British Journal of Anaesthesia 112 (2): 272–80 (2014)
Advance Access publication 16 October 2013 · doi:10.1093/bja/aet330

BJA

CLINICAL PRACTICE

Comparison of the effects of xenon and sevoflurane anaesthesia on leucocyte function in surgical patients: a randomized trial†

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Editor's key points

- While volatile anaesthetics generally have anti-inflammatory effects, the immune effects of xenon are controversial.
- In healthy subjects undergoing elective surgery, the immune effects of xenon or sevoflurane were compared.
- Xenon and sevoflurane had similar effects on immune function providing small anti-inflammatory, and no pro-inflammatory, effects.

Background. While most anaesthetics are known to suppress immune reactions, data from experimental studies indicate the enhancement of reactivity to inflammatory stimulators under xenon treatment. We investigated the effect of xenon anaesthesia on leucocyte function in surgical patients.

Methods. We performed a subgroup analysis of subjects undergoing xenon or sevoflurane anaesthesia in a randomized clinical trial. After oral premedication with midazolam, two separate blood samples were obtained from subjects undergoing elective abdominal surgery, directly before and 1 h after induction of anaesthesia. General anaesthesia was maintained with either 60% xenon or 2.0% sevoflurane in 30% O_2. Leucocyte count, phagocytotic function, and pro-inflammatory cytokine release after *ex vivo* lipopolysaccharide (LPS) stimulation were determined.

Results. Except for lymphocyte numbers, leucocyte subpopulations did not differ between the groups. Phagocytosis and oxidative burst of granulocytes were reduced in both groups after 1 h of anaesthesia, whereas monocytes were not affected. Pro-inflammatory cytokine release in response to LPS was not affected.

Conclusions. *In vivo*, xenon and sevoflurane anaesthesia did not have a pro-inflammatory effect, at least in combination with the types of surgery performed in this study. Notably, the impact of xenon anaesthesia did not differ significantly from sevoflurane anaesthesia with regard to leucocyte function. However, an underestimation of treatment effects due to limited sample sizes cannot be fully excluded.

Clinical trial registration. EudraCT 2008-004132-20.

Keywords: anaesthetics, inhalation; leucocytes; sevoflurane; xenon

Accepted for publication: 29 July 2013

Surgery is a stressor for the human body, resulting in a major activation of the immune system that involves cytokine release, activation of complement cascades, and mobilization of leucocytes.[1 2] The role of anaesthesia in this context has not been fully elucidated: different study results range from no effect to modulation of inflammatory activation.[1 3 4] The impact of anaesthesia on immune function differed between the anaesthetics used. In particular, volatile anaesthetics such as sevoflurane appear to mitigate pro-inflammatory stimuli such as surgery, extracorporeal circulation, or trauma, thereby potentially exerting protective effects.[5] There is additional evidence about anti-inflammatory effects from several *in vivo* and *in vitro* models.[6–8]

The noble gas xenon is an anaesthetic with many advantageous properties,[9] for example, its haemodynamic stability[10–12] and its neuroprotective effects.[13] While other volatile anaesthetics seem to suppress immune reactions, data from experimental xenon studies are controversial: xenon treatment alone and in combination with extracorporeal membranes did not enhance inflammatory mediators *in vitro*,[14 15] whereas other studies indicated the enhancement of reactivity to the inflammatory stimulus bacterial lipopolysaccharide (LPS).[15 16] The impact of these findings on general anaesthesia in humans has not yet been examined.

The aim of this study was to investigate a potential pro-inflammatory effect of xenon anaesthesia on leucocyte

† This article is accompanied by Editorial III.

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function in patients and compare it with sevoflurane anaesthesia, which has been shown to exert a predominantly anti-inflammatory potential. As a further stimulus of inflammation *ex vivo*, we used LPS, because *in vitro* studies showed an enhancement of immune reactivity under xenon treatment, whereas it was attenuated by sevoflurane.[8 15 16]

Methods

Study design

We studied blood samples from 60 subjects allocated to receive xenon or sevoflurane anaesthesia for elective abdominal surgery in a randomized, controlled, double-blind clinical trial (EudraCT No.: 2008-004132-20; NCT No.: 00793663 at http://clinicaltrials.gov). The study was designed as a subgroup analysis by amendment to the above-named randomized controlled trial and approved by the local clinical ethical review committee and the German authority for supervision and approval of pharmaceuticals (BfArM). Subjects did not receive any other study intervention than the above-mentioned anaesthesia before blood sampling took place.

Subjects

Subjects were enrolled between October 2010 and March 2011. All patients undergoing elective abdominal surgery (gynaecological, urological, or middle-sized general surgery, conducted either open or laparoscopic) with a planned duration $\geq$60 min and a planned admission to the ward after post-anaesthesia care unit stay were screened. Exclusion criteria were: severe cardiac, respiratory, liver or kidney disorders, history of hypersensitivity, suspicion of malignant hyperthermia, pregnancy and lactation, and legal incapacity to give informed consent. The described screening technique led to a screening rate of approximately five patients per day and a total of 650 patients over the recruitment period. A screening log was not listed. After written informed consent, 60 subjects 18–75 yr of age and ASA status I–III were enrolled. The study IDs of subjects enrolled in the trial were randomly assigned to one of the two study groups using a randomization-software (RandList version 1.2, DatInf) and blinded to receiving either sevoflurane or xenon before the beginning of the enrolment.

Trial procedure

Medical quality xenon in steel cylinders was provided by Air Liquide Santé International (Paris, France). Sevoflurane was provided by Abbott (Wiesbaden, Germany). Both anaesthetic agents were administered using a closed-circuit respirator (Felix Dual®, Taema, France) with appropriate software, which allowed the use of xenon only under closed-circuit conditions. Anaesthetic end-tidal concentrations were assessed by a respirator-incorporated thermo-conductivity meter (accuracy $\pm$3 vol%) with automatic calibration.

A sketch of the study procedure is displayed in Figure 1A. All subjects received premedication with 7.5 mg midazolam orally 45 min before admission to the operating theatre. After standard monitoring and epidural anaesthesia when indicated, the first blood sample was acquired directly before induction of anaesthesia. After 3 min preoxygenation, general anaesthesia was induced by propofol (2.0 mg kg^{-1} initially, repeating dose if necessary 0.5–1.0 mg^{-1} kg^{-1}) and 0.5 μg kg^{-1} min^{-1} remifentanil by infusion over a period of 60 s. Rocuronium 0.6 mg kg^{-1} was administered to facilitate tracheal intubation. Xenon or sevoflurane wash-in was started with a target end-tidal concentration of 60 (5) vol% xenon or 2 (0.2) vol% sevoflurane in 30% oxygen. General anaesthesia was maintained by inhalation of xenon or sevoflurane and supported by remifentanil infusion titrated to clinical needs (baseline 0.1 μg kg^{-1} min^{-1}). Standard monitoring included pulse oximetry, three-channel ECG, non-invasive arterial pressure measurement, control of tracheal tube cuff pressure, neuromuscular function, body core temperature, and oxygen, carbon dioxide, and end-tidal anaesthetic gas concentration. Ventilation control assured normoxia, physiological carbon dioxide concentration, and normothermia. Depth of anaesthesia was maintained according to physiological parameters (heart rate, arterial pressure, coughing, etc.), and BIS values were logged every 5 min. Standard treatment of blood loss, fluid replacement, and haemodynamic support were applied if necessary. One hour after wash-in of xenon or sevoflurane, the second blood sample was acquired. The postoperative examination was uneventful for all subjects.

Blood samples

Blood samples were harvested in lithium-heparin gel tubes (16 IE heparin ml^{-1}; Sarstedt-Monovetten®, Sarstedt AG & Co., Nümbrecht, Germany) and immediately processed.

Analysis of leucocyte subsets

Total leucocyte numbers were quantified with a CASY1 cell counter after lysis of erythrocytes with mö-lyse lysis solution (MöLab, Langenfeld, Germany). In parallel, whole blood samples (100 μl) were incubated with Simultest Leucogate antibodies (BD Biosciences, Heidelberg, Germany) against CD14 (PE) and CD45 (FITC) or the respective isotype-matched controls for 15 min at room temperature in the dark, followed by lysis with BD FACS lysing solution according to the manufacturer's instructions. Flow cytometric analysis was performed on a FACSCalibur flow cytometer using Simulset software (Becton Dickinson, Heidelberg, Germany) to calculate monocyte, lymphocyte, and granulocyte numbers.

Cytokine assay

Heparinized whole blood was diluted (1:1) with cell culture medium (RPMI 1640 containing 10% fetal calf serum, 2 mM L-glutamine, 100 U ml^{-1} penicillin, and 100 μg ml^{-1} streptomycin) and incubated in sterile polypropylene tubes with 0, 25, or 1000 ng ml^{-1} LPS (*Escherichia coli* strain 0111:B4, Sigma Aldrich, Taufkirchen, Germany) for 4 h at 37°C. Subsequently, samples were centrifuged at 500*g* for 5 min; supernatants were harvested and stored at −80°C until further use. For quantification of TNF-α, IL-1β, and IL-6, OPT-EIA ELISAs from BD Biosciences (Heidelberg, Germany) were used according

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