Clinical trial results:
Erector Spinae plane block for minimal invasive mitral valve surgery. A double blind, prospective randomized placebo-controlled trial.

Summary

EudraCT number	2019-001125-27
Trial protocol	BE
Global end of trial date	04 November 2021

Results information

Result version number	v1 (current)
This version publication date	26 October 2022
First version publication date	26 October 2022

Trial information

Trial identification

Sponsor protocol code	DH022019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Anesthesiology Research, University Hospitals Leuven, 0032 16344270, christel.huygens@uzleuven.be
Scientific contact	Anesthesiology Research, University Hospitals Leuven, 0032 16344270, 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	10 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2021
Global end of trial reached?	Yes
Global end of trial date	04 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of this study is to improve pain management after minimal invasive mitral valve surgery and to facilitate postoperative recovery. Our hypothesis is that patients having an Erector Spinae Block via intermittent boli ropivacain via catheter is associated with a reduction in postoperative morphine consumption.

Protection of trial subjects:

Patients received acetaminophen (15 mg kg-1) every 6 hours and morphine patient-controlled intravenous analgesia (PCIA) up to 24 hours post-extubation. Rescue analgesia consisted of a bolus of morphine, ketorolac, acetylsalicylic acid and/or removal or infiltration of chest tubes according to a standardized flowchart (supplementary figure S1). Twenty-four hours post-extubation, morphine PCIA was stopped and further analgesic treatment consisted of acetaminophen combined with tramadol or morphine.

Background therapy:

Irrespective of group allocation, every patient received a bolus of IV morphine (0.1 mg kg-1) and acetaminophen IV (1g) at thorax closure. After having received the interventional treatment, patients were transferred intubated to the PACU under analgosedation with dexmedetomidine and remifentanil. Following extubation (T0), patients received PCIA pump with morphine (on-demand-only mode with a morphine bolus of 1.5 mg up to every 7 minutes).

Evidence for comparator:

While in numerous case reports the ESP block has been described to adequately provide perioperative analgesia after adult cardiac surgery, the evidence from randomized controlled trials (RCT) is scarce. In the four RCTs that investigated the ESP block in adult cardiac surgery, bilateral ESP blocks were used for cardiac surgery cases requiring a sternotomy. In addition, double-blinding of allocation was limited to only 1 trial.

Actual start date of recruitment	02 July 2019
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: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	33
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment details:
112 patients between July 2nd 2019 and November 4th 2021 were screened of whom 72 were eligible for participation.

Pre-assignment

Screening details:

All consecutive adult patients scheduled for either MIMVS were evaluated for enrollment according to the inclusion criteria. They were included if 18-80 years of age, BMI <35, EuroSCORE <3, admitted to the PACU with our epilepsy, chronic opioid use or OSAS without treatment.

Period 1

Period 1 title	Surgery (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

All patients were randomized through a computer-generated permuted block randomisation sequence (variable block-size with 1:1 allocation). Enclosing assignments in opaque, sequentially numbered, sealed envelopes ensured allocation concealment. Following uneventful surgery and confirmation of post-anesthesia care unit (PACU) admittance, the envelope was opened by research personnel and the trial medication was prepared. Syringes were then labelled with the mark “trial medication”.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.

Arm type	Experimental
Investigational medicinal product name	Ropivacaine 0,5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

Dosage and administration details:
Initial dose of 30mL followed after 6, 12 and 18 hours with a dose of 20mL.

Arm title	Control

Arm description:

After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.

Arm type	Placebo
Investigational medicinal product name	normal saline 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Injection

Dosage and administration details:

Dosage and administration details:
Initial dose of 30mL followed after 6, 12 and 18 hours with a dose of 20mL.

Number of subjects in period 1	Intervention	Control
Started	36	36
Completed	36	36

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.	
Reporting group title	Control
Reporting group description:	
After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.	

Reporting group values	Intervention	Control	Total
Number of subjects	36	36	72
Age categorical 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)	14	19	33
From 65-84 years	22	17	39
85 years and over	0	0	0
Age continuous Units: years			
geometric mean	66	65	
standard deviation	± 9.2	± 8.7	-
Gender categorical Units: Subjects			
Female	10	11	21
Male	26	25	51

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.	
Reporting group title	Control
Reporting group description:	
After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.	

Primary: Morphine consumption 24 hours

End point title	Morphine consumption 24 hours
End point description:	
End point type	Primary
End point timeframe:	
Assessed 24 hours after extubation	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[1]	34[2]		
Units: mg				
median (inter-quartile range (Q1-Q3))	41 (30 to 55)	37 (29 to 50)		

Notes:

[1] - 2 early withdrawals due to 1 reintubation and 1 ischemic cerebral accident.

[2] - 2 early withdrawals due to epileptic seizure

Statistical analyses

Statistical analysis title	Primary outcome
Comparison groups	Intervention v Control
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.05
Method	t-test, 2-sided
Variability estimate	Standard deviation

Notes:

[3] - Mann-Whitney U test

Secondary: Numerical rating score for pain

End point title	Numerical rating score for pain

End point description:

Pain intensity as assessed with an 11-point numeric rating score (NRS) for pain

End point type	Secondary

End point timeframe:

Pain scores assessed 2 hours after extubation

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[4]	34[5]		
Units: NRS 0-10				
median (inter-quartile range (Q1-Q3))	2.5 (2 to 3)	3 (1 to 3)		

Notes:

[4] - 2 early withdrawals due to 1 reintubation and 1 ischemic cerebral accident

[5] - 2 early withdrawals due to epileptic seizure

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment until 24 hours after extubation.

Adverse event reporting additional description:

Incidence of adverse events (AE) related to the intervention or surgical procedure.
Early safety endpoints at 30 days as defined by Valve Academic Research Consortium-2 (VARC-2) (all-cause mortality, stroke, life-threatening bleeding, acute kidney injury (stage 2 or 3), major vascular complication or valve-related dysfunction) will be evaluated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Intervention

Reporting group description:

After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.

Reporting group title	Control

Reporting group description:

After completion of the surgery, an ESP block (with placement of a catheter) was performed with 30mL of trial medication. There after, 20mL trial medication through the ESP-catheter at the PACU was given every 6 hours after the first dose (B0 +6h, B0 +12h, and B0 +18h), three times in total.

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)	2 / 36 (5.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Epilepsy with myoclonic-atonic seizures			
subjects affected / exposed	0 / 36 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Respiratory fatigue			
subjects affected / exposed	1 / 36 (2.78%)	0 / 36 (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: 5 %

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 36 (38.89%)	17 / 36 (47.22%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	14 / 36 (38.89%)	17 / 36 (47.22%)	
occurrences (all)	14	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2021	Extension of recruitment period due to COVID-19 Pandemic. In addition, the planned blinded interim analysis for sample size recalculation (September 22nd 2020) revealed the need to include 4 additional patients in each group.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported