Rev Bras Anestesiol. 2014;64(2):73–78

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Intrathecal sufentanil for coronary artery bypass grafting

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Received 11 May 2012; accepted 11 December 2012
Available online 11 October 2013

KEYWORDS
Cardiac surgery;
Spinal anesthesia;
Sufentanil;
Interleukin 6

Abstract
Context: Cardiac surgery patients undergoing coronary artery bypass grafting with cardiopulmonary bypass.
Objective: Evaluate the effect of adding intrathecal sufentanil to general anesthesia on hemodynamics.
Design: Prospective, randomized, not blinded study, after approval by local ethics in Research Committee.
Setting: Monocentric study performed at Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil.
Patients: 40 consenting patients undergoing elective coronary artery bypass, both genders.
Exclusion criteria: Chronic kidney disease; emergency procedures; reoperations; contraindication to spinal block; left ventricular ejection fraction less than 40%; body mass index above 32 kg/m^2 and use of nitroglycerin.
Interventions: Patients were randomly assigned to receive intrathecal sufentanil 1 μg/kg or not. Anesthesia induced and maintained with sevoflurane and continuous infusion of remifentanil.
Main outcome measures: Hemodynamic variables, blood levels of cardiac troponin I, B-type natriuretic peptide, interleukin-6 and tumor necrosis factor alfa during and after surgery.
Results: Patients in sufentanil group required less inotropic support with dopamine when compared to control group (9.5% vs 58%, $p = 0.001$) and less increases in remifentanil doses (62% vs 100%, $p = 0.004$). Hemodynamic data at eight different time points and biochemical data showed no differences between groups.
Conclusions: Patients receiving intrathecal sufentanil have more hemodynamical stability, as suggested by the reduced inotropic support and fewer adjustments in intravenous opioid doses.

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0104-0014/$ - see front matter
http://dx.doi.org/10.1016/j.bjane.2012.12.004

Introduction

Intrathecal opioids in combination with general anesthesia reduce pain intensity and anesthetics consumption facilitating early removal of the endotracheal tube and improving postoperative analgesia in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). Furthermore, they can decrease surgical stress response and have cardioprotective effects.[1–5] In CABG surgery, prevention of perioperative adverse events, such as tachycardia and myocardial infarction, is advisable. Hemodynamic stability and reduction of stress response contribute, in part, to reduce myocardial damage.[1,6]

Compared to morphine, intrathecal sufentanil provides faster and more intense analgesia.[3,7] In fact, because of morphine's lipid solubility, analgesic effects after intrathecal injection are delayed and only large intrathecal doses (10 mg) may initiate reliable intraoperative analgesia in this setting.[3] Besides that, some authors suggest that intrathecal sufentanil provides better hemodynamic stability when compared to other opiods.[2,8]

The aim of this study was to evaluate, for the first time, the hemodynamic effects of adding intrathecal sufentanil to general anesthesia in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass.

Methods

Ethical approval for this study (protocol number CEP 3458) was provided by the Ethical Committee CEP Istituto Dante Pazzanese of São Paulo, Brasil on 29 August 2006. After written informed consent we enrolled 40 patients scheduled to undergo elective CABG with CPB with two to four grafts, with one graft always being the left internal mammary artery and the others the safena magna vein.

Exclusion criteria were: chronic kidney disease; emergency procedures; reoperations; contraindication to spinal block according to 2002 American Society of Regional Anesthesia Consensus Conference[9]; left ventricular ejection fraction less than 40%; body mass index (BMI) above 32 kg/m^2 and use of nitroglycerin.

Patients were randomly assigned to two different anesthetic protocols (sufentanil group or control group) depending on receiving or not intrathecal sufentanil. A computer generated random table determined in which group patients were allocated. The participants' randomization assignment was concealed in an envelope until the last available moment (start of anesthesia).

Patients received their usual medications until the day of operation, with the exception of oral hypoglycemic agents, which were discontinued and/or replaced by insulin at least three days before surgery. All patients received 7.5 mg of midazolam intramuscularly 1 h before surgery.

Monitoring included continuous electrocardiography of the DII and modified V5, analysis of the ST segment in DII, DI and modified V5 derivations, pulse oximetry, invasive mean blood pressure (MAP) positioned in the radial artery, analysis of the bispectral index (BIS), capnography, blood gas analysis, temperature measurement at the lower third of the esophagus, urinary catheterization, assessment of neuromuscular function with TOF WATCH and evaluation of hemodynamic data made with a pulmonary artery catheter (Swan-Ganz model, continuous output), positioned on the right subclavian vein (monitor Vigilance II®, Edwards Lifesciences, Irvine, CA, USA).

In sufentanil group, after initial monitoring, patients were placed in a sitting position and underwent lumbar puncture in the L3–L4 space with a 25 gauge Whitacre needle. After confirmation of puncture of the subarachnoid space, successful spinal was given to all these patients, 5 mL of saline solution 0.9% containing 1 μg/kg sufentanil (and never more than 100 μg) was injected over a 10 s period. General anesthesia was then initiated.

In control group, general anesthesia was initiated immediately after initial monitoring.

All patients underwent inhalation induction as follows: facial mask with using 2% sevoflurane in 100% oxygen and fresh gas flow of 6 L/min for 30 s. Inspired concentration of sevoflurane was then increased to 7% until loss of consciousness and then reduced to 2%. Next, intravenous infusion of remifentanil began at a dose of 1 μg/kg for 1 min and 0.1 mg/kg pancuronium was administered 3 min before tracheal intubation. Volume-controlled ventilation was started with the following parameters: tidal volume 8–10 mL/kg, respiratory rate adequate to maintain end Tidal CO_2 between 30 and 35 mmHg and fresh gas flow of 2 L with 60% fraction of inspired oxygen mixed with compressed air.

The maintenance of anesthesia in the period before and after CPB was performed with sevoflurane in the expired fraction with variation between 0.5% and 2% to maintain the BIS between 40 and 65. Remifentanil was administered at an infusion rate up to 0.4 μg/kg/min to maintain mean arterial pressure levels between 60 and 80 mmHg. A bolus of 0.02 mg/kg pancuronium was administered when the third response to the sequence of four stimuli appeared in the TOF WATCH monitor until the end of the procedure.

During CPB, anesthesia was maintained with sevoflurane at levels between 0.5% and 2% administered together with a mixture of oxygen and compressed air in the oxygenator circuit through calibrated vaporizer to maintain the BIS value between 40 and 65 and remifentanil up to 0.4 μg/kg/min for control of mean arterial pressure between 45 and 70 mmHg.

Upon completion of the surgical procedure, all patients received a continuous intravenous infusion of 2 μg/kg/min propofol as a sedative and were transferred to the ICU, where they remained sedated for a 1-h period. The analgesia protocol was initiated within the first 24 h with a single intravenous dose of 1 μg/kg fentanyl together with 1 g of dypirone. The same dose of dypirone was repeated every 6 h.

After tracheal extubation, patient control analgesia (venous PCA) with a Vigon® PCA pump was then installed with the following parameters: bolus only mode, 1 mg bolus and a fixed 7-min lockout interval. During this period, if there was significant pain (VAS > 7), 100 mg of tramadol was administered intravenously. Discharge from the ICU and hospital were followed by local protocols.

Hemodynamic goals during anesthesia were maintenance of central venous pressure (CVP) and pulmonary capillary wedge pressure (PCP) between 8 and 12 mmHg with administration of crystalloids and colloids and maintenance of mean arterial pressure (MAP) between 60 and 80 mmHg.

Hypotension was defined as a MAP < 60 mmHg (<45 mmHg during CPB), for more than 30 s. Hypertension was defined as MAP > 80 mmHg (>70 mmHg during CPB), for more than 30 s.

Management of hypotension included phenylephrine 0.1 mg bolus (when anesthetic agents were at minimum levels, could be repeated every minute), dopamine (when anesthetic agents were at minimum levels, filling pressures were high and when CI was less than 2.4 L/m^2/min) at a dose of 5 μg/kg/min with increments of 1 μg/kg/min until the desired MAP level was reached, norepinephrine (when the CI remained below 2.4 L/m^2/min at dopamine doses of 10 μg/kg/min) at a dose of 0.1 μg/kg/min, with increments of 0.1 μg/kg/min until the desired MAP level was reached. Dopamine use, as a primary endpoint, was strictly regulated by protocols, such as documented low CI (less than 2.4 L/m^2/min), high CVP or PCWP.

Hypertension management included remifentanil (bolus 0.5 μg/kg followed by an infusion dose increase of 0.1 μg/kg/min with the sequence repeated every minute till a maximum infusion rate dose of 0.4 μg/kg/min), followed by sodium nitroprusside (0.5 μg/kg/min and increased by 0.5 μg/kg/min increments until the maximum dose of 2 μg/kg/min was reached). Sevoflurane was used when the BIS value exceeded 65. The inspired sevoflurane concentration was increased to 4% and fresh gas flow to 6 L/min for 1 min while the fresh gas flow was returned to 2 L/min and the sevoflurane concentration was reduced to 2%. If the BIS did not return to pre-established levels, the procedure was repeated and in the absence of a response, a dose of 0.05 mg/kg midazolam was administered.

Clamping of the aorta (maximum duration 15 min with an interval of at least 2 min) was performed in mild hypothermia (34 °C). Saline solution was used to fill the membrane oxygenator (Vital® – Nipro, Brazil).

All data were collected by trained observers who were not blinded to the anesthetic regimen used.

Blood tests included cardiac troponin I (cTnI), measured using an immunoassay method (CMIA – Architect®; Abbott Laboratories, Brazil, – the normal range being 0–0.3 ng/mL), B-type natriuretic peptide (BNP), measured using an immunoassay method (MEIA – AxSIM® system; Abbott Laboratories, Brazil – with values of 1400 pg/mL for patients with NYHA functional class I and 3400 pg/mL for those with functional class II being considered normal limits), interleukin 6 (IL-6) and tumor necrosis factor α (TNFα) measured using an immunometric assay method by the IMMULITE® system – Siemens Medical, USA – the normal range being <3.4 pg/mL for IL 6 and <8.1 pg/mL for TNFα. All blood tests were measured at baseline while BNP and cTnI were measured 24 h after CPB and IL-6 and TNFα 10 min after anesthesia induction, 15 min, 6 h, 24 h after CPB and 4 days postoperatively.

On the basis of previous personal data we anticipated that the amount of patients needing inotropic support with dopamine would have been 10% and 50% in sufentanil and control group, respectively. We calculated that we would need a sample size of 20 patients per group. All patients were analyzed according to the intention-to-treat principles, beginning immediately after randomization.

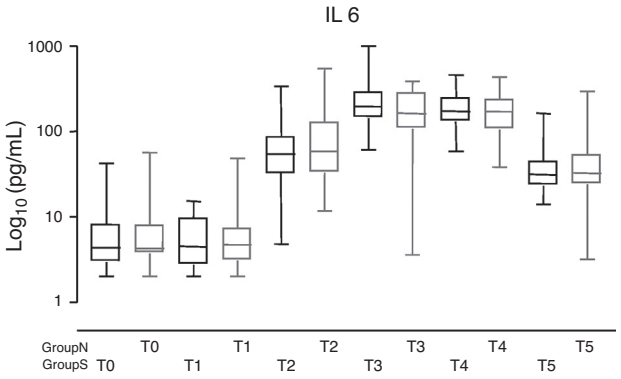

Figure 1 Blood levels of interleukin 6 (IL-6).

Statistical analysis

Data were expressed as number (percentage), mean ± standard deviation, or median (interquartile range). Student's *t*-test, Fisher's exact test, Pearson's chi-squared analysis and Mann–Whitney nonparametric test were used when appropriate using the Statistical Package for the Social Sciences software (SPSS). ANOVA analysis was used for repeated measures continuous data, such as biochemical markers.

Results

Preoperative data were well balanced between sufentanil and control group (Table 1). Patients in sufentanil group required less inotropic support with dopamine at weaning from CPB and after CPB when compared to control group (9.5% vs 58% $p = 0.001$) and less increases in remifentanil use (62% vs 100% $p = 0.004$) as showed in Table 2.

Cardiac troponin I was detectable in all patients postoperatively, with no differences between groups: 1.62 (0.80–5.59) ng/mL in sufentanil group vs 1.68 (0.73–3.53) ng/mL in control group ($p = 0.506$). Similarly, BNP was detectable in all patients postoperatively, with no differences between groups ($p = 0.667$). BNP increased from 36.13 (21.70–73.79) pg/mL preoperatively to 207.58 (89.95–236.77) pg/mL postoperatively in sufentanil group vs 39.15 (25.77–54.88) pg/mL to 188.97 (84.31–247.96) pg/mL in control group. Blood levels of IL-6 (Fig. 1) and TNFα (Fig. 2) were similar between groups.

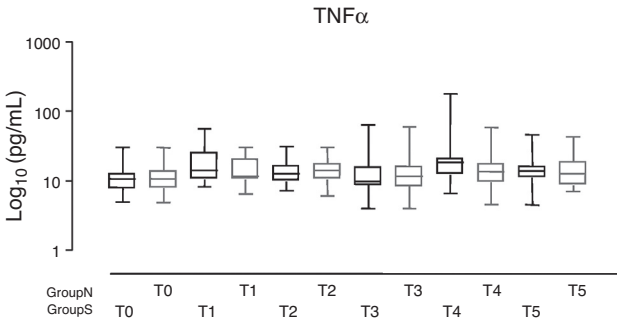

Figure 2 Blood levels of tumor necrosis factor α (TNFα).

Table 1 Patients' characteristics and surgical times. Data are expressed as number and percentages or as mean ± standard deviations.

	Control group $n = 19$	Sufentanil group $n = 21$
Preoperative data		
Female gender	6 (32%)	7 (33%)
Age (years)	56 ± 7.2	58 ± 6.7
Body mass index (kg/m)	26 ± 3.9	27 ± 2.5
ASA II	19 (100%)	20 (95%)
ASA III	0	1 (4.8%)
NYHA I	7 (37%)	9 (43%)
NYHA II	12 (63%)	12 (57%)
Diabetes Mellitus	6 (32%)	9 (43%)
Hypertension	15 (79%)	19 (90%)
Dyslipidemia	11 (58%)	16 (76%)
Smoking	5 (26%)	10 (48%)
Previous myocardial infarction	5 (26%)	6 (28%)
Intra-operative data		
Duration of anesthesia (min)	299 ± 57	292 ± 39.4
Duration of surgery (min)	235 ± 51.7	223 ± 35.5
Duration of ischemia (min)	52 ± 14.9	50 ± 15.0
Duration of perfusion (min)	74 ± 23.0	69 ± 20.0

Hemodynamic data at eight different time points (supplemental material I online) showed no differences between groups with exception of minor difference after CPB.

No episodes of awareness were detected in this study.

Table 3 shows similar consumption of analgesics during the first 24 postoperative hours between groups.

Time on mechanical ventilation was 300 (212–450) vs 255 (230–315) min in control and sufentanil group respectively ($p = 0.4$), while ICU stay was 2.7 + 0.89 vs 3.9 + 3.75 days ($p = 0.2$) and hospital stay was 8.9 + 6.98 vs 9.1 + 6.1 days, respectively.

Table 4 shows that there was no difference in postoperative complications except for the need for blood transfusion, which was significantly higher in control group (4 patients, 21%) vs sufentanil group (no patient), $p = 0.042$.

One patient in sufentanil group died on the fifth postoperative day because of a computed tomography documented stroke that occurred on the third postoperative day.

Discussion

The main result of this study is that patients in sufentanil group had more hemodynamic stability as suggested by reduced inotropic support and few adjustments in intravenous opioid doses.

Our study also confirms that neuraxial techniques produce effective analgesia in patients undergoing cardiac surgery as demonstrated by a reduced consumption of intravenous remifentanil in patients of sufentanil group.

On the contrary, no difference was noted in inflammatory markers (IL6 and TNFα) and in cardiac biomarkers (cTnI and BNP). Their release pattern (cTnI, IL6 and TNFα) along time was the same as observed by Meng et al.,[10] confirming that in both groups inflammatory response due to elevation in IL6 and TNFα was not attenuated and, no cardiac protection due to reduction in cTnI and BNP occurred.

Table 2 Drugs used in the intra-operative period. Data are presented as number (percentages) or mean ± standard deviation.

	Control group $n = 19$	Sufentanil group $n = 21$	p
Vasoactive drugs			
Dopamine	11 (58%)	2 (9.5%)	0.001
Phenylephrine	12 (63%)	9 (43%)	0.2
Sodium nitroprusside	17 (89%)	19 (90%)	0.9
Anesthetic agents			
Sevoflurane increases	0	3 (14%)	0.2
Remifentanil bolus	19 (100%)	13 (62%)	0.004
Sevoflurane (mL/h)	14 ± 2.4	14 ± 2.5	0.8
Remifentanil (μg/kg/min)	0.20 ± 0.05	0.05 + 0.04	<0.001

Table 3 Postoperative data. Data are expressed as number (percentage), median ± standard deviation or median (interquartile range).

Variables	Control group $n = 19$	Sufentanil group $n = 21$	p-Value
Tramadol within 24 h, no. of patients	13 (68%)	18 (86%)	0.3
Bolus of morphine, number of boluses per patient	1.5 ± 1.26	1.2 ± 0.98	0.5
PCA morphine consumption 24 h, mg per patient	8.0 ± 3.15	7.6 ± 3.25	0.8

Abbreviation: PCA, patient controlled analgesia.

Our study could only be compared to that of Bettex and colleagues[4] who performed the only randomized study administering or not intrathecal sufentanil in cardiac surgery, although they added morphine to sufentanil intrathecal. Their postoperative results showed that combined sufentanil and morphine allowed a shorter postoperative duration of intubation and adequate analgesia compared with a standard intravenous technique, which differs from ours, that showed no difference on these results.

In a non-randomized study, Swenson and colleagues[2] found that the combination of 50 μg intrathecal sufentanil and 500 μg intrathecal morphine in general anesthesia in patients undergoing CABG promoted greater intraoperative hemodynamic stability and reduced the intraoperative consumption of intravenous opioids. In our study, although we did not use morphine, we noted that the use of intrathecal sufentanil reduced intraoperative consumption of intravenous opioids.

Hansdottir and colleagues[11] performed the first study about plasma and cerebral spinal fluid pharmacokinetics of sufentanil administered intrathecal in thoracic surgery. In their experience, they concluded that in patients undergoing thoracotomy, administration of 15 μg of intrathecal sufentanil in combination with general anesthesia produced a more potent analgesic effect with a faster onset of action and a shorter duration compared to equipotent doses of morphine or meperidine. This was attributed to the high lipid solubility of sufentanil when present in the cerebrospinal fluid and to a fast transfer to the plasma. However, the same author showed that the cerebrospinal fluid (CSF) and plasma concentrations of sufentanil did not reach equilibrium even 10 h after initial injection. In fact, 10 h after initial injection, the CSF concentration was still 10 times higher than plasmatic one. This study clarified that the principal analgesic effect of sufentanil administered in subarachnoid space is via local rather than systemic absorption.

There are several factors that may determine the occurrence of pain, including an increase in time required to extubation and the occurrence of adverse events that result in deteriorations in ventricular function during postoperative period immediately after cardiac surgery.[12,13] Postoperative pain relief following cardiac surgery is difficult to control. In our study, there were no statistically significant differences between groups with respect to total consumption of analgesics over a 24-h period after extubation. These results demonstrated that the proposed scheme of a single high dose of intrathecal sufentanil was not sufficient to promote adequate analgesia over the initial 24-h period following removal of orotracheal cannula.

Hansdottir and colleagues[11] also showed that, although sufentanil is more lipophilic and is eliminated more quickly from cerebrospinal fluid than other opioids such as morphine, when 15 μg doses of sufentanil were injected into the subarachnoid space, the concentration of opioid in cerebrospinal fluid remained at residual concentrations 15 ± 5 times higher than in plasma for up to 10 h (600 min) following the injection. Fournier and colleagues,[14] in a study where patients underwent surgery for total hip replacement, concluded that a single 7.5 μg dose of intrathecal sufentanil was sufficient to reduce pain intensity and maintain the VAS value below 3 for a period of 224 ± 100 min. In our study, doses of intrathecal sufentanil administered were up to seven times higher than those proposed by Hansdottir and

Table 4 Postoperative complications. Data are expressed as number (percentages).

Variables	Control $n = 19$	Sufentanil $n = 21$	p-Value
Reoperation	1 (5.3%)	0	0.5
Re-intubation	0	1 (4.8%)	0.9
Major Arrhythmias	2 (11%)	0	0.2
Peri-operative awareness	0	0	–
Nausea and/or vomiting	5 (26%)	1 (4.8%)	0.085
Pruritus	0	0	–
Death	0	1 (4.8%)	0.9
Need for blood transfusion	4 (21%)	0	0.042

14 times higher than those proposed by Fournier but still had effect only in perioperative period and not in postoperative pain control.

Increased need for packed cells in control group was an unexpected finding and authors cannot find a physiopathological hypothesis to justify it (it is probably an effect of the small sample size).

In our institution, we considered inhalation induction for cardiac surgery because it is easy to perform even in adult patients and it has better hemodynamic stability compared to some intravenous agents, as described by other authors.[15,16]

The spinal dose of 1 μg/kg, limited to 100 μg, is used in our institution because we agree with authors that conclude the main action of sufentanil is in the spinal cord,[11] and so, doses related to weight or height would guarantee greater CSF dispersion in patients with more weight or height, resulting in higher levels of analgesia and hence better control of stimuli from the high thoracic incision, different from Swenson and Bettex,[2,4] that describe a single intrathecal dose of 50 μg of sufentanil for cardiac surgery.

Limitations of the study

The study was not blinded to use of intrathecal sufentanil. Nonetheless, all protocols included in the study were followed rigorously.

Conclusion

The main result of this study is that patients receiving intrathecal sufentanil have more hemodynamic stability when compared to those receiving a standard treatment, as suggested by reduced inotropic support (dopamine support at weaning from CPB and during the perioperative period to maintain hemodynamic values) and few adjustments in intravenous opioid doses.

Funding

This work was supported by Dante Pazzanese Institute of Cardiology and Federal University of São Paulo (UNIFESP).

Conflicts of interest

The authors have no conflicts of interest to declare.

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