



Clinical trial results:

Intrathecal morphine for minimally invasive direct coronary artery bypass surgery: a multicentre, double blind, prospective randomized placebo-controlled trial

Summary

EudraCT number	2022-003684-14
Trial protocol	BE
Global end of trial date	23 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	DH11/2022
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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, University Hospitals Leuven, +32 16344270, danny.hoogma@uzleuven.be
Scientific contact	Anesthesiology, University Hospitals Leuven, +32 16344270, danny.hoogma@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	15 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2024
Global end of trial reached?	Yes
Global end of trial date	23 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The goal of our study is to improve perioperative care with the use of a multimodal opioid sparing strategy after minimally invasive cardiac surgery for coronary bypass.

Protection of trial subjects:

Rescue analgesia will be provided according to a standardized protocol. Following extubation, the severity of pain will be assessed at rest and during coughing using an 11-point numeric rating scale (NRS) for pain. NRS 0 = no pain, 1-3 = presence of pain but no additional treatment necessary. In case of NRS > 4, a clinical bolus (1-2 mg) of morphine will be given to the patient. This can be repeated, if however, NRS is >5 during two consecutive assessments, morphine 0.1 mg/kg SC (minimum interval of 4 hours) will be administered. If the pain is localized to the drains insertion site and does not respond to morphine, an additional infiltration of 10 mL of ropivacaine 0.5 % can be considered or if deemed possible, the drain will be removed.

Moreover, morphine is not sufficient to treat 'pericarditis pain'. The latter is expressed as sharp, stabbing chest pain and is mainly diagnosed based on clinical suspicion AND the documentation of new widespread ST-segment elevations or PR depression on the electrocardiogram.¹⁵ These patients will be treated with acetylsalicylic acid 500 mg IV every 8 hours and colchicine 1 mg orally twice a day.¹⁵ Finally, if pain treatment is still considered insufficient (NRS for pain >6), ibuprofen IV 10 mg/kg (max 600 mg) will be administered or a bolus of ketamine IV 0.1 mg/kg will be given

Background therapy:

Multimodal analgesic treatment as per protocol in our ERACS program

Evidence for comparator:

The comparator is the standard of care.

Actual start date of recruitment	01 May 2023
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
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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)	36
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

113 patients between May 21th 2023 and July 18th 2024 were screened of whom 72 were eligible for participation.

Pre-assignment

Screening details:

All consecutive adult patients scheduled for either RAMIDCAB surgery were evaluated for enrollment according to the inclusion criteria. They were included if 18-75 years of age, BMI <35, EuroSCORE <3, and admitted to the postoperative ERAS program at the PACU or ICU.

Period 1

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

Blinding implementation details:

To avoid bias, treatment arms will be blinded to investigators, medical staff, nurses and participants as follows:

The IMP will be manufactured, packaged and labelled in such a way that the visual appearance, nor the smell and/or touch of the IMP can be distinguished from the comparator treatment and/or placebo.

Furthermore, to maintain the blind, the IMP and any comparator treatment(s) and/or placebo will follow the same administration route and process.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention group

Arm description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being 5 µg/kg morphine 0.1% (with a maximum of 500 µg), and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1ml/kg, being normal saline 0.9%.

Arm type	Experimental
Investigational medicinal product name	morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being 5 µg/kg morphine 0.1% (with a maximum of 500 µg), and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1ml/kg, being normal saline 0.9%.

Arm title	Control
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Arm description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being normal saline, and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1 ml/kg, being morphine 0.1%.

Arm type	Placebo
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Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intratracheal use

Dosage and administration details:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being normal saline, and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1 ml/kg, being morphine 0.1%.

Number of subjects in period 1	Intervention group	Control
Started	36	36
Included	36	36
Completed	35	36
Not completed	1	0
Failed spinal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Intervention group
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Reporting group description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being 5 µg/kg morphine 0.1% (with a maximum of 500 µg), and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1ml/kg, being normal saline 0.9%.

Reporting group title	Control
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Reporting group description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being normal saline, and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1 ml/kg, being morphine 0.1%.

Reporting group values	Intervention group	Control	Total
Number of subjects	36	36	72
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
geometric mean	64.3	64.9	
standard deviation	± 7.6	± 8.7	-
Gender categorical			
Units: Subjects			
Female	4	1	5
Male	32	35	67

End points

End points reporting groups

Reporting group title	Intervention group
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Reporting group description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being 5 µg/kg morphine 0.1% (with a maximum of 500 µg), and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1ml/kg, being normal saline 0.9%.

Reporting group title	Control
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Reporting group description:

This group will receive sequentially intrathecal 5 µl/kg of trial medication, being normal saline, and 0.125 mg/kg hyperbaric bupivacaine 0.5%.

At the end of surgery, the patient will receive an intravenous bolus of trial medication 0.1 ml/kg, being morphine 0.1%.

Primary: Quality of recovery 40

End point title	Quality of recovery 40
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End point description:

The primary outcome variable of this investigation will be the postoperative QoR-40 score taken approximately 24 hours postoperatively. This questionnaire consist of 40 items rated by the patient as valid or non-valid on a scale of 5 with a score range between 40-200. Assuming a SD QoR-40 score of 9 points in both groups and assuming no relevant differences between both study centres, 34 patients per group are required to have at least 80% power to show a minimal clinically important difference of 6.3 points between the intervention group and control group based on a two-sided two sample t-test with alpha=0.05.

End point type	Primary
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End point timeframe:

24 hours postoperatively

End point values	Intervention group	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35 ^[1]	36		
Units: 40-200				
median (inter-quartile range (Q1-Q3))	185.0 (175 to 193)	180.5 (170.5 to 189.5)		

Notes:

[1] - 1 failed spinal

Statistical analyses

Statistical analysis title	SAP
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Statistical analysis description:

A parametric regression model with the treatment group and the study centre as covariates was used.

Comparison groups	Intervention group v Control
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Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	10.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48 hours postoperatively

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28
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Reporting groups

Reporting group title	Adverse event postop
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Reporting group description: -

Serious adverse events	Adverse event postop		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 71 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Adverse event postop		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 71 (8.45%)		
Skin and subcutaneous tissue disorders			
Pruritis			
subjects affected / exposed	6 / 71 (8.45%)		
occurrences (all)	6		

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