Clinical trial results:
Intraoperative methadone for postoperative pain management in spinal fusion surgery: a prospective, double-blind, randomised controlled trial

Summary

EudraCT number	2020-004826-47
Trial protocol	DK
Global end of trial date	31 May 2024

Results information

Result version number	v1 (current)
This version publication date	20 March 2026
First version publication date	20 March 2026

Trial information

Trial identification

Sponsor protocol code	23956082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04764825
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AUH
Sponsor organisation address	Palle Juul-Jensens Blvd 99, Aarhus , Denmark,
Public contact	Lone Nikolajsen, Aarhus University Hospital, 0045 78464317, lone.nikolajsen@clin.au.dk
Scientific contact	Lone Nikolajsen, Aarhus University Hospital, 0045 78464317, lone.nikolajsen@clin.au.dk
Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensen Blvd. 99, Aarhus, Denmark, 8200
Public contact	MD, Ph.d. Camilla G Uhrbrand, Dept. of Anesthesia and Intensive Care, Aarhus University Hospital, 0045 23956082, camgaa@rm.dk
Scientific contact	Professor Lone Nikolajsen, Dept. of Anesthesia and Intensive Care, Aarhus University Hospital, 0045 23956082, loneniko@rm.dk

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	30 May 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2024
Global end of trial reached?	Yes
Global end of trial date	31 May 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Opioid consumption at 6 hours after extubation (mean cumulative opioid consumption)
Opioid consumption at 24 hours after extubation (mean cumulative opioid consumption)

Protection of trial subjects:

Informed written consent was obtained before surgery for all trial subjects.
Criteria for
exclusion included allergy to study drugs, preoperative opioid use [>60 mg oral morphine equivalents (OME) at least 7 days leading up to surgery], prolonged QTc-interval (>440 ms), planned postoperative epidural or ketamine infusion, American Society of Anesthesiologists Physical Status (ASA) IV or V, severe liver, kidney, lung or heart disease, pregnancy or breastfeeding, malignancy-related surgery or inability to provide informed consent.

Doses was decided from commonn practice.

Background therapy:

Anesthesia, surgery, and postoperative care followed standard protocols at our institution. Induction was achieved with propofol (1–3 mg/kg) and remifentanil (2–4 μg/kg), followed by maintenance doses of 5 mg/kg/h and 30 μg/kg/h, respectively. No fentanyl was administered after induction. Vasopressors and fluids were administered at the anesthetist’s discretion. Intraoperative monitoring included invasive blood pressure, continuous electrocardiogram, capnography, and oximetry. Spine fusion was performed using an instrumented posterior-only approach with patients in the prone position, adhering to international standards. Before closure, 100 mL ropivacaine 2 mg/mL, was infiltrated at the incision site. All patients were extubated in the operating theatre and transferred to the PACU. Discharge criteria from the PACU to the surgical ward were based on national recommendations.13 Pain management in the PACU was consistent with standard-ofcare. Intravenous alfentanil (0.25–0.5 μg) combined with intravenous fentanyl (0.1 mg/kg) was used as first-line treatment for Numeric Rating Scale (NRS, 0–10) ≥7. Intravenous morphine (0.05–1.0 μg/kg) was administered for NRS 4 to 6 and titrated every 5 to 10 minutes until NRS scores were below 4. Oxycodone was used as an alternative or supplement for moderate to severe pain in cases of morphine intolerance. Postoperative nausea and vomiting (PONV) treatment followed national guidelines.14
At extubation, all patients were equipped with a

patient-controlled analgesia (PCA) pump for demandonly morphine (2.5 mg per dose, max four doses/hour, 7-minute lockout).

Evidence for comparator:

The comparator in this trial was morphine. Morphine in this relation was pre trial our opioid of choice for this selected group of patients.

Actual start date of recruitment	01 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 124
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	62
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged 18 to 85 years scheduled for elective lumbar fusion surgery (<5 levels) were screened and at pre anesthesia consult asked to read information regarding the trial. They were able to ask follow up questions. At the day of surgery they were finally asked whether they wished to participate.

Pre-assignment

Screening details:

Between February 26, 2021, and March 19, 2024, 262 patients scheduled for spine fusion were screened for eligibility. Of these, 124 patients were enrolled and randomized to treatment groups. Eleven patients were excluded due to various reasons, leaving 113 patients in the final analysis

Period 1

Period 1 title	Overall trial (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:

The Hospital Pharmacy managed study medication, randomization, and blinding. Patients were randomized in a 1:1:1 ratio using permuted blocks of sizes 3, 6, and 9. To ensure blinding, study personnel received two identical 10 mL syringes, marked by the pharmacy with either A or B according to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	MET pre

Arm description:

receive methadone 0.15- 0.2 mg/kg ideal body weight (IBW) before incision

Arm type	Experimental
Investigational medicinal product name	Methadone
Investigational medicinal product code	N07BC02
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Single bolus use.

Arm title	MET post

Arm description:

Received methadone 0.15-0.2 mg/kg IBW before wound closure

Arm type	Experimental
Investigational medicinal product name	Methadone
Investigational medicinal product code	N07BC02
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:
Single dose use.

Arm title	MOR post

Arm description:
Received morphine 0.15- 0.2 mg/kg IBW before wound closure

Arm type	Active comparator
Investigational medicinal product name	Morphine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:
Single dose use.

Number of subjects in period 1	MET pre	MET post	MOR post
Started	44	41	39
Completed	39	38	36
Not completed	5	3	3
Surgery Cancelled	1	-	-
Consent withdrawn by subject	2	-	1
Physician decision	-	3	-
cancelled	-	-	1
Protocol deviation	2	-	1

Baseline characteristics

Reporting groups	
Reporting group title	MET pre
Reporting group description:	
receive methadone 0.15- 0.2 mg/kg ideal body weight (IBW) before incision	
Reporting group title	MET post
Reporting group description:	
Received methadone 0.15-0.2 mg/kg IBW before wound closure	
Reporting group title	MOR post
Reporting group description:	
Received morphine 0.15- 0.2 mg/kg IBW before wound closure	

Reporting group values	MET pre	MET post	MOR post
Number of subjects	44	41	39
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	64.9	63.7	63.8
standard deviation	± 12.2	± 11.7	± 10.8
Gender categorical Units: Subjects			
Female	23	26	19
Male	21	15	20
preoperative daily opioid use Units: Subjects			
yes	14	14	13
no	30	27	26

Reporting group values	Total		
Number of subjects	124		
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			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	68		
Male	56		
preoperative daily opioid use			
Units: Subjects			
yes	41		
no	83		

End points

End points reporting groups

Reporting group title	MET pre
Reporting group description:	
receive methadone 0.15- 0.2 mg/kg ideal body weight (IBW) before incision	
Reporting group title	MET post
Reporting group description:	
Received methadone 0.15-0.2 mg/kg IBW before wound closure	
Reporting group title	MOR post
Reporting group description:	
Received morphine 0.15- 0.2 mg/kg IBW before wound closure	

Primary: Cumulative opioid consumption at 24 hours

End point title	Cumulative opioid consumption at 24 hours
End point description:	

End point type	Primary
End point timeframe:	
Cumulative opioid requirements measured in oral morphine equivalents (OME) within 24 hours after extubation.	

End point values	MET pre	MET post	MOR post	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: mg oral morphine equivalents (OME)				
median (inter-quartile range (Q1-Q3))	141.5 (87.5 to 245.5)	153.25 (102.5 to 239)	183.8 (113.8 to 268.8)	

Statistical analyses

Statistical analysis title	primary outcome
Statistical analysis description:	
Continuous variables were assessed for distribution and reported as medians with interquartile ranges (IQR) when not normally distributed. Comparisons of cumulative opioid consumption (oral morphine equivalents, OME) between the three treatment groups were performed using the Kruskal–Wallis test. Pairwise comparisons were performed using the Mann–Whitney U test when appropriate. A two-sided p-value <0.05 was considered statistically significant.	
Comparison groups	MET pre v MET post v MOR post

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.518
Method	Kruskal-wallis

Secondary: Cumulative opioid consumption (oral morphine equivalents) at 6 hours

End point title	Cumulative opioid consumption (oral morphine equivalents) at 6 hours

End point description:

End point type	Secondary

End point timeframe:

6 hours

End point values	MET pre	MET post	MOR post	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: mg oral morphine equivalents (OME)				
median (inter-quartile range (Q1-Q3))	85 (27.5 to 112.5)	77.8 (45 to 120)	92.5 (48.8 to 146.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity at 24h

End point title	Pain intensity at 24h

End point description:

End point type	Secondary

End point timeframe:

24 hours

End point values	MET pre	MET post	MOR post	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: NRS (0–10)				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	0 (± 0)	

Attachments (see zip file)	6E91B9A3.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Patient satisfaction

End point title	Patient satisfaction

End point description:

Patient satisfaction with postoperative pain management measured on a Numeric Rating Scale (0–10).

End point type	Secondary

End point timeframe:

24 hours

End point values	MET pre	MET post	MOR post	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: NRS (0 to 10)				
median (inter-quartile range (Q1-Q3))	10 (9 to 10)	9 (8 to 10)	9 (7.5 to 10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hypoventilation in PACU

End point title	Hypoventilation in PACU

End point description:

Hypoventilation in the post-anaesthesia care unit defined as respiratory rate <10 breaths per minute.

End point type	Secondary

End point timeframe:

PACU time

End point values	MET pre	MET post	MOR post	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: No. of subjects	2	1	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

72 hours

Adverse event reporting additional description:

Adverse events were assessed during the postoperatively and recorded according to the study protocol. The trial was monitored by the Good Clinical Practice (GCP) unit at Aarhus University Hospital.

Assessment type	Systematic

Dictionary used

Dictionary name	CTR
Dictionary version	2014

Reporting groups

Reporting group title	overall trial population

Reporting group description:

All randomized patients receiving study medication (methadone before incision, methadone before wound closure, or morphine before wound closure).

Serious adverse events	overall trial population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 113 (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	overall trial population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 113 (9.73%)		
Respiratory, thoracic and mediastinal disorders			
Respiratory events	Additional description: Respiratory events during postoperative stay in the PACU, including hypoventilation (respiratory rate <10/min) and hypoxemia (oxygen saturation <90%).		
subjects affected / exposed	11 / 113 (9.73%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2023	Changed the handling of study drugs and inclusion criterias (QTc on ECG).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated before reaching the planned sample size and may therefore be underpowered to detect smaller differences between groups. In addition, the single-centre design may limit the generalizability of the results.

Notes: