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Original contribution

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

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ABSTRACT

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].

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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.