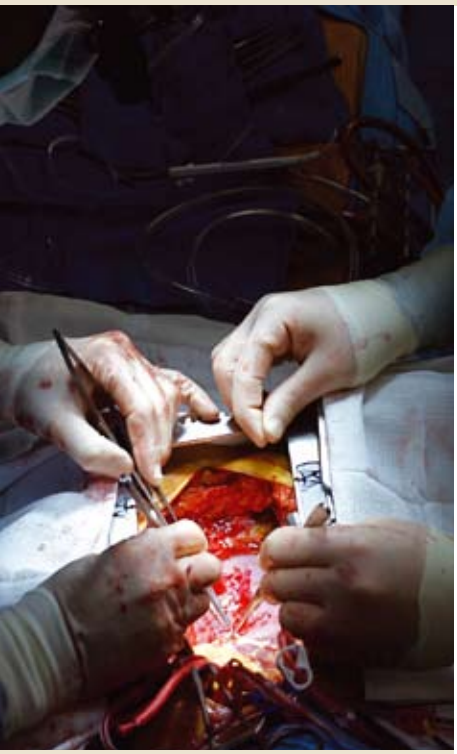
The Addition of a Tramadol Infusion to Morphine Patient-Controlled Analgesia after Coronary Artery Bypass Graft



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Abstract:

Background: Patient-controlled analgesia (PCA) has been advocated as superior to conventional controlled analgesia with less risk to patients in cardiac surgery. In this double-blinded, randomized controlled trial, we tested whether the addition of Tramadol to morphine for patient-controlled analgesia (PCA) resulted in improved analgesia efficacy and smaller morphine requirements compared with morphine PCA alone after Coronary Artery Bypass Graft (CABG) surgery in adults.

Methods: Seventy patients who were randomly allocated into two groups underwent anesthesia by Total IV anesthesia, midazolam, fentanyl and atracurim and, in end of surgery each group received morphine sulfat 0.2 mg/kg after arrived in ICU, morphin PCA was started with demand (bolus) dose 1mg, lockout interval 10 minutes. The Tramadol group after separated from cardiopulmonary bypass received an intra operative initial loading dose of Tramadol (1mg/kg) and a postoperative infusion of Tramadol at 0.2 mg• kg-1• h-1. The control group received an intra operative equivalent volume of normal saline and a postoperative saline infusion (placebo). The demographic data of both groups were the same. Post-operative data were recorded in the cardiac intensive care unit at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h after extubation by the same anesthesiologist, who had no knowledge of the groups, and the side-effects were also evaluated.

Results: Postoperatively, Tramadol was associated with improved subjective analgesic efficacy ($P = 0.031$) and there was significantly less PCA morphine use in the Tramadol group ($P = 0.023$). No differences between the groups were found with regard to nausea dizziness, itching, antiemetic use, sedation, or quality of recovery (all $P > 0.05$).

Conclusions: We conclude that a Tramadol infusion combined with PCA morphine improves analgesia and reduces morphine requirements after cardiac surgery compared with morphine PCA alone.

Key words: patient control analgesia, tramadol, CABG

Introduction

Pain after cardiac surgery may be intense and requires the administration of large doses of opioids (1,2). Pure opioids have a dose-dependent analgesic effect. However, opioid administration is also associated with a number of adverse effects, such as nausea, vomiting, depressed gastrointestinal motility, drowsiness, and, especially with larger doses, respiratory

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depression (3).Non-opioid analgesics, such as nonsteroidal antiinflammatory drugs and paracetamol (acetaminophen), may be useful adjuncts to opioids for postoperative pain relief. Non-opioid analgesics may significantly reduce opioid consumption and the resultant side effects. However, the efficacy of these adjuncts may be limited (4), or they may have potentially serious adverse effects after cardiac surgery, such as increased bleeding and renal failure with nonsteroidal antiinflammatory drugs (5). Tramadol is a unique analgesic with multiple sites of action. It is classified as an atypical centrally acting analgesic, and has opioid and nonopioid properties. Its action on μ-opioid receptors is weak, and naloxone antagonizes only 30% of its analgesic activity (6); -2 adrenoceptor antagonists such as yohimbine significantly reverse Tramadol analgesia (7). Therefore, much of its antinociceptive actions are likely to be via inhibition of reuptake of neurotransmitters, such as norepinephrine and serotonin in the central nervous system (8). Whereas there are data comparing the efficacy of morphine to Tramadol in several surgical populations (9–11), early extubation after cardiac surgery is an important part of fast-track cardiac anesthesia. Immediate extubation is usually safe if good analgesia can be achieved. Patient-controlled analgesia (PCA) has been advocated as superior to conventional controlled analgesia with less risk to patients. In this double-blinded, randomized controlled trial, we tested whether the addition of Tramadol to morphine for patient-controlled analgesia (PCA) resulted in improved analgesia efficacy and smaller morphine requirements compared with morphine PCA alone after Coronary Artery Bypass Graft (CABG) surgery in adults.

Methods:

The study population selected from Rajaei Heart Center, a tertiary center of cardiovascular diseases in Tehran which admitted patients from any part of IRAN. Seventy patients who scheduled for an elective coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass and younger than 70 yrs of age were considered eligible for the study, Patients with poor ventricular function (ejection fraction, > 40%), chronic opiate usage, allergy to opiates or Tramadol , epilepsy, psychiatric disorders involving the use of monoamine oxidase inhibitor or selective serotonin reuptake inhibitor drugs, sleep apnea, impaired hepatic or renal function, diabetes mellitus, unstable angina and previous sternotomy were excluded. All patients continued to receive their cardiac drugs until the morning of the operation, and were informed by the same anaesthesiologist 1 day prior to surgery about PCA, and the visual analogue scale (VAS). The technique of anaesthesia was standardized for all patients. Anaesthesia was induced with midazolam, 0.2mg/kg, and fentany l, 5 -10μg/kg. pancrunume 0.1 mg/kg, was used to facilitate endotracheal intubation. Anaesthesia was maintained with fentanyl, 5–10 μg/kg, and midazolam, 0.1–0.3 mg/kg/h ;and propofol 1.5mg /kg/h N2O was not used. The depth of anesthesia was adjusted with cerebral status monitoring. Throughout the operation, fentanyl, 3 μg/kg, was administered as a standard application before the incision and sternotomy, and at the beginning of cardiopulmonary bypass (CPB). Additional propofol was administered at a dose ranging from 1 to1. 5 mg/kg if the mean arterial pressure (MAP) was more than 100 mmHg before cannulation, more than 80 mmHg during cannulation, or more than 100 mmHg after CPB. In addition, the TNG(nitroglyserin) infusion dose was adjusted to 0.1–0.3 mg/kg/h according to the same criteria. Surgery was performed in a standard fashion through a median sternotomy with saphenous veins and internal thoracic arteries harvested as conduits. A standard crystalloid prime was used in the cardiopulmonary bypass (CPB) circuit. Myocardial protection was achieved with intermittent, antegrade, solution of cardioplegia. Nonpulsatile CPB flow was maintained between 1.5 and 2 L•min–1•m–1 using a membrane oxygenator. Patients were not actively cooled, but their core temperature was allowed to drift to 32 to 34°C. Active rewarming to 37°C was completed before aortic cross-clamp removal. Tracheal extubation was performed when the patient met the following criteria: chest tube output, < 100 ml/h; no arrhythmia; urine output, > 0.5 ml/kg/h; absence of residual muscle paralysis; adequate ventilatory parameters [vital capacity, > 12 ml/kg; respiratory rate, < 25 breaths/min; minute ventilation, > 90 ml/kg/min; fraction of inspired oxygen (Fio2) < 0.6; positive end-expiratory pressure (PEEP) < 7.5 cmH2O; oxygen pressure (Po2) > 90 mmHg].

After operation, all patients were transferred to the intensive care unit (ICU) Patients were randomly put into one of the two groups (group T, n = 35; group C, n = 35) post-operatively, and then Immediately after extubation, all patients

were allowed to use the morphine PCA device (Abbott Pain Management Provider, Class II, Type CF, North Chicago, IL) for 24 h post-operatively, with the initial settings for intravenous morphine as bolus dose of 1 mg, lockout time of 7 min and 4-h limit dosage of 20 mg. The Tramadol group after separated from cardiopulmonary bypass received an intra operative initial loading dose of Tramadol (1mg/kg) and a postoperative infusion of Tramadol at 0.2 mg • kg-1 • h-1 . The control group received an intra operative equivalent volume of normal saline and a postoperative saline infusion (placebo).

Post-operative data (VAS, Ramsay sedation, total morphine consumption and number of PCA demands and boluses) were recorded in the cardiac ICU at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h after extubation by the same anaesthesiologist who had no knowledge of the groups. Furthermore, the side-effects, such as itching, nausea, drowsiness vomiting and respiratory depression, were also evaluated.

Statistical analysis: was performed with intention-to-treat approach. Data were classified as mean ± standard deviation for interval and count (%) for categorical variables. Comparison of baseline data between the groups of study was performed by students' t test or its non-parametric equivalent, Mann Whitney U test for interval data and Chi square test for nominal data. Odds Ratio (OR) with 95% confidence interval (CI 95%) also computed to find the epidemiologic associations. P value less than 0.05 considered as statistically significant.

The trend of pain severity and changes of VAS results (among time intervals and between study groups) were investigated by a repeated measure analysis of variance (ANOVA) model.

Survival analysis was performed by Kaplan – Meier method to study the time of receiving the first dose of morphine sulfate, as a proxy of the time of intolerable pain by patients. Log rank test was used to compare the results between the study groups.

SPSS 15 for windows (SPSS Corporation, Chicago, Illinois) was used for statistical analysis.

Results:

seventy patients (mean age = 58 ± 11.0 years, range 24 to 69 years) enrolled the study. Mean left ventricular ejection fraction (LVEF) was 45 ± 8.4 percent. The average time of surgery and anesthesia was 3.8 ± 0.9 and 5 ± 0.9 hours, respectively. Amounts of fentanyl used peri-operatively were similar in both groups. Patients stayed in intensive care unit (ICU) after surgery with a mean time of 2.2 ± 0.5 days (range 2 to 4 days). (Table-1).Thirty five patients received intravenous tramadol and 35 got normal saline as placebo instead. Baseline data of the study groups are presented in Table-1. No important differences were observed between the groups.

Table-1- Comparison of Baseline Data between tramadol and Placebo Groups.

	tramadol (n = 35)	Placebo (n = 35)	P value
Age years	57 ± 11.5	59 ± 10.4	0.19
Weight (kg)	70 ± 11	68 ± 9	0.54
Height (cm)	168 ± 7	166 ± 7	0.52
Intra-operative fentanyl (µg)	1115 ± 323	1024 ± 288	0.55
Left Ventricular Ejection Fraction percent	44 ± 7.3	44 ± 9.5	0.64
Duration of Anesthesia hours	5 ± 0.7	5 ± 1.1	0.43
Duration of Operation hours	4 ± 0.7	4 ± 1.0	0.57
Cardio-Pulmonary Pump Time minutes	103 ± 58.3	104 ± 41.5	0.63
ICU Stay days	2 ± 0.4	2 ± 0.5	0.52
Number of the Grafts	3 ± 0.4	3 ± 0.3	0.19
Intubation Time hours	14.1 ± 4.3	16.5 ± 14.9	0.32

Severity of pain was measured by a 10-point visual analogue scale (VAS) in different time intervals. The results are summarized in Table-2. Note that the most severe pain had a point which was less than 3. After surgery, patients experienced a period of analgesia. The pain appeared gradually and became more severe by the 6th hour after finishing the operation. Then, the severity of pain decreased until it disappeared the 18th hour after surgery. The significance of this trend was proved by repeated measure ANOVA in both tramadol and placebo groups (p value < 0.001).

The severity of pain was equal in two groups in the first time after operation. The period of analgesia continued in patients

who received tramadol until the 3rd hour after surgery, while in placebo group, the severity of pain was rising. It was observed that in any time interval, the patients in tramadol group experienced a less severe pain, compared to placebo group. This difference was statistically significant (p value < 0.001). In the evaluation of the Ramsay sedation scores, no difference was found between the groups (Figure-1),

Table 2 –Pain Score in Different Time Intervals after Cardiac Surgery in Tramadol and Placebo Groups

	Mean Score ± Standard Deviation					
	1st Hour	3rd Hour	6th Hour	12th Hour	18th Hour	24th Hour
tramadol	0.29 ± 1.17	0.0 ± 0.0*	0.97 ± 2.02*	0.23 ± 1.0*	0.0 ± 0.0*	0.0 ± 0.0
Placebo	0.09 ± 0.59†	0.36 ± 1.26†	2.53 ± 2.43†	0.89 ± 1.83†	0.0 ± 0.0†	0.0 ± 0.0

P value for comparison between tramadol and Placebo (based on repeated measure ANOVA) < 0.001
P value for comparison among time intervals (based on repeated measure ANOVA) < 0.001
* and †: Statistically significant difference in pair wise comparisons (based on Bonferroni post-hoc test). P values range <0.001 to 0.006.

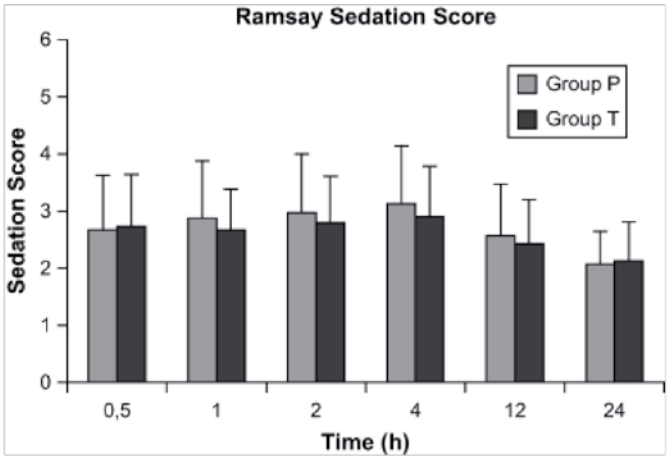

Fig.-1. Post-operative sedation scores. Scores were measured using a Ramsay sedation scale (1, agitated and uncomfortable; 2, cooperative and oriented; 3, obeys simple directions; 4, sleepy with strong reply to stimulation; 5, sleepy with slow reply to stimulation; 6, asleep and does not reply to stimulation). Sedation scores are expressed as the mean ± standard deviation for each group. Group P, saline; group T, tramadol.

The total morphine consumption was higher in group P at all evaluation times and the number of PCA demands and boluses were also higher in group P (P < 0.01) (Table-3).

Table-3:Number of patient-controlled analgesia (PCA) demands and boluses.

	Total demand (*n*)	**Total bolus (*n*)**
Group P	36.9 ± 9.2	30.6 ± 11.3
Group T	29.2 ± 12.3	23.1 ± 8.7

Group P, saline; group T, tramadol. Data are the mean ± standard deviation.

***P* < 0.01, between groups.**

The numbers of post-operative complications are shown in Table-4; there was no statistically significant difference between the two groups.

Table-4:Post-operative side-effects.

	Nausea	Vomiting	Itching	Respiratory depression
Group P	7	1	3	1
Group T	5	0	1	0

Group P, saline; group T, tramadol.

Conclusion:

This study has demonstrated infusion of tramadol following CABG is associated with reduction morphine consumption, a decrease in the VAS scores and an improvement in patient comfort within the first 4 h post-operatively.

Previous studies have demonstrated reduced morphine consumption with various agents employed in the post-operative period of cardiac surgery (5–7, 9). In this way, adverse effects caused by increased morphine doses are minimized. Rapanos et al. (6) reported a 38% decrease in morphine consumption within the first 24 h post-operatively after cardiac surgery with the administration of rectal indometacin, with VAS scores (when not coughing) reduced by 26–66%. Pettersson et al. (7) found a sharpes decrease (22%) in morphine consumption with intravenous rather than oral acetaminophen. In line with previous findings, Hynninen et al. (5) reported that non-steroidal

anti-inflammatory drugs, such as diclofenac, ketoprofen and indometacin, reduce morphine consumption after cardiac surgery, diclofenac being the most potent. Magnesium administration resulted in a decrease in VAS scores and morphine consumption after cardiac surgery in the study by Bolcal et al. (9). In contrast with the above findings, Lahtinen et al. (14) was unable to find a significant difference in pain scores or pulmonary function when propacetamol was administered with an opioid (i.e. oxycodone), and Rauf et al. (15) demonstrated an increase in morphine consumption with remifentanil infusion.

Immer et al. (16) compared the effects of diclofenac, etodolac and tramadol on pain and morphine consumption up to the fourth post-operative day after coronary surgery. Despite the absence of any significant difference between the agents in terms of VAS, morphine consumption and anti-emetic requirements up to the end of the first post-operative day, higher VAS scores and larger anti-emetic requirements were found in the tramadol group between the second and fourth post-operative days, and less morphine was consumed in the etodolac group than in the tramadol group on the fourth post-operative day.

Unlugenc et al. (10) used tramadol for pre-emptive purposes, and found a decrease in morphine consumption after major abdominal surgery. No study regarding pre-emptive agent use in the management of post-operative pain after CABG has been reported to our knowledge, and this may be because of the large amount of narcotics used in the peri-operative period and late extubation. Therefore, in the present study, we used tramadol as a single dose immediately before extubation, instead of pre-emptively.

In the present study, tramadol administration resulted in decreases in morphine consumption of 17%, 20%, 21%, 23%, 27% and 23% at 30 min, 1 h, 2 h, 4 h, 12 h and 24 h post-operatively, respectively. This was accompanied by decreases in the VAS score of 33%, 29%, 34% and 18% at 30 min, 1 h, 2 h and 4 h post-operatively, respectively. The comfort scores of patients receiving tramadol were higher within the first 4 h post-operatively. In addition, less patients required morphine (17%) or bolus doses administered via PCA (21%) in the tramadol group within the first 24 h post-operatively. Overall, these results indicate that the effects of tramadol are more prominent within the first 4 h post-operatively, suggesting a potential for better results with an additional tramadol dose administered at the end of the fourth hour.

When additional analgesic agents are used in the post-operative period, resulting in decreased morphine consumption, the anti-emetic requirement is reduced, gastrointestinal function is restored more rapidly and the post-operative morbidity and time needed for recovery from anaesthesia are decreased (6, 22). In our study, tramadol administration resulted in less frequent nausea, vomiting, respiratory depression and pruritus; however, the differences were not statistically significant.

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