," "moderate," or "bad"). During postoperative hours, if the NRS was ≥3 and PIS was ≥3, despite pain relief therapy, morphine sulfate at a dose of 0.05 mg/kg was administered. During follow-up, all patients were monitored by a single investigator. Pain was assessed, with each patient at rest, coughing, or moving by using an 11-point rating scale in which zero represented "no pain" and 10 indicated the "worst pain imaginable" by their nurse who was also blinded to the study. Pain scores were documented at arrival to the ICU and 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 40, and 48 hours after surgery. In addition, amounts of the PCA bolus, demands, and the requirement for morphine were measured 48 hours after surgery. The hourly measurement of mean arterial blood pressure and heart rate, electrocardiography with continuous ST-segment analysis, respiratory rate, and oxygen saturation were recorded. Arterial blood gas analysis was recorded 0, 2, 6, 12, and 24 hours after surgery. Respiratory depression was defined as apnea or a respiratory rate of fewer than 8 beats/min. A daily anteroposterior chest radiograph obtained until the fourth postoperative day was compared with a previous chest radiograph to detect atelectasis and other pulmonary complications. All chest radiographs were evaluated by a radiologist blinded to the treatment administered. The time of extubation, duration of the mechanical ventilation, and length of the CICU stay were recorded. Adverse events including atrial fibrillation, atelectesis, vomiting, constipation, difficulty staying awake hypotension (systolic blood pressure <90 mm Hg), bradycardia (heart rate <55 beats/min), and gastrointestinal problems were recorded. Vomiting was assessed within 15 minutes after the first cooperation and extubation, at the time of discontinuation of the PCA analgesic infusion in the first day, and 3 times in the second day.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS version 22 software (IBM Corporation, Armonk, NY). Postoperative NRS values were used as the primary variables, when the sample size was determined. All variables are were given in mean and SD, percentage (n), or median (range). After assessing the outcome distribution, pain and sedation scores were not normally distributed. These scores were expressed in median with a range and a nonparametric test was used to analyze the statistical significance. To compare the quantitative data between the study groups, *t* test was used for parametric variables and the Wilcoxon signed rank test for nonparametric variables. Qualitative data between the groups were compared with the χ^2 test. A P value of <.05 was considered statistically significant.

Calculation of the sample size was based on a power analysis for comparison of each drug group to placebo with respect to morphine sparing property. In the literature [10], a 30% decrease (=7.5 mg) in morphine consumption is regarded as a clinically significant result. To have a difference of 7.5 mg in 24-hour morphine consumption with 7.5 mg SD, we needed 22 subjects per group ($\alpha = .05$ and $\beta = 0.8$). Since at least 22 patients were needed in each group according to the power analysis, we took into account the risk of exclusion of some patients during the study and hence determined the number to 25; however, none of the patients were excluded from the study.

3. Results

The demographic characteristics of the patients were similar in both groups (Table 1). Preoperative patient characteristics, risk assessment, and intraoperative data were similar in both groups (Table 2).

No statistically significant difference in the heart rate and mean blood pressure during follow-up was found between the groups. The median respiratory rate and median arterial saturation as determined by pulse oximetry and peripheral arterial blood gas analysis were similar in both groups.

The cumulative morphine consumption was significantly higher in group P at all time points. The number of PCA demands and boluses was also higher in group P ($P < .01$). The amount of total morphine (mg) used as a rescue analgesia was also higher in group P compared with group T ($P < .001$; Table 3).

The duration of mechanical ventilation in group P was longer than group T (10.2 ± 2.4 [median, 10] hours 6.2 ± 1.5 [median, 6] hours, respectively; $P < .01$). The length of stay in the ICU was also longer in group P than in group T (63 ± 10.7 [median, 62] hours 49.7 ± 10.4 [median, 48] hours, respectively; $P < .01$; Table 4).

No statistically significant difference in the level of patients' satisfaction regarding pain therapy was noted between the 2 groups and no patient described the efficacy of their pain relief as "bad." However, it was available with the twice doses of morphine in group P with respect to group T ($P > .05$; Table 4).

The RSS scores were also higher at the 1st, 2nd, 4th, 8th, 12th, and 30th hours in group P compared with group T ($P < .01$ and $P < .05$; Fig. 1). There was a difficulty staying awaken in 8 patients in group P. In all other time points, there was no difference in the RSS scores between the groups ($P > .05$). No patient discontinued morphine due to its adverse effects. Postoperative complications are given in Table 5.

No statistically difference was observed in the PIS during the first 12 hours of the CICU stay between the groups ($P > .05$). The NRS values

Table 3
Number of PCA demands/boluses, requirement of additional analgesics, total morphine consumption

	Group T (n = 25; morphine + tramadol)	Group P (n = 25; morphine + placebo)	P
PCA demand[a] (mg), median (range)	40.48 ± 13.6 (34)	96.24 ± 16.5 (95)	.001
PCA given[a] (mg), median (range)	29.64 ± 10.25 (25)	58.24 ± 9.54 (58)	.001
Rescue analgesia[a] (mg), median (range)	2.37 ± 0.52 (2)	5.06 ± 1.0 (5)	.001
Total morphine consumption[a] (mg)	30.40 ± 9.92 (26)	61.72 ± 8.83 (62)	.001

PCA = patient-controlled analgesia.
[a] Mann-Whitney *U* test.

Table 4
MV time, CICU stay time, patient satisfaction, and adverse effects

	Group T (n = 25; morphine + tramadol)	Group P (n = 25; morphine + placebo)	P
MV time[a] (h), median (range)	6.2 ± 1.5 (6)	10.16 ± 2.4 (10)	.001**
Intensive care unit discharge time[a] (h), median (range)	49.4 ± 10.4 (48)	63.08 ± 10.7 (62)	.001**
Patient satisfaction[a], median (range)	3.76 ± 0.83 (4)	3.56 ± 0.65 (4)	.194
Adverse effects[b], n (%)			
Yes	7 (28)	16 (64)	.023*
No	18 (72)	9 (36)	

MV = mechanical ventilation; CICU = cardiac intensive care unit.
[a] Mann-Whitney *U* test.
[b] Continuity (Yates) correction.
* $P < .05$.
** $P < .01$.

were higher at 8th, 20th, 24th, and 30th hours in group P than in group T ($P < .05$); however, all values were less than 3.

4. Discussion

In this prospective, double-blind, randomized clinical study, we investigated the efficacy of oral tramadol + paracetamol combination to the morphine consumption after an uncomplicated elective CABG surgery using the PCA morphine protocol. We found that tramadol + paracetamol combination reduced morphine requirement up to 50% compared with the placebo group.

In the present study, oral tramadol + paracetamol administration resulted in morphine consumption in all time points. The RSS scores of patients receiving tramadol + paracetamol were lower within the first hours postoperatively. In addition, a lower number of patients required morphine (28%) as a rescue analgesia in the study group. Overall, these results indicate that the effects of tramadol + paracetamol are more prominent postoperatively.

Our results also showed that the patients receiving tramadol + paracetamol had significantly lower mean pain scores from the day of surgery to the second postoperative day. Because total morphine consumption and additional morphine requirements were higher in the placebo group, duration of mechanical ventilation and length of CICU stay were longer in the placebo group due to the high dose of opioid.

Previous studies demonstrated reduced morphine consumption with various agents in the postoperative period of cardiac surgery [5, 10-12]. Therefore, adverse effects caused by increased morphine doses can be minimized. Rapanos et al. [11] reported a 38% decrease in morphine consumption within the first 24 hour after cardiac surgery with the administration of rectal indomethacin, with reduced VAS scores (when not coughing) up to 26% to 66%. Petterson et al [5] also found a higher decrease (22%) in morphine consumption with IV rather than oral acetaminophen. In consistent with previous findings, Hynninen et al [10] reported that NSAIDs, such as diclofenac, ketoprofen, and indomethacin, reduced morphine consumption after cardiac surgery, with diclofenac being the most potent.

Furthermore, balanced or multimodal analgesia involves the selective use of specific drugs in combination. The concept relies on using multiple analgesic drugs with different modes of action (ie, nonopioids combined with an opioid). There is currently good evidence that this approach improves analgesia thanks to additive or synergistic effects, allowing the doses of the individual drugs to be reduced, thereby reducing the incidence and severity of adverse effects [12]. The administration of nonopioid oral agents for postoperative pain would avoid respiratory depression and drowsiness associated with opioids; however, the limited analgesia makes them useful only as adjuncts. When additional analgesic agents are used in the postoperative period, resulting in decreased morphine consumption, the antiemetic requirement can be also reduced, gastrointestinal function can be restored more rapidly, and the postoperative morbidity and time needed for recovery from anesthesia can be proportionally decreased [11,13]. In our study, tramadol + paracetamol administration resulted in less frequent nausea, vomiting, respiratory depression, and pruritus. Potential merits of tramadol for postoperative pain relief include long duration of action [14], rapid recovery [15], and limited respiratory depressant effects [16]. Several studies have shown that tramadol provides a comparable analgesic effect to morphine for postoperative pain relief in adults [14,15].

In the present study, we investigated a combination of oral drugs, tramadol and paracetamol, which are considered to have fewer adverse effects than the traditional drugs. Tramadol is a centrally acting analgesic with a double-action mechanism: one based on the m-receptor link and the other on serotonin and noradrenalin reuptake inhibition at the central synaptic level [17,18]. Unlike traditional opioids, it does not interact with either hemodynamic or respiratory function. Furthermore, tramadol does not cause the appearance of tolerance, so it is therefore unnecessary to increase the dosage to maintain the analgesic effect over time [9,18]. At recommended dosages, paracetamol is not associated with the increased incidence of nausea, vomiting, and respiratory depression observed with opioids [19]. Furthermore, paracetamol has distinct mechanism in which it does not interfere either platelet or kidney function [19]. Nonetheless, the analgesic action of paracetamol is not clear, although its central-level action has been hypothesized [19].

Our study showed that administration of oral tramadol + paracetamol moderately reduced overall morphine consumption after cardiac surgery without severe adverse effects. The patients' satisfaction levels were similar between the groups. This can be attributed to the fact

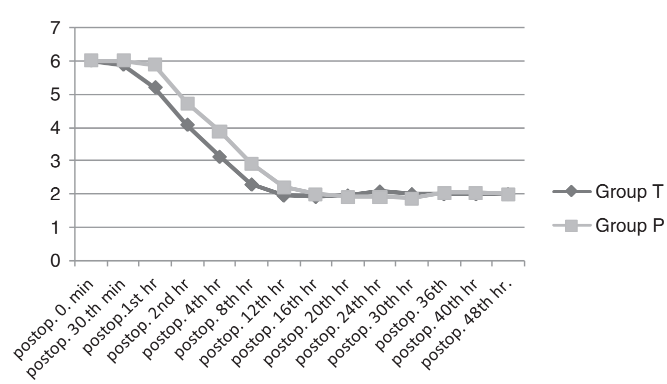

Fig. 1. RSS: postoperative sedation scores. Sedation scores are expressed as the mean ± SD for each group and were measured using RSS (1, agitated and uncomfortable; 2, cooperative and oriented; 3, obeys simple directions; 4, sleepy with strong reply to stimulation; 5, sleepy with slow reply to stimulation; 6, asleep and does not reply to stimulation). RSS = Ramsay Sedation Scale.

Table 5
Patient adverse events

	Group T (n = 25; morphine + tramadol)	Group P (n = 25; morphine + placebo)	*P*
Atrial fibrillation, n (%)	3 (12)	1 (4)	.6
Atelectasis, n (%)	4 (16)	6 (24)	.7
Vomiting, n (%)	–	4 (16)	.1
Constipation, n (%)	–	4 (16)	.1
Hypotension, n (%)	–	1 (4)	.9
Difficulty staying awake, n (%)	–	8 (32)	.004

Values are reported as number of patients and number (%) in each group experiencing the adverse effect.

that NRS scores were <3 in 2 groups and sedation depth was slightly higher in group P because of high levels of morphine, which might have resulted in the same satisfaction.

Because opioid consumption was less in group T, adverse events due to the twice amount of morphine were more common in group P than in group T. In the present study, complications were seen in 7 patients (28%) in group T and in 16 patients (%64) in group P. These complications included atrial fibrillation, atelectasis, vomiting, and constipation; the most seen were difficulty in staying awake, respiratory complications due to atelectasis, and respiratory depression. Because of these conditions, the patients required more pulmonary rehabilitation during weaning period.

Moreover, high-dose opioids can be used to resolve stress responses after cardiac surgery [20]. This approach may also reduce postoperative complications. However, high-dose opioids are associated with longer tracheal extubation times and prolonged ICU stays [7,20]. In the present study, extubation times and CICU stays were significantly longer in group P than in group T ($P < .01$).

In conclusion, our study results suggest that using tablet forms of tramadol + paracetamol combination with PCA morphine decreased the cumulative amount of morphine used postoperatively and VAS scores. In addition, this regimen can significantly reduce the duration of mechanical ventilation and the length of stay in the CICU, and adverse events were reduced in the study group.

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