Clinical trial results:
Xenon as an adjuvant to sevoflurane anaesthesia in children younger than four, undergoing interventional or diagnostic cardiac catheterization: a pilot study.

Summary

EudraCT number	2015-002329-20
Trial protocol	BE
Global end of trial date	01 April 2016

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	SR052015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 Leuven, +32 16344620, christel.huygens@uzleuven.be
Scientific contact	Anesthesia Research, University Hospitals Leuven, +32 16344620, 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 1901/2006 apply to this trial?	No
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	23 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2016
Global end of trial reached?	Yes
Global end of trial date	01 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

We hypothesized that the administration of 50-65 % xenon as an adjuvant to general anaesthesia with sevoflurane would result in superior hemodynamic stability when compared to sevoflurane anesthesia alone.

Protection of trial subjects:

The interventional treatment was administered to patients with standard haemodynamic monitoring in the setting of a fully equipped cardiac catheterization room. This enabled immediate detection and treatment of adverse events. Xenon inhalation was to be immediately stopped in case that the study patient showed a life-threatening deterioration. Also after leaving the operation room, all patients were closely monitored by the study team for the occurrence of eventual (S)AE's, first on the PACU, later on the normal ward. 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	26
Children (2-11 years)	13
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From September 2015 to April 2016, 69 children scheduled for elective heart catheterization were screened. A total of 40 were included and randomized to receive general anesthesia either with xenon plus sevoflurane or sevoflurane alone.

Pre-assignment

Screening details:

A screening failure occurred in 29 patients (16 met exclusion criteria, 7 declined to participate, and 6 had other reasons that excluded them from the participation in the trial).

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:

Two investigator types conducted the trial. Investigator I accomplished the enrollment (day prior to intervention) and all postoperative visits and was, similar to the patient and his parents, blinded to treatment allocation. Investigator II performed randomization and the GA and could not be blinded to the treatment due to the kind of intervention (adminis- tration and monitoring of either one or two inhalational anesthetics).

Arms

Are arms mutually exclusive?	Yes
Arm title	Xenon

Arm description:

General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane

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 administration via inhalation via endotrecheal tube

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	Sevoflurane

Arm description:

General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 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

Number of subjects in period 1	Xenon	Sevoflurane
Started	20	20
Blinded dample size re-estimation	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Xenon
Reporting group description:	
General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane	
Reporting group title	Sevoflurane
Reporting group description:	
General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 0.4).	

Reporting group values	Xenon	Sevoflurane	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	1	1
Infants and toddlers (28 days-23 months)	12	14	26
Children (2-11 years)	8	5	13
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	18	8	
inter-quartile range (Q1-Q3)	2 to 39	3 to 26	-
Gender categorical Units: Subjects			
Female	11	8	19
Male	9	12	21

End points

End points reporting groups

Reporting group title	Xenon
Reporting group description:	
General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane	
Reporting group title	Sevoflurane
Reporting group description:	
General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 0.4).	

Primary: Intraprocedural hemodynamic instability

End point title	Intraprocedural hemodynamic instability
End point description:	
intrapro- cedural hemodynamic instability, defined by the occurrence of one of following events: (i) a heart rate (HR) change >20% from baseline (not caused by interventional manipulation); (ii) a change in mean arterial blood pressure (MAP) >20% change from baseline (this change has been recently demonstrated to be associated with cerebral desaturations in infants and is frequently used as intervention trigger in pediatric studies); or (iii) the requirement for an hemodynamic intervention performed by investigator II to treat hemodynamic instability as defined above (assessed as the composite of using either vasopressors, inotropes, chronotropes, or fluid boluses). Isolated blood pressure drops >20% from baseline were treated with phenylephrine (2-3 mikrog/kg) and/or a fluid bolus (crystalloid 10 mL/kg), isolated bradycardia with atropine (10-20 mikrog/kg), and the combination of bradycardia with hypotension with ephedrine (50-100 mikrog/kg).	
End point type	Primary
End point timeframe:	
During the administration of IMP/comparator	

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Number	20	20		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Phenylephrine requirements

End point title	Phenylephrine requirements

End point description:

End point type	Secondary

End point timeframe:

During administration of IMP/active comparator

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mikrogram/kg				
median (inter-quartile range (Q1-Q3))	0 (0 to 2.49)	4.93 (0 to 15.37)		

Statistical analyses

Statistical analysis title	Phenylephrine
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Secondary: Incidence of cerebral desaturation

End point title	Incidence of cerebral desaturation

End point description:

Incidence of cerebral desaturation, defined as a decrease in rScO2 of >20% from baseline.

End point type	Secondary

End point timeframe:

During administration of IMP/active comparator

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Numbers	2	10		

Statistical analyses

Statistical analysis title	Cerebral desaturation left side
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fisher exact

Statistical analysis title	Cerebral desaturation right side
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Fisher exact

Secondary: Recovery index

End point title	Recovery index

End point description:

End point type	Secondary

End point timeframe:

During administration of IMP/active comparator

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: /min				
median (inter-quartile range (Q1-Q3))	0.44 (0.39 to 0.69)	0.27 (0.19 to 0.40)		

Statistical analyses

Statistical analysis title	Recovery index
Comparison groups	Xenon v Sevoflurane

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From enrollment until the first postinterventional day	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Xenon
Reporting group description:	
General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane	
Reporting group title	Sevoflurane
Reporting group description:	
General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 0.4).	

Serious adverse events	Xenon	Sevoflurane	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	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	Xenon	Sevoflurane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 20 (45.00%)	14 / 20 (70.00%)	
Nervous system disorders			
Emergence agitation	Additional description: assessed by four-point agitation scale		
subjects affected / exposed	1 / 20 (5.00%)	8 / 20 (40.00%)	
occurrences (all)	1	8	
Gastrointestinal disorders			

Postoperative vomiting subjects affected / exposed occurrences (all)	4 / 20 (20.00%) 4	2 / 20 (10.00%) 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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28872734