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Comparison of Remifentanil and Low-Dose Fentanyl for Fast-Track Cardiac Anesthesia: A Prospective Randomized Study

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ABSTRACT

Background: Different anesthetic techniques have been used for fast tracking in cardiac anesthesia. Remifentanil, with its unique pharmacokinetic profile, could be an ideal drug for fast tracking. Possible limitations of remifentanil are rapid onset of postoperative pain after discontinuation of the drug infusion, which may increase the risk of an ischemic event. We conducted this randomized study to compare the efficacy of remifentanil versus low doses of fentanyl in fast-track cardiac anesthesia. It has been hypothesized that remifentanil would provide a safe anesthesia with no impact on myocardial function and with positive effects on extubation time and mobilization.

Methods: We compared the postoperative course of patients, the remifentanil group (RG) and the low-dose fentanyl group (LDFG), in whom remifentanil and low-dose fentanyl, respectively, were used for fast-track cardiac anesthesia. The study was designed as a prospective randomized study. The primary outcomes were changes in the cardiac index and creatine kinase MB fraction (CKMB), extubation times, mobilization times, and lengths of stay in the intensive care unit (ICU) and the hospital. Frequency of myocardial infarction (MI), reoperations due to excessive bleeding, renal impairment, and cerebral complications were registered as well.

Results: Seventy-one patients were enrolled in the study, and 7 were excluded due to difficult airway, bleeding, and technical difficulties. The RG comprised 33 patients and the LDFG comprised of 31 patients. There were no differences between the groups in terms of age, Euroscore, types of surgery, extracorporeal circulation, and aortic cross-clamp time. We did not find significant difference in cardiac index, CKMB, extubation times, mobilization times, length of stay in the ICU and in the hospital between the groups. Postoperative complications such as MI, rates of reoperations, renal and cerebral complications and incidence of atrial fibrillation did not show any significant differences.

Conclusions: Remifentanil fast-track anesthesia for cardiac patients has no negative impact on myocardial function. Both remifentanil and low-dose fentanyl are equally effective and safe for fast-track cardiac anesthesia. The study did not highlight any statistical superiority of remifentanil anesthesia over low-dose fentanyl anesthesia.

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INTRODUCTION

Fast-track cardiac anesthesia is now considered as a standard of care for less complicated cardiac cases in order to facilitate early extubation and reduce the length of stay in the intensive care unit (ICU) and the hospital, thus reducing the cost involved in the patient management [Ender 2008; Silbert 2009; Svircevic 2009]. Traditionally, cardiac anesthesia consists of high doses of opiate analgesics such as fentanyl or sufentanil [Bell 1994; Myles 2002; Ender 2008; Svircevic 2009]. There are controversial data concerning fentanyl in fast-track procedures for cardiac surgery related to the use of large doses of opiate that can hinder fast postoperative recovery [Lison 2007]. Low-dose opioid-based fast-track cardiac anesthesia has shown safety similar to that of non–fast-track care [Zhu 2012].

There is an increasing interest in the use of the ultrashort-acting opiate remifentanil in cardiac anesthesia due to its unique pharmacokinetic profile [Weale 2004; Panzer 2009]. Possible limitations of remifentanil use include a rapid onset of postoperative pain after discontinuation of the drug infusion, which may increase the risk of ischemic events [Sullivan 2012].

We conducted this randomized study to compare the efficacy of remifentanil versus low-dose fentanyl in fast-track cardiac anesthesia, and we hypothesized that remifentanil would provide a safe anesthesia with no impact on myocardial function and with a positive effect on extubation time and mobilization.

METHODS

The study was designed as a single-center prospective randomized study. Elective patients scheduled to undergo, for the first time, coronary artery bypass grafting (CABG), aortic valve replacement (AVR), or mitral valve surgery were considered for enrollment at a single institution. The Euroscore did

not exceed 9. Exclusion criteria included emergency operations, double procedures, infective endocarditis, off-pump CAB (OPCAB) surgery, and risk of difficult airways.

Due to the nature of the study and the well-known anesthetic technique, formal evaluation by the institution's ethics committee and informed consent were waived [Weale 2004; Komatsu 2007; Ender 2008; Winterhalter 2008; Svircevic 2009].

All patients were randomized by sealed envelopes into 2 groups. In the low-dose fentanyl group (LDFG) the anesthetic technique comprised low-dose fentanyl. In the remifentanil group (RG) remifentanil based anesthesia was used.

Patients were monitored with a 5-lead electrocardiogram, pulse oximetry, invasive arterial pressure, capnography, and cardiac output (CO) measurement using a pulmonary artery catheter. CO and cardiac index were measured after intubation, after weaning from extracorporeal circulation (ECC), and after closure of the sternum.

Patients were ventilated with a tidal volume of 10 ml/kg, adjusting end-tidal carbon dioxide to 4.2-5.2 k Pa. ECC was standardized by using a crystalloid prime membrane oxygenator and 4:1 blood cardioplegia and maintaining normothermia. The core temperature in both groups at the termination of bypass was 37C. The blood gas protocol was alfa-stat, which is standard in the institution.

Extubation criteria included FiO_2 0.4, positive end expiratory pressure 5 cm H_2O, pressure support 10 cm H_2O, and bleeding 200 mL per hour.

Tracheal extubation was performed when the patient was fully awake and cooperative, had a respiratory rate of more than 8 breaths/min, and had satisfactory arterial blood gases.

Mobilization time was defined as the time to the ability to perform bedside sitting after admission to the ICU.

All patients included in the study were treated by 3 dedicated senior anesthesiologists, anesthetic nurses, and ICU staff.

Anesthetic Techniques

LDFG Patients. All LDFG patients were premedicated with triazolam 0.125-0.25 mg orally. Anesthesia was induced with midazolam 0.05-0.1 mg/kg, fentanyl 8-10 μg/kg, propofol 1-2 mg/kg if necessary, and rocuronium 0.6-0.9 mg/kg. Anesthesia was maintained with 1%-4% sevoflurane before bypass, with infusion of propofol 2-4 mg/kg per hour, and fentanyl 3-4 μg/kg as required while on bypass and by 1%-4% of sevoflurane (Abbott, Copenhagen, Denmark) and fentanyl 3-4 μg/kg as required after termination of bypass. The patients were transferred to the ICU without sedation and weaned from the ventilator. Postoperative pain management included intravenous morphine 2.5-5 mg, intravenous ketorolac 15 mg, and intravenous acetaminophen 1 g.

RG Patients. Patients in RG were premedicated with triazolam 0.125-0.25 mg orally. Anesthesia was induced with fentanyl 3-4 μg/kg, propofol 1.5-2.5 mg/kg, and rocuronium 0.6-0.9 mg/kg. Anesthesia was maintained with 1%-4% sevoflurane. Remifentanil infusion was started at a dosage of 0.2-0.5 μg/kg per minute after the insertion of a central venous catheter. Anesthesia was maintained with a continuous infusion of propofol 2-4 mg/kg per hour and a remifentanil infusion of 0.2-0.5 μg/kg per minute while on bypass and with sevoflurane 1%-4% together with a remifentanil infusion of 0.2-0.5μg/kg per minute after termination of bypass. After the closure of the sternum, patients in the RG received 5-10 mg morphine intravenously. Postoperatively patients were transferred to the ICU with a remifentanil infusion of 0.1-0.2 μg/kg per minute. Patients received 2.5-5 mg morphine intravenously and 1 g acetaminophen intravenously within 30 minutes after arriving in the ICU. The remifentanil infusion was reduced 25% after 15 minutes. The remifentanil infusion was reduced a further 25% if the patient did not show any signs of pain and was hemodynamically stable. Patients were extubated at all stages of weaning provided the extubation criteria were fulfilled.

Statistical Analysis

Data are displayed throughout the manuscript as mean and standard deviations (SD), with the 95% confidence interval (CI) for normally distributed variables and as the median and interquartile range, equal to the difference between the first (25% of the distribution [25th]) and the third (75% of the distribution [75th]) quartiles for all non-normally distributed continuous variables. The normality assumptions were tested using histograms and normal probability plots.

Continuous outcome measures were compared using the 2-sample t-test or the Mann-Whitney test, where appropriate. For qualitative data, the Chi-squared test was used. A probability value less than 0.05 was considered significant.

Statistical analysis was performed with STATA/IC software version 11.0 (StataCorp, College Station, TX, USA).

RESULTS

Seventy-one patients were enrolled in this study, with subsequent exclusion of 7 patients (early surgical complications, 1; bleeding, 3; difficult intubation, 1; technical difficulties with retrieving data, 2).

The RG comprised 31 patients and the LDFG 33 patients. The groups were well matched for relevant perioperative factors (Table 1).

There were no significant differences between 2 groups in age, Euroscore, ECC time, aortic cross-clamp (AXC) time, and type of surgery.

Table 2 shows the postoperative results in both groups.

Our analysis revealed no significant differences between the 2 groups regarding extubation time, mobilization time, length of stay in the ICU, or length of stay in the hospital. Myocardial function measured by cardiac index and myocardial ischemia monitored by creatine kinase MB fraction (CKMB) did not reveal any significant differences between the groups. There were no significant differences in cardiac complications such as MI and AF, postoperative bleeding, and mortality rates between the groups.

We did not register any cases of postoperative renal failure or cerebral complications (Table 3). Cerebral complications included all clinical signs for transitory cerebral ischemia or apoplexy, postoperative confusion, and delirium.

Table 1. Patients and Perioperative Characteristics

	LDFG (n = 31)	RG (n = 33)	*P*
Age, years, mean ± SD (95% CI)	65 ± 10 (61.4-68.8)	64.7 ± 8 (61.7-67.8)	0.88
Sex, male, %	76.7 (23)	75.8 (25)	0.88
Body mass index, mean ± SD (95% CI)	28 ± 4.3 (26-30)	29 ± 4.8 (27-31)	0.52
Euroscore, median (25th-75th)	4 (2-7)	3 (1-7)	0.35
Ejection fraction <40, %	16.13 (n = 5)	12.12 (n = 4)	0.64
Diabetes mellitus, %	23.3 (n = 9)	18.2 (n = 6)	0.3
Hypertension, %	46.7 (n = 14)	27.27 (n = 9)	0.13
Smoking, %	9.7 (n = 3)	18 (n = 6)	0.32
CABG, n	25	26	0.85
AVR, n	5	6	0.83
Mitral surgery, n	0	1	0.33
ECC time, min, mean ± SD (95% CI)	94 ± 24 (85-103)	84 ± 26 (75-93)	0.12
AXC time, minutes, mean ± SD (95% CI)	58 ± 17 (52-65)	57 ± 21 (49-64)	0.76

DISCUSSION

The concept of fast track in cardiac anesthesia emerged in the 1990s when it became difficult to cope with the increasing number of cardiac surgical patients due to the limitations of intensive care capacity, and physicians became more conscious of the fact that prolonged stay in the ICU resulted in an increased risk of complications, which in turn resulted in an increased duration of stay in the hospital, increased morbidity, and increased costs. Different anesthetic techniques have been adopted to achieve the fast track in cardiac anesthesia. In 1994, Bell et al. [Bell 1994] showed that patients can be extubated earlier if the dosage of fentanyl is reduced.

A recent review [Zhu 2012] of 25 randomized controlled trials involving 4118 patients aimed to update the evidence on the safety of low-dose opioid-based fast-track cardiac care compared to conventional care in adult patients undergoing cardiac surgery has shown similar risks of mortality and major postoperative complications. The authors concluded that low-dose opioid anesthesia appears to be safe in patients considered to be at low to moderate risk during cardiac surgery.

In our study we chose to use lower fentanyl doses (8-10 µg/kg) because high doses of opioid anesthesia lead to increased time to extubation and prolonged lengths of stay in the ICU and in the hospital and influence the number of readmissions to the ICU [Myles 2002; Svircevic 2009] and thus conflict with a fast-track concept. It was also reported that high doses of fentanyl are associated with a higher frequency of delirium after cardiac surgery [Burkhart 2010]. Postoperative delirium was not registered in the LDFG in our study.

Remifentanil, which is nonaccumulative and has an ultrashort half-life and for which metabolism is not dependent on renal or hepatic function, can be an ideal drug for fast-track use in cardiac anesthesia [Panzer 2009].

Table 2. Postoperative data for Both Groups

	LDFG	RG	*P*
Cardiac index, L/min per m², mean (95% CI)	2.66 ± 0.56 (2.45-2.86)	2.72 ± 0.56 (2.52-2.93)	0.63
CKMB, ug/L, median (25th-75th)	32 (23-41)	32 (20-41)	0.82
Extubation time, minutes, median (25th-75th)	240 (180-340)	195 (150-300)	0.66
Mobilization time, minutes, median (25th-75th)	690 (510-705)	600 (480-720)	0.47
Length of ICU Stay, hours, median (25th-75th)	23 (22-24)	22 (20-23)	0.085
In-hospital stay, days, median (25th-75th)	5 (5-7)	5 (4-7)	0.25

Table 3. Postoperative Complications

Complication	LDFG	RG	*P*
MI, % (n)	6.45 (2)	3 (1)	0.51
Reoperation for bleeding, % (n)	3.22 (1)	3 (1)	0.95
AF, % (n)	25.8 (8)	27.2 (9)	0.91
Renal insufficiency requiring dialysis	0	0	0
Cerebral complications	0	0	0

Investigations have shown that remifentanil-based anesthetic regimes can facilitate early extubation, reduce the length of stay in the ICU, reduce the length of stay in the hospital, and achieve a better reduction of the stress response. These regimes are not associated with more complications, and the overall cost remained the same as that for an anesthetic technique using fentanyl [Myles 2002]. Studies have also shown that remifentanil suppresses the stress response better than fentanyl [von Dossow 2008; Winterhalter 2008].

On the other hand, a remifentanil infusion can be accompanied by hypotension during the time of use and after the termination of the infusion, which could contribute to development of difficult and uncontrolled postoperative pain and shivering [Komatsu 2007]. This hyperdynamic state could lead to hemodynamic deterioration, which serves the development of hypoxemia, contributing to myocardial dysfunction.

Our results revealed no significant differences in cardic index or levels of CKMB and no differences in rates of MI and AF. On this basis we conclude that remifentanil anesthesia has no negative impact on myocardial function compared to low-dose fentanyl anesthesia in cardiac surgery.

We found minor difference in extubation time in the RG compared to the LDFG, but it was not statistically significant. This finding, attributable to comparing remifentanil with low- dose fentanyl anesthesia, is in contrast to that most published studies in which high-dose fentanyl anesthesia was used in similar settings [Myles 2002; Ender 2008; Svircevic 2009].

In our study we hypothesized that the use of remifentanil could have a positive influence on mobilization time after elective cardiac operations. There was no significant difference in this parameter and this allowed us to conclude that fentanyl is as effective as remifentanil in this regard.

In our opinion, successful fast-track procedures in patients undergoing cardiac surgery should include a specially developed protocol for the fast-track technique in the ICU, outlining the precise method for weaning from the remifentanil infusion and at the same time ensuring adequate pain therapy before extubation. Preparedness of the ICU staff to follow such a protocol is an important factor for early extubation, early mobilization, and shorter ICU stays. The presence of these conditions is decisive and probably more important than use of one or another opioid.

We suggest that proper training of the ICU staff is essential to a successful and safe fast-track regime in cardiac anesthesia. Fast-track cardiac anesthesia can be achieved safely and effectively with both remifentanil and low-dose fentanyl anesthesia, but a successful outcome is possible only with the coordinated efforts of anesthetists, surgeons, and the nursing staff.

Limitations

The main limitations of the study were the single institution design and the small numbers of patients. The sample size was underpowered to demonstrate statistical differences between the 2 groups or to assert that remifentanil is not superior to fentanyl.

CONCLUSIONS

Remifentanil fast-track anesthesia for cardiac patients has no negative impact on myocardial function. Remifentanil and low-dose fentanyl are equally effective and safe for fast-track cardiac anesthesia. The study did not highlight any statistical superiority of remifentanil anesthesia over low-dose fentanyl anesthesia.

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