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Remifentanil versus sufentanil regimen for intensive care unit (ICU) postoperative sedation after coronary artery bypass graft surgery: a prospective, randomised and double-blinded study

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Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title

Study objectives
The anaesthetic regimen used during and immediately after coronary artery bypass graft (CABG) surgery is important as it could influence the function of major organ systems, minimise the risks of myocardial ischaemia and hence have direct and indirect implications on the early postoperative evolution of patients admitted to the intensive care unit (ICU). Remifentanil hydrochloride is a potent selective μ opioid receptor agonist characterised by a rapid onset and highly predictable offset of action (context-sensitive half-time of 3 to 6 minutes). In contrast to other opioids it does not accumulate, even after prolonged infusion or high administrated doses and its clearance is unaffected by hepatic or renal dysfunctions. Although its pharmacokinetics properties could be advantageous for postoperative balanced anaesthesia, without compromising early patient extubation, its withdrawal requires a specific strategy for postoperative pain management. Thereby, remifentanil is still not regularly used in the ICU and particularly in the postoperative period of cardiac surgery. The aim of this study was to compare remifentanil combined with propofol to conventional sufentanil-based anaesthesia (sufentanil stopped at the end of the surgery), during the postoperative period of an elective cardio-pulmonary bypass graft surgery with extra corporeal circulation. The haemodynamic effects as well as the influence on early postoperative pain relief and the repercussions on the patients' respiratory status were analysed. We also compared the duration of recovery from anaesthesia and the time for eligible and actual tracheal extubation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee for Biomedical Research (Commission dEthique Biomédicale Hospitalo-Facultaire), Catholic University of Louvain (Université Catholique de Louvain), Faculty of Medicine. Date of approval: 01/03/2005 (ref: 2005/11FEV/23)

Study design
Prospective, randomised, double-blind, single-centre trial

Primary study design
Interventional

Study type(s)
Not Specified

Health condition(s) or problem(s) studied
Postoperative sedation of an elective coronary artery bypass graft surgery (CABG)

Interventions
After approval by our ethics committee and written consent obtained the day before surgery, forty patients scheduled for elective CABG with CBP were randomised, using a closed-envelope system, to receive either remifentanil (R group, n = 20) or sufentanil (S group, n = 20) as part of a totally intravenous anaesthesia regimen with propofol.

Chronic preoperative medications were continued until surgery except for platelet inhibitors. All patients received intramuscular morphine chlorydrate (0.1 - 0.15 mg/kg) and scopolamine (0.25 mg) before surgery as premedication.

Standard monitoring for cardiac surgery was used and included a CCO/SvO2 pulmonary artery catheter (Edwards Lifesciences, USA) and a bispectral (BIS) monitoring (Aspect Medical Systems, USA) to control the depth of anaesthesia.

A radial artery catheter was placed before induction of anaesthesia. Induction sequence was similar in both groups, with intravenous administration of ketamine (0.5 mg/kg), midazolam (0.05 mg/kg), sufentanil (0.5 mcg/kg) and rocuronium (1.2 mg/kg). Anaesthesia was maintained by Target Controlled Infusion (TCI) of propofol 2% (Asena PK®, Alaris medical systems, USA) adjusted to a plasma concentration of 1 - 2 mcg/ml, in order to maintain the BIS index between 45-60. Intraoperative analgesia was provided in the R group by a TCI (Asena PK®, Alaris medical systems) of remifentanil (50 mcg/ml) adjusted to a target plasma concentration of 4 ng/ml, and in S group, by continuous infusion of sufentanil (50 mcg/ml) started at 0,5 mcg/kg/h. During surgery the adaptation of doses, depending on the haemodynamic responses to surgical stress, was left to the discretion of the anaesthetist in charge of the patient.

Standard institutional methods were used for normothermic (36°C) CBP and myocardial protection. At the end of surgery, the propofol infusion was maintained in both groups. The TCI of remifentanil was maintained at a target concentration of 4 ng/ml in the R group while the sufentanil was stopped in the S group. In order to blind the ICU team to the group assignment, the anaesthetist in charge of the patient prepared 40 ml syringes labelled "substance X" containing either remifentanil (50 mcg/ml) for R group or normal saline solution for S group. He also prepared another 20 ml syringe labelled "substance Y" for the postoperative relay of analgesia containing piritramide (0.20 mg/kg) for patients in R group, and normal saline for S group. These syringes accompanied the patient to the ICU.
The time of the patient's arrival to the ICU was defined as H0. From H0 to H4, all patients were maintained intubated and sedated by continuous administration of propofol 2% and TCI of "substance X" (remifentanil or NaCl 0.9% according to the allocated group). In both groups, the target concentration of substance X was set to 4 ng/ml, whereas propofol infusion was adapted to maintain the bispectral index between 60 and 70. During this period, patients were mechanically ventilated in a pressure-controlled mode (Servo-i Maquett Critical Care, Sweden) with a rate of 10 inflations/min and tidal volume of 8 ml/kg. Arbitrarily, the positive-end expiratory pressure (PEEP) was set at 5 cmH2O and the inspired fraction of oxygen (FiO2) was adjusted to maintain pulse oxygen saturation (SpO2) above 95%. Minute-volume was adjusted to maintain an arterial pH between 7.35 and 7.45 and arterial carbon dioxide tension (PaCO2) between 35 and 45 mmHg.

The weaning of anaesthesia was as follow: at H3, analgesic treatment including paracetamol (1 g), tramadol (100 mg) and "substance Y" (20 ml piritramide in R group or saline solution in S group) was slowly administered.

At H4, if all the criteria for weaning were present (temperature >36.5 °C, no sign of haemodynamic impairment, chest tube output <50 ml/h, adequate respiratory exchanges with arterial oxygen tension (PaO2) >=80 mmHg with FiO2 <40%, PaCO2 <=45 mmHg with pH >7.35, urine output >0.5 ml/kg/h), both propofol and "substance X" were stopped.

Pressure support ventilation was started immediately at patient's awakening. When all the weaning criteria were fulfilled (patient responding adequately to verbal commands, no major organ dysfunction), a T-piece trial was performed during a few minutes. During this period, pain evaluation was assessed by Visual Analogue Scale (VAS) ranging from 0: no pain to 100: worst imaginable pain. Pain relief was achieved with repeated intravenous administrations of piritramide (1 mg/1 mg), until VAS became less than 30 for all patients. Then, if the SpO2 could

be maintained above 95% and if the respiratory rate was between 12 and 20/min, patients were extubated.

From extubation to the discharge from the ICU, every patient received nasal oxygen guided by SpO2 and arterial blood gas measurements. Hypoxemia and/or respiratory acidosis was treated with non-invasive ventilation (VNI) and if necessary with invasive ventilation.

After extubation, all patients received a continuous intravenous infusion of tramadol (400 mg) during 24 hours, associated with regular administration of paracetamol (1 g every 6 hours). Patient controlled analgesia (PCA) with piritramide provided additional analgesia during 72 hours (concentration of 2 mg/ml, bolus of 1mg, minimal interval of 5 minutes and maximum cumulative dose of 25 mg/4 h).

During the sedation period, hypotension (mean AP <65 mmHg) and/or inadequate cardiac output for tissue perfusion (CI <2.5 l/min/m2, SvO2 <65%, arterial lactates >1.5 mM/l, urine output <0.5 ml/kg/h) required a decrease in propofol if the BIS level was lower than 60 and fluid loading was administered if filling was inadequate (CVP <12 mmHg and PCWP <15 mmHg). If these measures were insufficient, atrial pacing was initiated at a rate of 90 to 100/min if the intrinsic rate was lower. Continuous intravenous administration of noradrenaline or dobutamine was initiated if hypotension persisted and if CI was respectively higher or lower than 2.5 l/min /m^2.

Hypertension (mean AP >80 mmHg) required an increase of propofol doses if the BIS level was higher than 70 and if necessary, was treated by afterload reduction with intravenous nicardipine chlorhydrate.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Remifentanil, sufentanil

Primary outcome(s)
We analysed the effects of these two anaesthetic regimens, used in order to maintain the same depth of anaesthesia, during the early postoperative period:
1. Haemodynamic effects: Standard monitoring was used and included a CCO/SvO2 pulmonary artery catheter (Edwards Lifesciences, USA)
2. The following haemodynamic parameters were recorded every 30 minutes from H0 to H4 (duration of the sedation), then hourly until H8 and finally every 2 hours for the next 16 hours:
2.1. Heart rate (HR)
2.2. Invasive mean arterial pressure (mean AP)
2.3. Central venous pressure (CVP)
2.4. Mean pulmonary arterial pressure (mean PAP)
2.5. Pulmonary capillary wedge pressure (PCWP)
2.6. Continuous cardiac output (CCO)
2.7. Cardiac index (CI)
2.8. Mixed venous oxygen saturation (SvO2)
3. Biochemical markers of myocardial damage including troponine I and CPK-MB were analysed

before surgery, and repeated at H0, H3, H8, H16 and H30
4. Respiratory effects: Arterial blood gases evaluated respiratory state, every 4 hours from H0 to 24 hours after extubation
5. Pain management: Pain evaluation was assessed by VAS ranging from 0: no pain to 100: worst imaginable pain. Each evaluation was performed at rest and just after deep inspiration (stress test). Use of VAS score and PCA recording of piritramide requirements evaluated the efficacy of pain control.

Key secondary outcome(s))
1. Duration of non-invasive ventilation (VNI)
2. Duration of patient's recovery from anaesthesia
3. Time to eligible and actual tracheal extubation

Completion date
01/09/2006

Eligibility

Key inclusion criteria
1. Both males and females, age >18 years
2. Patients scheduled for elective CABG with cardiopulmonary bypass (CBP)
3. Signed informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Simultaneous valve surgery or any other combined surgery
2. Poor preoperative cardiac function (ejection fraction <30%, severe congestive heart failure)
3. Liver or renal disorders
4. Chronic respiratory diseases
5. Alcohol or drugs abuse and neurological or psychiatric conditions that might impair pain evaluation

Postoperative exclusion criteria:
6. Situations where the administration of the anaesthetic regimen was maintained after the fourth postoperative hour

Date of first enrolment
26/09/2005

Date of final enrolment
01/09/2006

Locations

Countries of recruitment
Belgium

Study participating centre
Cliniques Universitaires Saint-Luc, 10
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Sponsor information

Organisation
Saint Luc University Clinic (Cliniques Universitaires Saint Luc) (Belgium)

ROR
https://ror.org/03s4khd80

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Saint Luc University Clinic (Cliniques Universitaires Saint Luc) (Belgium)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration