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Clinical Investigation

CLINICAL INVESTIGATION

Intraoperative xenon for prevention of delirium after on-pump cardiac surgery: a randomised, observer-blind, controlled clinical trial

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Initial results of the current study were presented as a chapter of the PhD thesis of L. Al tmimi, November 12, 2018.

Abstract

Background: Older patients undergoing cardiac surgery have a 40–60% risk of developing postoperative delirium (POD), which is associated with increased morbidity and mortality. In animals, xenon has been found to be neuroprotective. Little is known about its neuroprotective effects in humans. We evaluated whether xenon anaesthesia prevents POD in patients undergoing cardiac surgery.

Methods: We conducted a randomised, observer-blind, controlled trial in which 190 patients 65 yr or older undergoing on-pump cardiac surgery were randomly allocated to xenon or sevoflurane anaesthesia. During cardiopulmonary bypass, propofol infusion was used for anaesthetic maintenance. Subjects were screened for POD daily during the first 5 postoperative days using the 3-Minute Diagnostic Interview for Confusion Assessment Method (CAM) or with a CAM version for patients in ICU (CAM-ICU). Other methods to detect delirium, such as chart review, were also used. Secondary outcomes included the duration and severity of POD, and postoperative cognitive function.

Results: The overall incidence of POD was 41% (78/190). There was no statistically significant difference in the POD incidence between the xenon and sevoflurane groups (42.7% [41/96] *vs* 39.4% [37/94], $P=0.583$). The odds ratio for POD when comparing xenon with sevoflurane was 1.18 (95% confidence interval, 0.65–2.16).

Conclusions: In older patients undergoing cardiac surgery, xenon anaesthesia did not result in a significant reduction in POD. Based on these results alone, use of xenon cannot be recommended for this purpose.

Clinical trial registration: EudraCT: 2014-005370-11 (May 13, 2015; https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-005370-11).

Keywords: cardiac surgery; cardipulmonary bypass; delirium; postoperative care; propofol; sevoflurane; xenon

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Editor's key points

- Xenon is neuroprotective in animal experiments.
- This small randomised trial in older patients undergoing cardiac surgery found that intraoperative xenon compared with sevoflurane anaesthesia was not associated with a decrease in postoperative delirium incidence.
- Given that delirium is a complex syndrome with multiple contributing causes, it is unsurprising that a single intraoperative intervention does not result in a large decrease in postoperative delirium incidence.
- Even if xenon does not prevent delirium, it remains possible that it might protect against other neurological complications, such as overt and covert stroke.

Postoperative delirium (POD) is an acute neurocognitive disorder occurring after surgery, characterised by changes in the level of consciousness, arousal, and cognition.[1] POD is particularly common after cardiac surgery, with reported incidences of 11–55%.[2,3] Although typically transient in nature, POD is associated with increased mortality and morbidity, prolonged ICU and hospital lengths-of-stay, and long-term functional and cognitive decline.[4] Its pathophysiology is multifactorial and incompletely understood. Several factors are thought to be involved.[5,6] Patient-related factors (particularly age) also predispose individuals to POD.[3]

The noble gas xenon has neuro- and cardio-protective effects in animal studies,[7] and affects blood pressure and myocardial contractility less than other anaesthetic agents.[8] The neuroprotective properties of xenon have been found in various models of traumatic brain injury,[9] neuronal ischaemia,[7] cardiac arrest,[10] intracranial bleeding,[11] and cardiopulmonary bypass (CPB).[12]

As xenon binds to the *N*-methyl-D-aspartate (NMDA) receptor,[13] but does not interact with GABA receptors,[14] its neuroprotective effects might be achieved through NMDA receptor blockade[15] and suppression of ischaemia-induced neurotransmitter release.[16] It may also enhance synthesis of pro-survival proteins and suppress apoptosis.[17,18] Moreover, xenon activates plasmalemmal ATP-sensitive potassium channels,[19] thereby reducing neuronal excitability and hence providing protection against ischaemic injury.[20] These properties of xenon make it an attractive anaesthetic option for patients who are at high risk of postoperative neurological and neurocognitive complications.

Notably, in patients undergoing off-pump coronary artery bypass surgery, one study found that xenon was associated with a decreased incidence of POD, when compared with sevoflurane.[21] In the current study, we hypothesised that xenon anaesthesia would decrease POD incidence in older patients undergoing on-pump cardiac surgery.

Methods

Study design and participants

This prospective, randomised, observer-blinded, controlled trial was approved by the Ethics Committee of the University Hospitals Leuven, Belgium (SR12/2014, version 2, May 4, 2015) and the Federal Agency for Medicines and Health Products, Brussels, Belgium (April 16, 2015). Details regarding the methods are provided in the published protocol.[22]

We applied a masked randomisation procedure, using closed, sequentially numbered, opaque envelopes that were unsealed upon the patients' arrival in the operating theatre. Patients were randomised by computer-generated software, using permuted blocks (variable block size, 1:1 allocation). Randomisation was stratified by dichotomising the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) with a cut-off score of 3 (Stratum 1: EuroSCORE II $\leq$3; Stratum 2: EuroSCORE II >3).[23] Two investigators conducted the study. Investigator 1 was responsible for patient screening, enrolment, preoperative neurological assessments, and the postoperative follow-ups, and was unaware of the treatment allocation. Subjects, surgeons, and other caregivers were also blinded to treatment allocation. Investigator 2 performed general anaesthesia for the cardiac surgical procedure and could not be blinded because of the required monitoring of anaesthetic agents concentrations.

All subjects provided written, informed consent. Patients were eligible if they were $\geq$65 yr old and scheduled for cardiac surgery on CPB. Patients were excluded if they were incapable of providing informed consent; had a language barrier; had severe chronic obstructive pulmonary disease; disabling neuropsychiatric illness, such as dementia, schizophrenia, epilepsy, or mental retardation; a recent history of drug or alcohol abuse (as defined by a CAGE score $\geq$ 2)[24]; signs or symptoms of increased intracranial pressure; a history of stroke or traumatic brain injury with residual neurological signs; risk factors for or history of malignant hyperthermia; allergy or hypersensitivity to study medications; or delirium at baseline, as defined by the 3-Minute Diagnostic Interview for Confusion Assessment Method (CAM) (3D-CAM).[25] Patients in a critical state perioperatively[23] or who required single-lung ventilation were also excluded.

Study visits are depicted in Supplementary Figure S1. One day before the scheduled operation, Investigator 1 obtained written informed subject consent, recorded all demographic data, and assessed baseline neuropsychological status using the 3D-CAM, Mini-Mental State Examination, and Geriatric Depression Scale. Additionally, an interview with a family member (short-form Informant Questionnaire on Cognitive Decline in the Elderly), an alcohol-abuse screening test (CAGE [cut, annoyed, guilty, eye] questionnaire), and assessment of the patient's preoperative functional status (Katz Index of Activities of Daily Living], were performed.

General anaesthesia and haemodynamic management

Subjects were premedicated with lorazepam 0.03 mg kg^{-1} or with 0.5 mg alprazolam, 1 h before surgery. For subjects >80 yr, these doses were halved. General anaesthesia was induced with remifentanil 0.5 μg kg^{-1} min^{-1}, followed by an intravenous bolus of propofol 0.5–1 mg kg^{-1}. Tracheal intubation was facilitated with a bolus of cisatracurium 0.2 mg kg^{-1}. Subsequently, randomisation envelopes were unsealed, and subjects were randomly allocated to one of the two treatment groups, in which general anaesthesia was maintained before and after CPB with either xenon 40–60% in oxygen, or sevoflurane 1.0–1.4%. Anaesthetic concentrations were titrated, based on clinical signs of anaesthetic depth (HR, arterial blood pressure, sweating, and movement) and continuous electroencephalographic monitoring, to achieve a bispectral index (BIS) of 40–60. Haemodynamic management approaches are detailed in the Supplementary Material.

Surgical intervention and cardiopulmonary bypass

Based on the individual cardiac surgeon's decision, normothermic or mild-to-moderate hypothermic CPB was used with a conventional CPB circuit. Xenon and sevoflurane administration was ceased when CPB commenced and propofol infusion was instituted. After weaning from CPB, the investigational treatment was re-administered until completion of surgery. See Supplementary Material for further details.

Postoperative care management

After completing the surgery, xenon or sevoflurane administration was discontinued, and an intravenous bolus of morphine 0.1–0.2 mg kg^{-1} was administered. All subjects were transferred to the ICU with propofol sedation. Local standard-of-care criteria were applied for weaning from ventilation and ICU discharge. A battery of non-pharmacological interventions was applied to prevent POD development (see Supplementary Material). When a subject developed POD, treatment was initiated based on hospital standards-of-care.

Study outcomes

Primary outcome

The primary endpoint was the POD incidence during the first 5 postoperative days, as determined using the 3D-CAM for non-ventilated patients, or the confusion assessment method adapted for ventilated patients in the ICU (CAM-ICU).[26] Daily POD screening was performed by trained research nurses who were blinded to group allocation. Inter-rater reliability for delirium assessments was not determined in the current study, but had been confirmed in two of our previous studies.[27,28] All research nurses had received specific training based on the 3D-CAM Training Manual For Clinical Use,[29] which facilitates achievement of high-quality delirium assessments, before the initiation of the study.[30] In addition, a daily chart review was performed by the bedside ICU nurse to

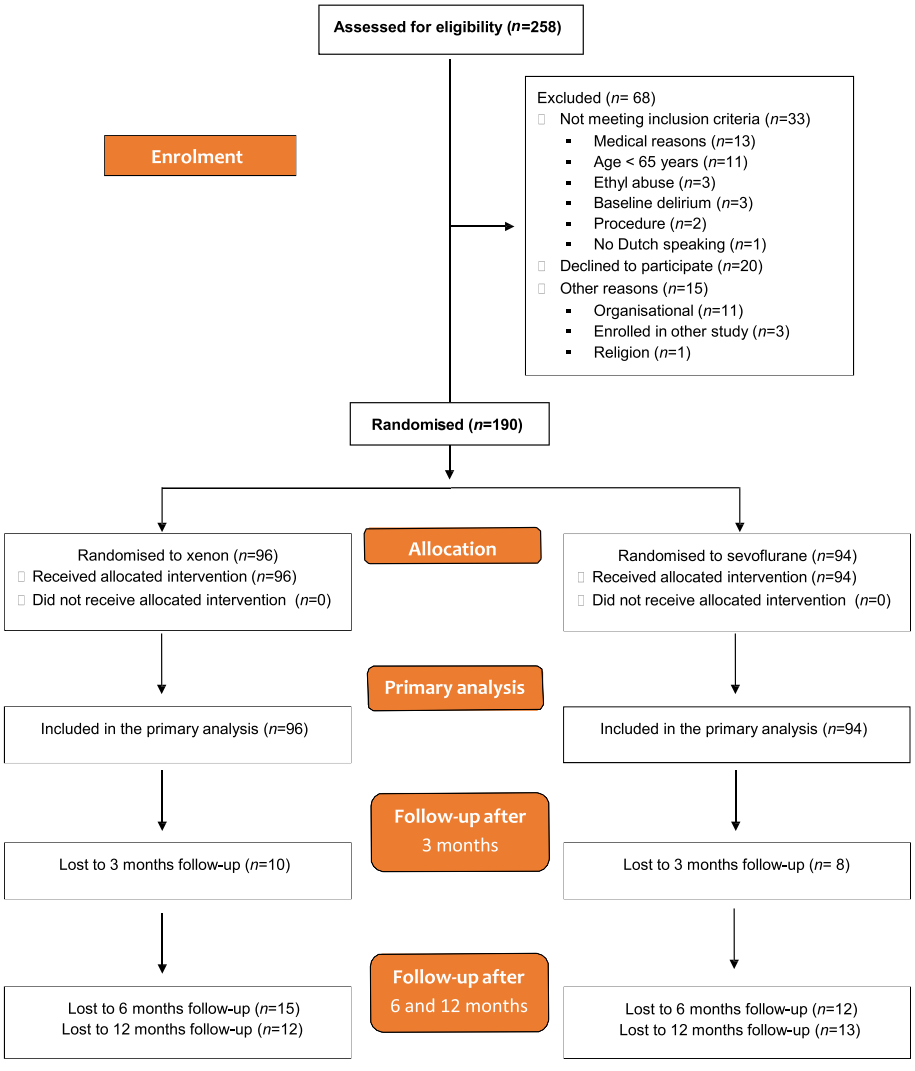

Fig 1. Study diagram based on CONSORT standards of reporting trials.[37] CONSORT, Consolidated Standards of Reporting Trials.

establish Intensive Care Delirium Screening Checklist scores[31] for the previous 24 h. POD could not be evaluated in subjects who were deeply sedated (Richmond Agitation–Sedation Scale of ≤−3).[32]

On the ward, a daily chart review for the results of the Delirium Observation Scale (DOS)[33] over the previous 24 h was performed by nurses. Moreover, subjects' records over the previous 24 h were checked for keywords suggestive of POD (e.g. 'confused', 'aggressive', 'disorientated', 'agitated', 'drowsiness', and 'delirious') and for administration of antipsychotic therapy.

Secondary outcomes

Secondary study endpoints comprised the duration and severity of POD. In patients who had POD on day 5, daily clinical assessments were continued until POD was resolved or until the patient was discharged from the hospital. POD severity was evaluated with the delirium severity measure based on the CAM (CAM-S).[34] Other secondary study endpoints are illustrated in the Supplementary Material.

Statistical analysis

The present study was powered to detect the difference in POD incidence within 5 days after surgery between the xenon and sevoflurane groups. Based on our own observations and those of other groups, POD incidence after cardiac surgery with sevoflurane anaesthesia was assumed to be approximately 40%.[4,21] In a recent trial, we found that xenon could reduce delirium rates by 75%.[21] Based on a two-sided χ^2 test with continuity correction and with alpha=5%, 91 patients in each group were required for 80% power to show a 50% reduction in POD incidence in the xenon group compared with the sevoflurane group (Supplementary Table S1). To compensate for possible drop-outs, 190 subjects were enrolled. As the required sample size depended strongly on the presumed POD incidence, a blinded and *a priori* planned sample size recalculation (SSR) was performed after inclusion of 100 subjects.[35]

To compare the primary outcome between groups, logistic regression analysis, adjusting for the stratification variable 'EuroSCORE II ≤3 *vs* >3', was performed. A subject was defined as POD-positive if at least one POD episode occurred within the first 5 postoperative days, as indicated by a positive 3D-CAM or CAM-ICU assessment. Delirium was also diagnosed based on a positive DOS, relevant documentation in the chart, the requirement for physical restraint, the administration of medications administered for agitation, or both.

To address missing delirium assessments, a multiple imputation approach (Supplementary Table S2) was used, with 20 imputed datasets, and results were averaged using Rubin's rule. Multivariate imputation was performed using the fully conditional specification approach,[36] considering age, sex, EuroSCORE II, results of POD screening on days 1–5, presence of a positive POD screening in the period beyond the first 5 postoperative days, and duration of CPB. The imputation model was fitted in both groups separately.

All statistical analyses were conducted with SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). All data were analysed on an intention-to-treat basis. A *P*-value <0.05 was considered statistically significant. Statistical analyses of secondary endpoints are presented in the Supplementary Material.

Table 1 Baseline characteristics and demographic data. Data are presented as median and inter-quartile range (IQR) or *n/N* (%). ASA, American Society of Anesthesiologists; BSA, body surface area; CVA, cerebrovascular accident; EF, ejection fraction; LV, left ventricle; MMSE, mini-mental state examination; POD, postoperative delirium; EuroSCORE II, European System for Cardiac Operative Risk Evaluation.

Variable	Xenon (*n*=96)	Sevoflurane (*n*=94)
Subject characteristics		
Age, yr	76 (71–80)	76 (70–81)
BMI, kg m^{-2}	26.9 (24–30)	26.3 (24–29)
BSA, m^2	1.8 (1.7–2.0)	1.8 (1.7–2.0)
Weight, kg	74 (67–85)	74 (64–84)
Female	43/96 (45)	48/94 (51)
Non-smoking	37/96 (38.5)	46/94 (49)
Alcohol use		
Infrequent/never	54/96 (56)	59/94 (63)
Regular	37/96 (39)	33/94 (35)
Stopped	5/96 (5)	2/94 (2)
$MMSE_{baseline}$	28 (27–29)	28 (27–29)
Education, yr	17 (14–19)	18 (15–19)
Education level		
Primary education	5/95 (5)	9/94 (9)
Lower secondary education	38/95 (40)	26/94 (28)
Higher secondary education	34/95 (36)	43/94 (46)
Higher education	12/95 (13)	10/94 (11)
University	6/95 (6)	6/94 (6)
Preoperative status		
EuroSCORE II	4.1 (2.5–8.4)	3.8 (2.5–7.6)
Stratum 'EuroSCORE II'		
≤3	32/96 (33)	30/94 (32)
>3	64/96 (67)	64/94 (68)
ASA physical status		
ASA 3	6/96 (6)	6/94 (6)
ASA 4	90/96 (94)	88/94 (94)
LV EF%		
EF <30%	3/96 (3)	5/94 (5)
EF ≥30–50%	20/96 (21)	19/94 (20)
EF >50%	73/96 (76)	70/94 (75)
No history of POD	90/96 (94)	92/94 (98)
No history of CVA	87/96 (91)	82/94 (87)
Diabetes mellitus		
No	68/96 (71)	74/94 (79)
Oral medication	21/96 (22)	17/94 (18)
Insulin	7/96 (7)	3/94 (3)
Preoperative medications		
Benzodiazepines for premedication		
No benzodiazepines	34/96 (35)	37/94 (39)
Alprazolam	42/96 (44)	40/94 (43)
Lorazepam	20/96 (21)	17/94 (18)
Alprazolam, mg	0.5 (0.5–1.0)	0.5 (0.5–1.0)
Lorazepam, mg	2.5 (1.3–2.5)	2.5 (1.0–2.5)
Statins	69/96 (72)	65/94 (69)
Beta blocker	57/96 (59)	58/94 (62)

Results

From November 2015 to December 2017, 258 patients scheduled for on-pump cardiac surgery were screened. After inclusion of the first 100 patients, a blinded SSR was performed as predefined,[22] and revealed an overall POD incidence of 42%, which was slightly higher than originally presumed. Consequently, the sample size was not adjusted. In total, 190

Table 2 Anaesthesia and surgery-related data. Data are presented as median and inter-quartile range (IQR) or *n*/*N* (%). CABG, coronary artery bypass grafting, CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; n.a., not applicable; PRBCs, packed red blood cells. †Replacement/repair of two or more valves, combined with other procedures.

Variables	Xenon (*n*=96)	Sevoflurane (*n*=94)	*P*-value
Anaesthesia and surgery-related data			
Anaesthesia time, min	277 (230–324)	275 (226–319)	0.754
Surgery time, min	243 (190–280)	236 (189–273)	0.602
CPB time, min	117 (89–148)	115 (83–145)	0.378
Aorta cross-clamp time, min	82 (63–112)	83 (62–107)	0.636
Remifentanil, median, μg	4300 (3300–5742)	4225 (3330–5202)	0.583
Propofol: induction dose, mg	97 (80–118)	94 (80–110)	0.620
Propofol: total dose, mg	877 (668–1108)	812 (634–1040)	0.141
Xenon consumption, L	22 (19–27)	–	n.a.
Sevoflurane consumption, ml	–	16 (11–22)	n.a.
Surgical procedure			0.516
Aortic valve repair/replacement	31/96 (32)	34/94 (36)	
Mitral valve repair/replacement	9/96 (10)	3/94 (3)	
Tricuspid valve repair/replacement	1/96 (1)	0/94 (0)	
Aortic valve with CABG	22/96 (23)	24/94 (26)	
Mitral valve with CABG	2/96 (2)	2/94 (2)	
Others,†	31/96 (32)	30/94 (32)	
CABG	0/96 (0)	1/94 (1)	
Intraoperative fluid management, ml			
Fluid balance	2083 (1527–2880)	2076 (1583–2952)	0.660
Colloids	500 (0–500)	500 (0–500)	0.402
Crystalloids	2000 (1500–2500)	2000 (2000–2750)	0.424
PRBCs	256 (0–533)	251 (0–520)	0.444
FFP	0 (0–0)	0 (0–0)	0.911
Blood platelets	0 (0–340)	0 (0–359)	0.174
Cell saver	0 (0–212)	0 (0–222)	0.639
Blood loss	125 (0–410)	100 (0–378)	0.586

subjects were included and randomly assigned to the xenon (*n*=96) or sevoflurane (*n*=94) groups (Fig. 1).[37] All subjects received the allocated treatment and were eligible for the final analysis of the primary outcome (Fig. 1). Baseline characteristics and demographic data of both groups are shown in Table 1. Groups did not differ with regard to anaesthesia or surgery-related data (Table 2).

Incidence of postoperative delirium

Seventy-eight patients developed POD during the first 5 postoperative days, equating to an overall incidence of 41%. The POD incidence was similar between the two groups (Table 3). The odds ratio (95% confidence interval [95% CI]) for POD when comparing xenon with sevoflurane was equal to 1.18 (0.65; 2.16) (Table 3). After multiple imputation to address the issue of unevaluable days, the odds ratio was 1.09 (0.59; 2.01), *P*=0.793 (Supplementary Table S2).

Secondary outcomes

Neither the duration nor the severity of POD differed significantly between the groups (Table 3). Likewise, the duration of mechanical ventilation, ICU, and hospital length of stay

Table 3 Postoperative delirium. The incidence, duration and severity of postoperative delirium (POD) in the xenon and the sevoflurane group. †Odds ratio (OR) with 95% confidence interval (CI) for the incidence of POD after xenon or sevoflurane anaesthesia, obtained with a stratified logistic regression (stratification on EurosSCORE II). ‡Geometric mean with (95% CI) after correction for the stratification variable (EuroSCORE II). ¶Ratio with 95% CI of geometric mean xenon to sevoflurane. EuroSCORE II, European System for Cardiac Operative Risk Evaluation; N.A., not applicable; SD, standard deviation.

Variables	Xenon			Sevoflurane			Odds ratio (95% CI)	*P*-value
	EuroSCORE II		All	EuroSCORE II		All		
	≤3 (*n*=8)	>3 (*n*=33)	(*n*=41)	≤3 (*n*=5)	>3 (*n*=32)	(*n*=37)		
Incidence of POD, *n*/*N* (%)	8/32 (25)	33/64 (52)	41/96 (43)	5/30 (17)	32/64 (50)	37/94 (39)	1.18 (0.649; 2.158)†	0.583
POD duration, mean (SD), days	7.5 (14)	4.8 (3.5)	3.35 (2.4; 4.6)‡	3.8 (2.8)	8.3 (17.9)	3.7 (2.6; 5.3)‡	0.89 (0.6; 1.33)¶	0.592
POD severity, median (range)	4 (1–6)	4.1 (1–6)	4 (1–6)	3 (2–6)	4.5 (1–7)	4 (1–7)	N.A.	0.895

Table 4 Postoperative data. Data are presented as geometric means with 95% confidence intervals (CI), after correction for the stratification variable EuroSCORE II), as mean (SD) with difference between means or as an absolute number with the percentage (%) of the whole. †Ratio of geometric means xenon/sevoflurane with 95% CI. ‡Difference in geometric mean with (95% CI). ¶Analysed with a stratified Mann–Whitney U-test (Van Elteren test). §Odds ratio with 95% confidence interval. ||Analysed with a stratified logistic regression (stratification on EuroSCORE). #Mean (standard deviation) with difference between means. AKI, acute kidney injury; CVA, cerebrovascular accident; ICU, intensive care unit; LOS, length of stay; MMSE, mini-mental state examination; MV, mechanical ventilation; n.a. not applicable; SD, standard deviation; SOFA, sequential organ failure assessment; TICS, telephone interview for cognitive status.

Outcomes	Xenon (n=96)	Sevoflurane (n=94)	ICU and hospital data	P
Duration of MV, h	13.9 (12.4;15.7)	14.7 (13.1;16.5)	0.949 (0808;1.115)†	0.523
LOS_{ICU}, h	49.2 (41.79;57.9)	51.5 (43.66;60.79)	0.955 (0.763;1.195)†	0.684
$LOS_{Hospital}$, days	9.9 (9.00;10.9)	10.1 (9.16;11.07)	0.981 (0.863;1.116)†	0.772
Mean $MMSE_{at\ discharge}$	27.3 (26.72;27.8)	27.3 (26.71;27.83)	0.000 (−0.763;0.763)‡	0.999
Mean $KATZ_{at\ discharge}$	1.46 (1.06;1.9)	1.22 [62−107]	−0.239 (−0.780;0.302)‡	0.384
SOFA				0.286¶
$SOFA_{EuroSCORE \leq 3}$, mean (SD)	10.5 (1.01)	9.7 (1.99)	n.a.	
$SOFA_{EuroSCORE >3}$, mean (SD)	11.0 (1.86)	10.8 (1.44)	n.a.	
Adverse events				
Wound infection	1 (1)	1 (1.1)	1.000 (0.062;16.164)§	1.000||
Respiratory infection	8 (8)	12 (13)	0.626 (0.241;1.623)§	0.350||
Sepsis	3 (3)	1 (1.1)	3.073 (0.313;30.152)§	0.619||
AKI	22 (23)	17 (18)	1.370 (0.670;2.800)§	0.468||
CVA	3 (3)	1 (1.1)	3.073 (0.313;30.152)§	0.619||
Seizure	5 (5)	0 (0)	n.a.	0.059||
Pericardial tamponade	1 (1)	2 (2)	0.488 (0.044;5.408)§	0.620||
Mortality rate				
In-hospital mortality	2 (2)	0 (0)	5.000 (0.236;105.6)§	0.497
3-month mortality	0 (0)	0 (0)	1.000 (0.019;51.0)§	1.000
6-month mortality	1 (1)	0 (0)	3.032 (0.121;75.4)§	1.000
TICS within 6 months, mean (SD)	31 (4.2)#	32 (3.9)#	(0.617 [0.638])#	0.334
Hospital readmission within 6 months	16 (17)	11 (12)	1.56 (0.67;3.6)§	0.300

were similar in both groups (Table 4). Cognitive function evaluated at hospital discharge and at 6 months after surgery, and the incidence of in-hospital acute kidney injury did not differ significantly between groups. Mortality rates (in-hospital, 3 months, and 6 months) were similar in both groups (Table 4). Furthermore, there was no significant difference between groups with regard to the sequential organ failure assessment score and the incidence of adverse events (Table 4).

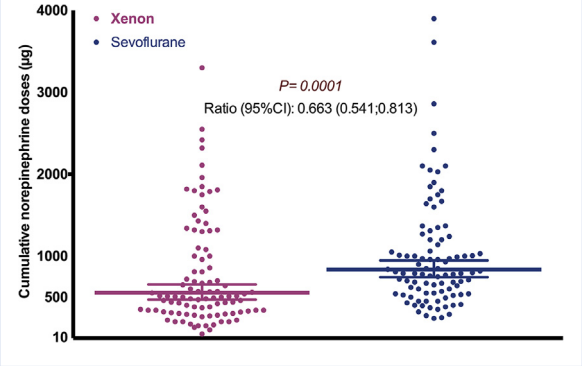

Fig 2. Cumulative intraoperative norepinephrine consumption (thick bar, geometric mean; thin bars, 95% confidence interval [CI]) in the xenon and the sevoflurane groups. Individual values of norepinephrine consumption are depicted as closed circles. Ratio of the geometric mean xenon/sevoflurane with 95% CI.

Intraoperative vasopressor requirements and blood pressure

Intraoperatively, the xenon group required significantly less norepinephrine than the sevoflurane group to obtain the target MAP (i.e. MAP >65 mm Hg in the pre- and post-CPB periods). The norepinephrine consumption was 33.7% lower (ratio=0.663) for xenon than for sevoflurane subjects. Xenon patients received 541 (467; 627) µg norepinephrine (geometric mean [95% CI]), compared with 816 (702; 948) µg in sevoflurane patients (P<0.001) (Fig. 2). Intraoperative MAP and BIS values were similar in the two groups (Supplementary Table S3). No episodes of intraoperative awareness with recall were reported by the patients when interviewed after operation with the Brice questionnaire.[38]

Perioperative myocardial and renal injury

No significant difference was noticed between the xenon and sevoflurane groups with respect to the perioperative serum concentrations of cardiac enzymes/peptides and creatinine (Supplementary Table S4).

Discussion

In this randomised trial, xenon anaesthesia did not reduce POD incidence, duration, or severity in older patients undergoing on-pump cardiac surgery, as compared with sevoflurane anaesthesia. Secondary outcomes were also not significantly different between the groups, except for reduced vasopressor requirements in patients who received xenon.

Our findings contrast with those of our earlier study, in which xenon anaesthesia was associated with a lower POD incidence than sevoflurane anaesthesia in 42 patients undergoing off-pump coronary artery bypass surgery.[21] However, that study was neither specifically designed nor adequately powered to assess this specific outcome. Our present results are in line with a recent multicentre study of 256 patients >75 yr old undergoing surgery for hip fracture, in which xenon anaesthesia also failed to reduce POD incidence.[39]

Xenon anaesthesia has a superior haemodynamic profile over those of traditional agents.[21,40,41] In our high-risk population of cardiac surgical patients, those receiving xenon required less intraoperative vasopressors to achieve the predefined haemodynamic goals than those receiving sevoflurane. Notably, in the present trial, intraoperative haemodynamic changes were not associated with POD, consistent with previous reports.[42,43] In on-pump coronary artery bypass grafting surgery, xenon was recently found to be non-inferior to sevoflurane concerning postoperative troponin release and was rated at least as cardio-protective as sevoflurane.[44] We also observed a comparable postoperative troponin release in both groups.

Our study has several important limitations. Of note, xenon anaesthesia was administrated for a relatively short period (approximately one-fifth of the total intra- and postoperative mechanical ventilation time) and standard postoperative sedation (i.e. with propofol) was used in the ICU. For POD diagnosis, we used the 3D-CAM,[25] which was performed by trained study nurses at arbitrary time points, and only once daily. In contrast, some studies have evaluated patients twice daily.[39] To overcome this possible limitation and to account for the fluctuating course of POD, we checked the patients' charts for reports suggesting the presence of POD. The current study was powered to detect a reduction from 40% to 20% in POD incidence, similar to assumptions in some other multicentre POD studies.[39,45] Thus, our study was not powered to detect differences smaller than halving of the POD incidence. Discontinuation of xenon or sevoflurane on CPB and replacement of these inhalation anaesthetics with a continuous propofol infusion during CPB may be a limitation of the current trial. Notably, propofol counteracts the protective effects of volatile anaesthetics on the heart[46] and provokes more neuroapoptosis than sevoflurane in the neonatal mouse brain.[47] Hence, the administration of propofol may have confounded the observed effects. The use of propofol was necessary because we could not administer xenon during CPB. Moreover, despite reassuring findings from a small trial in humans,[48] xenon is suspected to enlarge intravascular gas bubbles and increase the risk of cerebral air embolism during CPB.[49] Other and difficult-to-control postoperative factors—such as delayed tracheal extubation, haemodynamic deterioration, and perioperative administration of deliriogenic medication, including opioids and benzodiazepines—may have abolished any potentially neuroprotective effects of xenon and may also have increased the POD incidence in the present study. Therefore, it would be interesting to investigate the effects of xenon in high-risk patients scheduled for complex surgery, such as cardiac surgery, but without the use of CPB and multiple hypnotic agents, such as propofol and benzodiazepines. However, this approach would markedly increase the costs of xenon treatment. A further limitation of the study might be that we titrated anaesthetic agents using BIS monitoring. This approach has recently been questioned by a retrospective study in which the relationship between age-adjusted end-tidal minimum alveolar concentration and the BIS was found to be nonlinear, and in which older patients paradoxically showed higher BIS values despite receiving higher age-adjusted anaesthetic concentrations.[50] Moreover, although intraoperative EEG monitoring is recommended for the prevention of POD,[51,52] there is mixed evidence on the efficacy of EEG monitoring for reducing delirium rates.[53–55]

In conclusion, intraoperative use of xenon did not significantly decrease POD incidence, duration, or severity in older patients undergoing on-pump cardiac surgery when compared with sevoflurane anaesthesia. The failure of xenon to reduce POD incidence suggests that simply avoiding the use of anaesthetic drugs that act at $GABA_A$ receptors, such as by using an anaesthetic like xenon, might be insufficient to reduce POD risk. Future studies could investigate the effects of using xenon during and after operation in high-risk patients, without the addition of other hypnotic agents, such as propofol and benzodiazepines.

Authors' contributions

Principle investigator: SR.
Study design and protocol: SR, LA, MVdV, GM, PV, BM, KM, SF.
Clinical examination: LA, SR.
Data acquisition: LA, SR.
Statistical analysis: SF, LA.
Drafting of the manuscript: LA, KM, SF, GM, PV, SR.
LA and SR had full access to all data presented in the current study and take responsibility for the accuracy and integrity of these data.
All authors critically revised the manuscript draft, and read and approved the final version.

Declaration of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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