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Cardiovascular

Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial†

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Abstract

Background: Off-pump coronary artery bypass (OPCAB) surgery carries a high risk for haemodynamic instability and perioperative organ injury. Favourable haemodynamic effects and organ-protective properties could render xenon an attractive anaesthetic for OPCAB surgery. The primary aim of this study was to assess whether xenon anaesthesia for OPCAB surgery is non-inferior to sevoflurane anaesthesia with regard to intraoperative vasopressor requirements.

Methods: Forty-two patients undergoing elective OPCAB surgery were enrolled in this prospective, single-blind, randomized controlled pilot trial. Patients were randomized to either xenon (50–60 vol%) or sevoflurane (1.1–1.4 vol%) anaesthesia. Primary outcome was intraoperative noradrenaline requirements necessary to achieve predefined haemodynamic goals. Secondary outcomes included safety variables such as the occurrence of adverse events (intraoperatively and during a 6-month follow-up after surgery) and the perioperative cardiorespiratory and inflammatory profile.

Results: Baseline and intraoperative data did not differ between groups. Xenon was non-inferior to sevoflurane, as xenon patients required significantly less noradrenaline intraoperatively to achieve the predefined haemodynamic goals {geometric mean 428 [95% confidence interval (CI) 312, 588] *vs* 1702 [1267, 2285] µg, $P<0.0001$}. No differences were found for safety. Significantly more sevoflurane patients developed postoperative delirium (POD) (hazard ratio 4.2, $P=0.044$). The average arterial pressure was lower in the sevoflurane group {median75 [interquartile range (IQR) 6] *vs* 72 [4] mmHg, $P=0.002$}. No differences were found for other haemodynamic parameters, the respiratory profile and the perioperative release of inflammatory cytokines, troponin T, serum protein S-100β and erythropoietin.

Conclusions: Compared with sevoflurane, xenon anaesthesia allows a significant reduction in vasopressor administration in OPCAB surgery. Moreover, xenon anaesthesia was associated with a lower risk for POD, a finding that has to be confirmed in larger studies.

Clinical trial registration: ClinicalTrials.gov (NCT01757106) and EudraCT (2012-002316-12).

Key words: noradrenaline dose; OPCAB; postoperative delirium; sevoflurane anaesthesia; xenon anaesthesia

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Editor's key points

- The noble gas xenon is an anaesthetic agent with a favourable haemodynamic profile.
- The authors performed a non-inferiority study comparing xenon with sevoflurane anaesthesia among cardiac surgery patients.
- Non-inferiority was demonstrated with regard to vasopressor requirements.
- Xenon was associated with lower vasopressor requirements and also less postoperative delirium.

In non-cardiac surgery, the noble gas xenon has been reported to produce only minimal haemodynamic side effects when compared with other anaesthetics, even in high-risk cardiovascular patients.[1 2] These observations were confirmed by multicentre randomized controlled trials in which xenon was compared with isoflurane and was found to slightly decrease heart rate and to preserve or moderately increase arterial pressures.[3 4] Such haemodynamic effects may result in an overall improvement of the balance between myocardial oxygen delivery and consumption. Moreover, xenon is virtually devoid of negative inotropic effects,[5] preserves myocardial blood flow,[6] improves recovery from post-ischaemic contractile dysfunction,[7] and limits adverse remodelling after perioperative myocardial infarction.[8] As the course of off-pump coronary artery bypass (OPCAB) surgery entails significant haemodynamic alterations, OPCAB patients carry a high-risk for perioperative myocardial ischaemia and perioperative haemodynamic instability.[9] This contributes to the development of perioperative organ injury, including myocardial infarction, stroke, and acute kidney injury.[10 11] The favourable haemodynamic profile of xenon anaesthesia and its organ-protective properties could render xenon an attractive option for patients undergoing OPCAB surgery. Until now, experience with xenon in cardiac anaesthesia has been limited and was obtained in surgical procedures using cardiopulmonary bypass.[12 13] To the best of our knowledge, the present investigation is the first clinical study of xenon in patients undergoing OPCAB surgery. We hypothesized that xenon anaesthesia during OPCAB surgery is non-inferior to sevoflurane in terms of haemodynamic stability (as reflected by vasopressor requirements). Secondary aims of the study included the assessment of various perioperative safety parameters.

Methods

Study design and population

The study was approved by the local ethics committee (s54450, Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven) and by the Federal Agency for Medicines and Health Products, Brussels, Belgium (reference FAGG/R&D/WHH/mm 445642). It was registered at ClinicalTrials.gov (NCT01757106), the European Medicines Agency (EudraCT 2012-002316-12) and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see Supplementary material, supplementary document).[14] After obtaining written informed consent, 42 patients scheduled for elective OPCAB surgery were enrolled in this prospective, single-centre, randomized, single-blinded, controlled pilot study. Patients were randomized to receive general anaesthesia with xenon or sevoflurane. Randomization was performed using a software-generated allocation sequence. Selection bias was avoided by a masked randomization procedure using sealed, opaque, sequentially numbered envelopes that were opened only upon arrival of the patient in the operating room (OR). Two investigator types conducted the study: investigator I completed patient enrolment and postoperative follow-ups and was, like the patient, blinded to the study group.[15] Investigator II performed randomization and general anaesthesia for OPCAB surgery and could not be blinded due to the administration of the anaesthetic via a dedicated anaesthesia machine and the mandatory monitoring of anaesthetic concentrations. Patients could be included if they were >18 years of age and scheduled for elective OPCAB surgery. Exclusion criteria were as follows: lack of informed consent; chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage >II; renal dysfunction, defined as serum creatinine >1.5 mg dl^{-1}; acute coronary syndrome during the last 24 h; left ventricular ejection fraction ≤30%; haemodynamic instability with preoperative requirement of inotropic support; single-vessel grafting; low preoperative cognitive state [mini-mental state examination (MMSE) at baseline <25][16]; delirium [as assessed by the Confusion Assessment Method (CAM)][17]; depression (as assessed by the Geriatric Depression Scale)[18]; history of stroke with residuals; hypersensitivity to the study medication; patients at risk for malignant hyperthermia; uncooperativeness or legal incapacity.

Anaesthesia and intervention

Patients received perioperative care according to our institutional routine.[19] All patients were premedicated with sublingual lorazepam 0.03 mg kg^{-1} an hour before surgery. In the OR, standard cardiorespiratory monitoring was instituted, including electrocardiogram pulse oximeter and invasive registration of arterial blood pressure (IntelliVue MX800 patient monitor, Philips, Boeblingen, Germany). In addition, the bispectral index (BIS) (Covidien, Dublin, Ireland) and regional cerebral oxygen saturation (rSO_2) (FORE-SIGHT®, Casmed, Branford, CT, USA) were continuously recorded. General anaesthesia was induced with propofol (0.5–1 mg kg^{-1}) and sufentanil (0.25–0.5 μg kg^{-1}). Tracheal intubation was facilitated by rocuronium (1 mg kg^{-1}). In both groups, intraoperative analgesia was achieved with a sufentanil infusion (0.5–1 μg kg^{-1} h^{-1}). Subsequently the randomization envelope was opened and general anaesthesia was maintained with either

xenon 50–60% in oxygen [fraction of inspired oxygen (FI_{O_2} = 0.3–0.4)] or

sevoflurane 1.0–1.4% in oxygen and medical air (FI_{O_2} = 0.3–0.4).

Anaesthetics were administered with a closed circuit respirator (Felix Dual™, AirLiquide Medical Systems, Paris, France) in the automatic mode.[20] In both groups, anaesthetic depth was assessed by surveillance of vegetative signs and continuous BIS monitoring. In addition, anaesthetic concentration was titrated to obtain a BIS value between 40 and 60. Tidal volume and FI_{O_2} were adjusted to maintain normocapnia and arterial oxygen saturation >95%.

After induction of anaesthesia, a central venous catheter and a pulmonary artery catheter were inserted to continuously measure central venous pressure, cardiac output, and mixed venous oxygen saturation (Sv_{O_2}).

All cardiorespiratory parameters were continuously documented throughout the procedure (ICM+® software, Cambridge Enterprise, University of Cambridge, Cambridge, UK). In addition, a complete cardiopulmonary profile [including the measurement of pulmonary capillary wedge pressure (PCWP) and arterial and mixed venous blood gas analyses] was obtained at the following