



Clinical trial results:

The use of xenon and dexmedetomidine for the prevention of postoperative emergence delirium after anaesthesia for pediatric cardiac catheterization: A randomized, controlled, observer-blinded pilot trial.

Summary

EudraCT number	2018-002258-56
Trial protocol	BE
Global end of trial date	10 October 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	SD-DXP
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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	Department Anesthesiology-Research, University Hospitals Leuven, 32 16344620, christel.huygens@uzleuven.be
Scientific contact	Department Anesthesiology-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	26 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2020
Global end of trial reached?	Yes
Global end of trial date	10 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this pilot trial is to estimate the effect size for xenon-dexmedetomidine anaesthesia vs. sevoflurane anaesthesia with respect to the incidence of Emergency Delirium.

We hypothesize that in children undergoing cardiac catheterization, the use of dexmedetomidine as an adjunct to xenon-anaesthesia reduces the incidence of ED when compared to the conventionally used anesthetic sevoflurane.

Protection of trial subjects:

The interventional treatment was administered to patients with standard harm-dynamic monitoring in the setting of a fully equipped cardiac catheterisation room. This enabled immediate detection and treatment of adverse events. Xenon inhalation or dexmedetomidine infusion was to be immediately stopped in case that the pt showed a life-threatening deterioration. After leaving the operating room the patients were closely monitored by the study team for the occurrence of (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:

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Evidence for comparator:

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Actual start date of recruitment	06 December 2018
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: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	56
Children (2-11 years)	24
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 December 2018 to October 2020, 145 children scheduled for elective heart catheterization were screened. A total of 80 were included and randomized to receive GA either with xenon plus dexmedetomidine or sevoflurane. All patients received the allocated intervention.

Pre-assignment

Screening details:

We screened 145 consecutive children scheduled for heart catheterization under GA. Inclusion: children 1 mth-3 yrs. Exclusion criteria: lack of informed consent, cyanotic heart defect requiring $FiO_2 > 50\%$, high-risk/complex interventional procedures, behavioural/cognitive deficit and contra-indication for studied drugs. We had screening failure of 65.

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

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 all the postoperative visits and was, similar to the patient and his parents, blinded to treatment allocation. Investigator II performed randomization and general anesthesia and could not be blinded to the treatment due to the kind of intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	dex/xenon

Arm description:

General anesthesia was maintained with xenon (50-65%) in oxygen and dexmedetomidine infusion (0.5-1.2 $\mu\text{g/kg/hr}$)

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 ET tube

Investigational medicinal product name	dexmedetomidine
Investigational medicinal product code	
Other name	dexdor
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

bolus dose was given 1 $\mu\text{g/kg}$ and continuous infusion was started at 0.5-11 $\mu\text{g/kg/hr}$ titrated following EEG

Arm title	sevoflurane
Arm description:	
General anesthesia was maintained with sevoflurane (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 ET tube	

Number of subjects in period 1	dex/xenon	sevoflurane
Started	40	40
Completed	40	40

Baseline characteristics

Reporting groups

Reporting group title	dex/xenon
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Reporting group description:

General anesthesia was maintained with xenon (50-65%) in oxygen and dexmedetomidine infusion (0.5-1.2 µg/kg/hour)

Reporting group title	sevoflurane
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Reporting group description:

General anesthesia was maintained with sevoflurane (FiO₂ 0.25-0.4)

Reporting group values	dex/xenon	sevoflurane	Total
Number of subjects	40	40	80
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	26	30	56
Children (2-11 years)	14	10	24
Age continuous			
Units: months			
median	19.5	11.5	
inter-quartile range (Q1-Q3)	7 to 30	1 to 46	-
Gender categorical			
Units: Subjects			
Female	20	24	44
Male	20	16	36

End points

End points reporting groups

Reporting group title	dex/xenon
Reporting group description: General anesthesia was maintained with xenon (50-65%) in oxygen and dexmedetomidine infusion (0.5-1.2 µg/kg/hour)	
Reporting group title	sevoflurane
Reporting group description: General anesthesia was maintained with sevoflurane (FiO ₂ 0.25-0.4)	
Subject analysis set title	xenon/dex
Subject analysis set type	Intention-to-treat
Subject analysis set description: Effect size estimation	

Primary: • Incidence of ED as assessed by the Watcha-scale

End point title	• Incidence of ED as assessed by the Watcha-scale
End point description:	
End point type	Primary
End point timeframe: 60 minutes after extubation	

End point values	dex/xenon	sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: number of subjects				
number (not applicable)	39	39		

Statistical analyses

Statistical analysis title	primary endpoint
Comparison groups	sevoflurane v dex/xenon
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.1
Method	Fisher exact

Notes:

[1] - effect size: The presented trial was designed as a pilot trial with the aim to estimate the effect size for xenon-dexmedetomidine anaesthesia vs. sevoflurane anaesthesia regarding the incidence of ED.

Secondary: ED as assessed by the PAEDScore

End point title	ED as assessed by the PAEDScore
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End point description:

End point type	Secondary
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End point timeframe:

60 minutes after extubation

End point values	dex/xenon	sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: number of subjects				
number (not applicable)	39	39		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment until the first postinterventional day

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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Reporting groups

Reporting group title	dex/xenon
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Reporting group description: -

Reporting group title	sevoflurane
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Reporting group description: -

Serious adverse events	dex/xenon	sevoflurane	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
Vascular disorders			
Pulmonary hypertension			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	dex/xenon	sevoflurane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 40 (35.00%)	32 / 40 (80.00%)	
Vascular disorders			

Hypotensive during anaesthesia procedure subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 8	23 / 40 (57.50%) 23	
Cardiac disorders arterial hypertension subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 40 (0.00%) 0	
Bradycardia	Additional description: bradycardia during anesthesia		
subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4	5 / 40 (12.50%) 5	
catheter induced AV-block subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 40 (2.50%) 1	
repolarisation subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 40 (2.50%) 1	
Respiratory, thoracic and mediastinal disorders coughing during anesthesia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 40 (2.50%) 1	
Skin and subcutaneous tissue disorders desaturation subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	0 / 40 (0.00%) 0	
Musculoskeletal and connective tissue disorders movement of legs during surgery subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	1 / 40 (2.50%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2019	1. The loading dose of dexmedetomidine will be increased (1µg/kg instead of 0.5 µg/kg) and the continuous infusion will be titrated between 0.5 -1 µg/kg (instead of 0.3-0.8 with a maximum of 1µg/kg/h in case of insufficient depth of anesthesia) in order to be equivalent to our clinical routine in children undergoing sedation for magnetic resonance imaging (2µg/kg dexmedetomidine as a bolus, followed by a 1 µg/kg bolus 20 minutes later) and in order to be equivalent to an ongoing international multicenter trial in which dexmedetomidine is also studied in a comparable patient population undergoing major surgery (for further information, see https://clinicaltrials.gov/ct2/show/NCT03089905). We have also seen in our first patients that the originally proposed doses of dexmedetomidine were too low to achieve an adequate depth of anaesthesia. 2. With respect to the titration of anaesthetic depth, we will in this version primarily rely on physiological signs indicative for a sufficient depth of anaesthesia (as the validity of the BIS-monitoring in little children remains controversial). 3. For the prophylaxis of postoperative nausea and vomiting, we will also administer ondansetron during the induction of anaesthesia. This is our institutional routine. 4. For rescue sedation, we will not administer a bolus of remifentanyl, but a bolus of fentanyl.
12 November 2019	extension of recruitment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported