Clinical trial results:
The analgesic effect of local anaesthetic only compared to local anaesthetic with adjunct of short acting opioid and adrenaline in a continuous paravertebral block for analgesia after VATS – a prospective randomised study.

Summary

EudraCT number	2015-002169-50
Trial protocol	SE
Global end of trial date	14 September 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	Parav20150511

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	Nobels väg 6, Solna, Sweden, 17177
Public contact	Mark Larsson, Department of Thoracic Surgery, Karolinska, 46 (0)8517 70 914, mark.larsson@karolinska.se
Scientific contact	Mark Larsson, Department of Thoracic Surgery, Karolinska, 46 (0)8517 70 914, mark.larsson@karolinska.se

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	03 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 September 2021
Global end of trial reached?	Yes
Global end of trial date	14 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that the addition of sufentanil and epinephrine to levobupivacaine in continuous paravertebral block will increase its analgesic potency, resulting in better pain relief and enhanced recovery after Video-Assisted Thoracoscopic Surgery despite the lower total levobupivacaine dose administered.

Protection of trial subjects:

Except for the allocated treatment and the use of a patient-controlled analgesia (PCA) pump, all study participants received care according to standard departmental practice.
Investigator ML obtained written informed consent from each patient who agreed to participate in the study after having received oral and written information about the study.
All participants were monitored for any adverse events.
The trial was approved by the Ethical Review Agency (registration no. 2015/1389-31).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2017
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	Sweden: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	16

From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients scheduled for lung resection by VATS at the Karolinska University Hospital were considered for enrolment. From 23 October 2017 to 27 April 2020, 76 patients scheduled for VATS were asked to participate. Sixteen patients were ineligible, and the remaining 60 patients were enrolled. After enrolment, 4 were excluded - total = 56 patients.

Pre-assignment

Screening details:

Patients aged >20 years, with an American Society of Anesthesiologists (ASA) physical status classification of II or III, and the ability to give informed consent were eligible for participation. Reasons for ineligibility were allergy to LAs, pronounced hepatic disease, psychiatric disease or use of psychoactive medication, cognitive impairment.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	levobupivacaine-sufentanil-adrenaline (LBSA)

Arm description:

Trial participants were given a continous infusion of levobupivacaine, sufentanil and adrenaline.

Arm type	Experimental
Investigational medicinal product name	levobupivacaine
Investigational medicinal product code	
Other name	Chirocaine
Pharmaceutical forms	Infusion
Routes of administration	Extrapleural use

Dosage and administration details:

Continous infusion of 1.25 mg/ml levobupivacaine at a rate of 5 ml/h

Investigational medicinal product name	sufentanil
Investigational medicinal product code	
Other name	Sufenta
Pharmaceutical forms	Infusion
Routes of administration	Extrapleural use

Dosage and administration details:

Continous infusion of 0.5 µg/ml sufentanil at a rate of 5 ml/h

Investigational medicinal product name	adrenaline
Investigational medicinal product code	
Other name	adrenalin mylan
Pharmaceutical forms	Infusion
Routes of administration	Extrapleural use

Dosage and administration details:

Continous infusion of 2 µg/ml adrenaline at a rate of 5 ml/h

Arm title	Levobupivacaine (LB)

Arm description:

Trial participants were given a continous infusion of levobupivacaine alone

Arm type	Active comparator
Investigational medicinal product name	levobupivacaine
Investigational medicinal product code	
Other name	Chirocaine
Pharmaceutical forms	Infusion
Routes of administration	Extrapleural use

Dosage and administration details:

Continous infusion of 2.7 mg/ml levobupivacaine at a rate of 5 ml/h

Number of subjects in period 1[1]	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)
Started	27	29
Completed	25	27
Not completed	2	2
Lost to follow-up	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: From 23 October 2017 to 27 April 2020, 76 patients scheduled for VATS were asked to participate. Sixteen patients were ineligible, and the remaining 60 patients were enrolled. After enrolment, 4 were excluded - total = 56 patients.

Baseline characteristics

Reporting groups	
Reporting group title	levobupivacaine-sufentanil-adrenaline (LBSA)
Reporting group description:	
Trial participants were given a continous infusion of levobupivacaine, sufentanil and adrenaline.	
Reporting group title	Levobupivacaine (LB)
Reporting group description:	
Trial participants were given a continous infusion of levobupivacaine alone	

Reporting group values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)	Total
Number of subjects	27	29	56
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			
median	68	72	
inter-quartile range (Q1-Q3)	62 to 75	65 to 76	-
Gender categorical Units: Subjects			
Female	12	16	28
Male	15	13	28
surgical procedure Units: Subjects			
Wedge resection, single	0	3	3
Wedge resection, multiple	0	1	1
Segmentectomy	4	4	8
Lobectomy	23	20	43
Bilobectomy	0	1	1
Number of ports Units: Subjects			
One	11	16	27
Two	9	8	17
Three	7	5	12
weight Units: kilogram(s)			
median	81	71	

inter-quartile range (Q1-Q3)	64 to 90	64 to 84	-
Height			
Units: centimetre			
median	174	167	
inter-quartile range (Q1-Q3)	164 to 182	163 to 175	-

End points

End points reporting groups

Reporting group title	levobupivacaine-sufentanil-adrenaline (LBSA)
Reporting group description: Trial participants were given a continous infusion of levobupivacaine, sufentanil and adrenaline.	
Reporting group title	Levobupivacaine (LB)
Reporting group description: Trial participants were given a continous infusion of levobupivacaine alone	

Primary: Cumulative PCA-morphine dose at 48 hours

End point title	Cumulative PCA-morphine dose at 48 hours
End point description:	
End point type	Primary
End point timeframe: 48 hours after surgery	

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	27		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	7 (3 to 13.5)	6 (2 to 10)		

Statistical analyses

Statistical analysis title	Difference in cumulative PCA-morphine dose 48h
Statistical analysis description: Difference in cumulative PCA-morphine requirement at 48 hours	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.378
Method	Wilcoxon (Mann-Whitney)

Primary: Cumulative PCA-morphine dose at 72 hours

End point title	Cumulative PCA-morphine dose at 72 hours

End point description:

End point type	Primary

End point timeframe:

72 hours after surgery

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: milligram(s)				
median (inter-quartile range (Q1-Q3))	12.5 (4 to 21)	10 (3 to 21.9)		

Statistical analyses

Statistical analysis title	Difference in cumulative PCA-morphine dose 72h

Statistical analysis description:

Difference in cumulative PCA-morphine requirement at 72 hours

Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.738
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative Pain score at rest - 48 hours

End point title	Cumulative Pain score at rest - 48 hours

End point description:

Pain score, indicated by numerical rating scale (NRS) at rest, cumulative over 48 hours

End point type	Secondary

End point timeframe:

cumulative over 48 hours

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	23		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	5.5 (1.5 to 10)	4 (3 to 6)		

Statistical analyses

Statistical analysis title	Difference in pain score at rest 48h
Statistical analysis description: Difference in pain score at rest, cumulative over 48 hours	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative Pain score at rest - 72 hours

End point title	Cumulative Pain score at rest - 72 hours
End point description: Pain score, indicated by numerical rating scale (NRS) at rest, cumulative over 72 hours	
End point type	Secondary
End point timeframe: cumulative over 72 hours	

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	9 (4 to 15)	6 (3 to 12)		

Statistical analyses

Statistical analysis title	Difference in pain score at rest 72h
Statistical analysis description: Difference in pain score at rest, cumulative over 72 hours	

Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain score deep breaths - 24 hours

End point title	Pain score deep breaths - 24 hours
End point description: Pain score, indicated by numerical rating scale (NRS) after two deep breaths, at 24 hours	
End point type	Secondary
End point timeframe: after two deep breaths, at 24 hours	

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	3 (2 to 5)	2.5 (1 to 3)		

Statistical analyses

Statistical analysis title	Difference in pain score - deep breaths - 24h
Statistical analysis description: Difference in pain score after two deep breaths, at 24 hours	
Comparison groups	Levobupivacaine (LB) v levobupivacaine-sufentanil-adrenaline (LBSA)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Wilcoxon (Mann-Whitney)

Secondary: Pain score deep breaths - 30 hours

End point title	Pain score deep breaths - 30 hours
End point description: Pain score, indicated by numerical rating scale (NRS) after two deep breaths, at 30 hours	
End point type	Secondary

End point timeframe:
after two deep breaths, at 30 hours

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	3 (2 to 4)	1 (0 to 3)		

Statistical analyses

Statistical analysis title	Difference in pain score - deep breaths - 30h
Statistical analysis description: Difference in pain score after two deep breaths, at 30 hours	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative Pain score deep breaths - 48 hours

End point title	Cumulative Pain score deep breaths - 48 hours
End point description: Pain score, indicated by numerical rating scale (NRS) after two deep breaths, cumulative over 48 hours	
End point type	Secondary
End point timeframe: after two deep breaths, cumulative measurement over 48 hours	

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	22		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	14 (8 to 20)	9.5 (6 to 15)		

Statistical analyses

Statistical analysis title	Difference in pain score - deep breaths - 48h
Statistical analysis description: Difference in pain score after two deep breaths, cumulative over 48 hours	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	Wilcoxon (Mann-Whitney)

Secondary: Cumulative Pain score deep breaths - 72 hours

End point title	Cumulative Pain score deep breaths - 72 hours
End point description: Pain score, indicated by numerical rating scale (NRS) after two deep breaths, cumulative over 72 hours	
End point type	Secondary
End point timeframe: after two deep breaths, cumulative over 72 hours	

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: NRS score				
median (inter-quartile range (Q1-Q3))	20 (17 to 23)	12 (6 to 23)		

Statistical analyses

Statistical analysis title	Difference in pain score - deep breaths - 72h
Statistical analysis description: Difference in pain score after two deep breaths, cumulative over 72 hours	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of recovery - POD1

End point title	Quality of recovery - POD1

End point description:

Quality of recovery according to quality of recovery(QoR)-15 questionnaire - POD1 (day 1 after surgery)

End point type	Secondary

End point timeframe:

Day 1 after surgery

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: QoR-15 score				
median (inter-quartile range (Q1-Q3))	117 (99 to 126)	118 (106 to 126)		

Statistical analyses

Statistical analysis title	Difference in QoR-15 score POD1

Statistical analysis description:

Difference in QoR-15 score 1 day after surgery

Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491
Method	Wilcoxon (Mann-Whitney)

Secondary: Quality of recovery - POD21

End point title	Quality of recovery - POD21

End point description:

Quality of recovery according to quality of recovery(QoR)-15 questionnaire - POD21 (day 21 after surgery)

End point type	Secondary

End point timeframe:
21 days after surgery

End point values	levobupivacaine-sufentanil-adrenaline (LBSA)	Levobupivacaine (LB)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	27		
Units: QoR-15 Score				
median (inter-quartile range (Q1-Q3))	124 (109 to 135)	131 (112 to 143)		

Statistical analyses

Statistical analysis title	Difference in QoR-15 score POD21
Statistical analysis description: Difference in QoR-15 score 21 days after surgery	
Comparison groups	levobupivacaine-sufentanil-adrenaline (LBSA) v Levobupivacaine (LB)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In-hospital from the start of the intervention to discharge at 48- or 72 hours as well as out-of-hospital up to 21 days after the intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	Free text
Dictionary version	n/a

Reporting groups

Reporting group title	All study subjects

Reporting group description: -

Serious adverse events	All study subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All study subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 56 (42.86%)		
Surgical and medical procedures			
chest tube remained in place after POD1			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	10		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 11		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1		

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