Clinical trial results:
The safety and feasibility of administering xenon to patients undergoing off-pump coronary artery bypass graft surgery: a pilot study

XOPCAB – Xenon in Off-Pump Coronary Artery Bypass Grafting

Summary

EudraCT number	2012-002316-12
Trial protocol	BE
Global end of trial date	14 January 2014

Results information

Result version number	v1 (current)
This version publication date	20 December 2019
First version publication date	20 December 2019

Trial information

Trial identification

Sponsor protocol code	SR052012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01757106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Anesthesia Research, University Hospitals of the KU Leuven, 0032 016344620, christel.huygens@uzleuven.be
Scientific contact	Anesthesia Research, University Hospitals of the KU Leuven, 0032 016344620, christel.huygens@uzleuven.be
Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Christel Huygens, Department of Anesthesiology, University Hospitals Leuven, 0032 16344720, christel.huygens@uzleuven.be
Scientific contact	Christel Huygens, Department of Anesthesiology, University Hospitals Leuven, 0032 16344720, christel.huygens@uzleuven.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2013
Global end of trial reached?	Yes
Global end of trial date	14 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to assess whether opioid-based xenon-anaesthesia is non-inferior to opioid-based sevoflurane anaesthesia in terms of haemodynamic stability (as reflected by vasopressor requirements). Secondary aims of the study included the assessment of various perioperative safety parameters.

Protection of trial subjects:

The interventional treatment was administered to patients under advanced hemodynamic monitoring in the setting of a fully equipped cardiac surgical operating room. This enables immediate detection and treatment of adverse events. Xenon inhalation was immediately stopped in case that the study patient shows a life-threatening deterioration. After leaving the operation room, all patients were closely monitored by the study team for the occurrence of eventual adverse or serious adverse events (S) AE’s during the whole postoperative period until hospital discharge. Moreover, the inclusion of each individual patient into the study was indicated in the electronic hospital information system and hence visible to all physicians and nurses involved in the care of this patient. This facilitates reporting of (S)AE’s to the principal investigator. Finally, suspected unexpected serious adverse reactions were reported by the principal investigator to the federal health authorities.

Background therapy:

In noncardiac 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. 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. Such haemodynamic effects may result in an overall improvement of the balance between myocardial oxygen delivery and consumption.

Evidence for comparator:

Wappler F, Rossaint R, Baumert J, et al. Multicenter randomized comparison of xenon and isoflurane on left ventricular function in patients undergoing elective surgery. Anesthesiology 2007; 106: 463–71.

Rossaint R, Reyle-Hahn M, Schulte Am Esch J, et al. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. Anesthesiology 2003; 98: 6–13.

Stoppe C, Fahlenkamp AV, Rex S, et al. Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study. Br J Anaesth 2013; 111: 406–16.

Actual start date of recruitment	03 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	33
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

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 recruitment started in December 2012 to July 2013, 79 patients scheduled for elective OPCAB surgery were screened.

Pre-assignment

Screening details:

Patients could be included if they were >18 years, scheduled for elective OPCAB surgery. Exclusion criteria were: lack of informed consent; chronic obstructive pulmonary disease(GOLD) stage >II; renal dysfunction, defined as serum creatinine >1.5mg/dl; acute coronary syndrome during the last 24h; LV EF≤30%; MMSE < 25, delirium at baseline, etc.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

A masked randomization procedure using sealed, opaque, sequentially numbered envelopes that were opened only upon arrival of the patient in the operating room (OR). Investigator I completed patient enrolment & postoperative follow-ups & was, like the patient, blinded to the study group. Investigator II performed randomization and general anaesthesia for OPCAB surgery and could not be blinded due to administration of the anaesthetic via a dedicated anaesthesia machine & the mandatory monitoring.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sevoflurane group

Arm description:

sevoflurane1.0 1.4% in oxygen and medicalair (FO2 =0.3–0.4).

Arm type	Active comparator
Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

EEG-titrated administration via inhalation via endotracheal tube

Arm title	Xenon group

Arm description:

xenon 50–60% in oxygen [fraction of inspired oxygen (FO2 = 0.3–0.4)] .

Arm type	Experimental
Investigational medicinal product name	Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

EEG-titrated application via inhalation via endotracheal tube

Number of subjects in period 1	Sevoflurane group	Xenon group
Started	21	21
Completed	21	21

Baseline characteristics

Reporting groups	
Reporting group title	Sevoflurane group
Reporting group description:	
sevoflurane1.0 1.4% in oxygen and medicalair (FO2 =0.3–0.4).	
Reporting group title	Xenon group
Reporting group description:	
xenon 50–60% in oxygen [fraction of inspired oxygen (FO2 = 0.3–0.4)] .	

Reporting group values	Sevoflurane group	Xenon group	Total
Number of subjects	21	21	42
Age categorical			
Patients could be included if they were >18 years of age and scheduled for elective OPCAB surgery.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	7	15
From 65-84 years	11	13	24
85 years and over	2	1	3
Age continuous			
Patients could be included if they were >18 years of age and scheduled for elective OPCAB surgery.			
Units: years			
median	68	68	
full range (min-max)	47 to 86	55 to 84	-
Gender categorical			
Units: Subjects			
Female	4	5	9
Male	17	16	33

End points

End points reporting groups

Reporting group title	Sevoflurane group
Reporting group description:	
sevoflurane1.0 1.4% in oxygen and medicalair (FO2 =0.3–0.4).	
Reporting group title	Xenon group
Reporting group description:	
xenon 50–60% in oxygen [fraction of inspired oxygen (FO2 = 0.3–0.4)] .	

Primary: Hemodynamic stability

End point title	Hemodynamic stability
End point description:	
The primary outcome was the dose of noradrenaline that was required intraoperatively to achieve the predefined haemodynamic goals (Mean arterial pressure > 65 mmHg).	
End point type	Primary
End point timeframe:	
Start of anaesthesia induction to end surgery (Intraoperatively)	

End point values	Sevoflurane group	Xenon group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: µg				
median (inter-quartile range (Q1-Q3))	1700 (1320 to 3160)	470 (320 to 740)		

Statistical analyses

Statistical analysis title	Primary outcome
Comparison groups	Xenon group v Sevoflurane group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	t-test, 2-sided

Notes:

[1] - For the statistical analysis of the primary outcome, a 95% confidence interval (CI) was constructed for the ratio of the (geometric) mean comparing the intraoperative noradrenaline consumption of xenon with sevoflurane. For a single patient in the xenon group that did not require noradrenaline at all, the minimal observed consumption was assumed to allow the necessary log transformation.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Patients randomization - hospital discharge	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Sevoflurane group
Reporting group description: sevoflurane1.0 1.4% in oxygen and medicalair (FO2 =0.3–0.4).	
Reporting group title	Xenon group
Reporting group description: xenon 50–60% in oxygen [fraction of inspired oxygen (FO2 = 0.3–0.4)] .	

Serious adverse events	Sevoflurane group	Xenon group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 21 (14.29%)	1 / 21 (4.76%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke	Additional description: Cerebrovascular accident		
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Sevoflurane group	Xenon group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 21 (76.19%)	13 / 21 (61.90%)	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 21 (33.33%)	8 / 21 (38.10%)	
occurrences (all)	7	8	
pericardial tamponade			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 21 (9.52%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Sepsis			
subjects affected / exposed	6 / 21 (28.57%)	2 / 21 (9.52%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported