Fast-Track Coronary Artery Bypass Grafting Surgery Under General Anesthesia With Remifentanil and Spinal Analgesia With Morphine and Clonidine

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Objective: **Effective postoperative analgesia is a critical part of fast-track cardiac surgery. This study compared the postoperative analgesic effect of fast-track anesthesia with remifentanil and spinal morphine and clonidine with that of sufentanil anesthesia followed by patient-controlled administration of intravenous morphine.**

Design: **Prospective, blinded, randomized study.**

Setting: **Single private institution.**

Participants: **Forty patients selected for coronary artery bypass graft surgery allocated randomly into 2 groups.**

Interventions: **General anesthesia was performed with etomidate, isoflurane, cisatracurium, and either remifentanil (0.10-0.25 μg/kg/min) or sufentanil (up to 3.5 μg/kg). In the remifentanil group, patients received spinal morphine (4 μg/kg) and clonidine (1 μg/kg) before induction. Postoperatively, patients in both groups were connected to an intravenous patient-controlled analgesia (PCA) morphine pump that delivered a 1-g bolus with a 7-minute lockout interval.**

Measurements and Main Results: **Patients were evaluated for pain on a visual analog scale (VAS), at rest and on deep breathing, and for intravenous PCA morphine consumption during 24 hours. The intravenous PCA morphine 24-hour cumulative dose was lower in the fast-track than in the control group (15.8 ± 12.6 *v* 32.7 ± 22.3 mg, $p < 0.05$). Before extubation, VAS scores were higher in the fast-track group, but after they were lower both at rest and during deep breathing. Extubation delay was shorter in the fast-track group (156.5 ± 46.1 *v* 272 ± 116.4 minutes, $p < 0.05$).**

Conclusion: **The combination of anesthesia with remifentanil and spinal analgesia with morphine and clonidine produces effective analgesia after coronary artery surgery and a rapid extubation time.**

KEY WORDS: analgesics, spinal morphine, clonidine, analgesia, postoperative, surgery, cardiac

NEW ANESTHETIC and analgesic techniques developed for coronary artery bypass graft surgery (CABG) aim to achieve a more rapid emergence from anesthesia and to guarantee adequate analgesia.[1] Indeed, a tight control of extracorporeal circulation and body temperature changes gives the opportunity to a more rapid weaning from controlled ventilation and extubation after uncomplicated CABG. This could be achieved by using opioids with a short context-sensitive half-life such as remifentanil.[2-6] Nevertheless, the use of remifentanil requires that postoperative analgesia would be adapted to the rapid reversal of its analgesic effect; in CABG patients, this is commonly achieved by maintaining remifentanil infusion with or without propofol infusion for a couple of hours in the postoperative intensive care unit. Spinal administration of morphine before surgery may also allow postoperative pain control without the need for maintaining patients under intravenous infusion hypnotic and analgesic agents. High spinal morphine doses convey the risk of respiratory depression,[7] but the authors recently showed that the addition of spinal clonidine to morphine produced better postoperative analgesia with lower spinal morphine dose and consequently decreased this risk.[8] The authors thus conducted a new prospective study in CABG patients to compare the quality of analgesia provided by a general anesthesia with remifentanil with that of conventional anesthesia with sufentanil and postoperative patient-controlled intravenous morphine administration.

PATIENTS AND METHODS

Forty patients scheduled for CABG surgery in a prospective blinded, randomized study were recruited after ethics committee approval and informed written consent. Patients with a left ventricular ejection fraction <40%, with chronic respiratory insufficiency (leading in chronic hypoxia or hypercapnia), with chronic renal failure, and with a previous history of stroke and those scheduled for a simultaneous repair of a cardiac valve were excluded from the study. Patients receiving anticoagulants, clopidogrel, or with a platelet count $<100/10^9$/L before surgery were also excluded.

On the morning of surgery, patients were allocated randomly to 1 of 2 groups with a computer-generated random number table. According to the randomization, patients were given either spinal morphine 4 μg/kg and clonidine 1 μg/kg (fast-track group) or no spinal injection (control group). Lumbar puncture was done at the L3-4 or L4-5 interspace with an intramuscular needle in the control group and with a 27-G Whitacre needle in the other group. A dressing was placed over the puncture site in all patients. Morphine was diluted in a 100-μg/mL solution with clonidine, 75 μg/mL. In the control group, anesthesia was induced with etomidate, 0.25 mg/kg, and sufentanil, 50 μg, and cisatracurium, 0.20 mg/kg, was used to facilitate intubation. Anesthesia was maintained with sufentanil, up to 3.5 μg/kg, and isoflurane, 0.3% to 1.2%. In the remifentanil/morphine/clonidine (RMC) group, anesthesia was induced by etomidate at the same dose and a continuous infusion of remifentanil at 0.12 to 0.20 μg/kg/min for 5 to 8 minutes. Cisatracurium was given for orotracheal intubation, and remifentanil was continued at 0.10 to 0.25 μg/kg/min in combination with isoflurane, 0.3% to 1.2%.

During bypass, patients received a continuous infusion of propofol, 2%, at a rate of 0.1 to 0.2 μg/kg/min. During cardiopulmonary bypass, the nasopharyngeal temperature was maintained at 37°C, perfusion pressure ranged between 40 and 95 mmHg, and pump flow was set at 3.5 L/kg/min. They received heparin, 3 mg/kg, to achieve an activated prothrombin time (APT) value >400 seconds. Anticoagulation was reversed by protamine (heparin dose × 1.3) after aortic cannula with-

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Table 1. Patients' Characteristics and Intraoperative Data Expressed as Mean ± Standard Deviation or Median (25th-75th percentiles)

	Fast-track Group (Remifentanil + Spinal Morphine + Clonidine)	Control Group (Sufentanil)	*p*
Age (yr)	66.4 ± 8.3	66.2 ± 8.3	NS
Sex ratio M/W	17/3	15/5	NS
Weight (kg)	78 ± 11	74 ± 15	NS
Opioid dose during surgery	Remifentanil: 0.13 ± 0.04 μg/kg	Sufentanil: 4.3 ± 1.3 μg/kg	
Duration of cardiopulmonary bypass (min)	57 (40-77)	63 (44-85)	NS
Duration of aortic clamping (min)	39 (29-48)	44 (28-53)	NS
Duration of surgery (min)	210 (202-259)	240 (232-272)	NS

NS, not significant.

drawal to obtain a value of APT <135 seconds. All the patients received 30 mg/kg of tranexamic acid in 2 boluses, 1 before anesthetic induction and 1 after the end of cardiopulmonary bypass.

In the postoperative period, the physician and nurses were blinded to treatment allocation of the patients. Patients were extubated in the intensive care unit (ICU) when they were awake, oriented, and cooperative, with a stable hemodynamic condition, a temperature above 36.5°C, minimal chest drain loss, and after a 30-minute trial of spontaneous ventilation on a T-piece ($PaCO_2$ <45 mmHg, SaO_2 >93%). After extubation, patients were given access to an intravenous patient-controlled analgesia pump (PCA) (APM; Abbott, Rungis, France) delivering a 1-mg dose of morphine with a 7-minute lockout interval for 24 hours. Morphine was diluted to 1 mg/mL in a solution also containing droperidol, 5 mg in 30 mL. The maximum dose of intravenous PCA morphine was set at 30 mg for 4 hours. All patients received concomitantly 1 g of intravenous paracetamol (Perfalgan, UPSA, Paris, France) every 6 hours, beginning on the patient's arrival in the ICU. Pain was measured in the ICU with a visual analog scale (VAS) graded from 0 (no pain) to 100 (worst pain imaginable) every 30 minutes for the first 4 hours, every hour for the next 4 hours, then every 2 hours until the 20th hour, and finally at 24 hours. Pain was measured at rest before extubation and at rest and during deep breathing after extubation.

The authors noted any evidence of respiratory depression (respiratory rate <10 cycles/min), hypertension (systolic arterial pressure >150 mmHg), and hypotension (systolic arterial pressure <75 mmHg). Hypertension was planned to be treated by a continuous infusion of nicardipine, 1 to 5 mg/h intravenously, and hypotension by a rapid fluid infusion followed by inotropic agents if necessary. Arterial blood gases were measured before induction of anesthesia and at 3, 6, and 12 hours after extubation.

The cardiac isoform of troponin (troponin Ic) was measured on admission to the ICU and at 6 and 24 hours after surgery. A troponin Ic concentration ≥13.5 μg/L was considered as indicative of myocardial damage.[9] The main objective of the study was to obtain a 50 % decrease in intravenous PCA morphine consumption in the RMC group compared with the control group. From the previous experience with intravenous PCA morphine requirements in CABG patients in the authors' institution, the authors calculated that a sample size of 20 patients in each group would detect such a difference with a type I error of 0.05 and a type II error of 0.10.

A descriptive statistical analysis by calculation of mean, standard deviations, median, and maximum and minimum values was used. Comparative statistical analysis was performed after checking for normal distribution. A Student *t* test was used to compare independent variables with a normal distribution; Kruskal-Wallis test or Mann-Whitney *U* test was used otherwise. The analysis of variance for repeated measures was used in cases with normal distribution and the Friedman nonparametric test otherwise. If one of these tests appeared significant, a comparison of paired values was done using a Student *t* test or a nonparametric Wilcoxon test with Bonferroni adjustments in multiple comparisons. Significance was tested to a 0.05 risk or below. Results are presented as mean (SD) or median (25th-75th percentiles).

RESULTS

Patients were comparable in the 2 groups for mean age (66.4 ± 8.3 *v* 66.2 ± 8.3 years in the fast-track and control groups, respectively), sex ratio (17 men/3 women *v* 15 men/5 women in the fast-track and control groups, respectively), and weight (78 ± 11 *v* 74 ± 15 kg in the fast-track and control groups, respectively). The mean doses of opioid administered during surgery were 0.13 ± 0.04 μg/kg/min for remifentanil and 4.3 ± 1.3 μg/kg for sufentanil. The duration of surgery, bypass time, and aortic clamping time were comparable between the 2 groups (Table 1). The intubation time was significantly shorter in the fast-track group (Table 2). In the 2 groups, all patients were extubated within 24

Table 2. Postoperative Data

	Fast-track Group (Remifentanil + Spinal Morphine + Clonidine)	Control Group (Sufentanil)	*p*
Extubation delay (min)	152.5 (120-180)	270 (232-300)	<0.0003
Duration of hypertension (min)	0 (0-10.5)	25.0 (0.5-65.0)	<0.05
Duration of nicardipine infusion	0 (0-28)	60 (0-165)	<0.05
24 hours morphine dose (mg)	15.0 (6.7-24.2)	26.9 (17.5-47.0)	<0.01
Troponin Ic on arrival in ICU ($\mu g.L^{-1}$)	0.67 (0.45-1.03)	2.38 (0.52-1.32)	NS
Troponin Ic at H6 ($\mu g.L^{-1}$)	3.33 (2.49-3.79)	2.94 (1.60-4.87)	NS
Troponin Ic at H12 ($\mu g.L^{-1}$)	1.41 (1.07-1.88)	1.24 (0.84-3.67)	NS

NOTE. Values are expressed as median (25th-75th percentiles).
Abbreviation: NS, not significant.